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Time	SUNDAY 3	MONDAY 4	TUESDAY 5
8.30	**Technical workshops** 1. Brain imaging 2. Calcium imaging 3. Brain banking 4. Gene transfer 5. Spinal cord trauma 6. Quant. morphology 7. Neural modelling	**2. Plenary Lecture** Meldolesi **Ca^{2+} signalling in neurons** Dr Saal van Zwanenberg lecture	**19. Plenary Lecture** Schertler **3D structure of rhodopsin** Hillarp lecture
9.00			
9.30		**Symposia** 4. Glia in neuronal regeneration 5. Genes & neurologic disease 6. Presynaptic Release 7. Real Time Measures **Oral Presentations** 11. Learning & Memory	**Symposia** 20. Ca-signalling in neurons 21. Development of language 22. Rational drug design 23. Robotics and vision **Oral Presentations** 28. Neural disorders
10.00			
10.30			
11.00			
11.30			
12.00		**Poster Sessions** 14. Neurotransmitters, modulators, receptors I 15. Disorders of the nervous system I 16. Sensory systems I 17. Development & plasticity I 18. Motor systems, sensory motor integration I 75. Electronic Posters	**EuroNeuro Orchestra**
12.30			**Poster Sessions** 31. Neurotransmitters, modulators, receptors II 32. Sensory systems II 33. Behaviour I 34. Development & plasticity II 35. Motor systems, sensory motor integration II 36. Other systems I 75. Electronic Posters
13.00			
13.30			
14.00			
14.30	**Registration:** the registration desk is open on – sunday: 14.00 - 20.00 – all other days: 08.00 - 18.00	**Symposia** 8. Signal transduction & disease 9. Suprachiasmatic nucleus 10. Microcircuits **Oral Presentations** 12. Neurodegenerative diseases 13. Plasticity	**Symposia** 24. Parkinson's disease 25. Intracellular trafficking 26. Face processing **Oral Presentations** 29. Receptors 30. Imaging
15.00			
15.30			
16.00			
16.30			
17.00	**Opening Ceremony** **1. Plenary Lecture** Mallet **Catecholamines** TINS/TIPS Lecture	**3. Plenary Lecture** Desimone **Single-neuron memory** EBBS - Annual Review	***27.* Forum symposium** **Plasticity:** **from molecules to cognition**
17.30			
18.00	**Get-together** – music – drinks – snacks		
18.30			
19.00		**Welcome Reception** Rijksmuseum Municipal museum	
19.30			
20.00			**EBBS Banquet**
20.30			
21.00			
21.30			
22.00			

WEDNESDAY 6	THURSDAY 7	Time	BEFORE & AFTER
37. Plenary Lecture O'Keefe **HIPPOCAMPAL PLACE NEURONS** MORUZZI LECTURE	**54. Plenary Lecture** Le Doux **EMOTION & LIMBIC SYSTEM**	8.30 9.00	**Satellite symposia** 31 August-3 September, Rotterdam THE CEREBELLUM: FROM STRUCTURE TO CONTROL 1-2 September, Amsterdam THE DYNAMICS OF THE OUTER RETINA 2 September, Amsterdam CONTRIBUTIONS OF THE RHINAL CORTICES TO THE MEDIAL TEMPORAL LOBE MEMORY SYSTEM 2-3 September, Amsterdam BRAIN AND BEHAVIOURAL APPROACH TO SPATIAL PROCESSING AND NAVIGATION IN ANIMAL AND MAN 3 September, Amsterdam NITRIC OXIDE IN MEMORY AND BEHAVIOUR 3 September, Amsterdam NEUROPEPTIDE RECEPTORS 8-9 September, Groningen THE NEUROBIOLOGY OF STRESS
Symposia 39. VAN DER LOOS MEMORIAL 40. FUNCTIONAL IMAGING 41. NEURO-COGNITIVE DRUGS 42. SPACE COGNITION **Oral Presentations** 46. NEUROTRANSM. & INTRACELL CA	**Symposia** 57. SCHIZOPHRENIA 58. CONSTRUCTION ODOUR WORLD 59. ELECTRIC ACTIVITY IN DENDRITES 60. DECADE OF THE BRAIN I **Oral Presentations** 64. SYNAPTIC PLASTICITY	9.30 10.00 10.30 11.00	
Annual General Meeting - ENA	**Annual General Meeting - EBBS**	11.30	
Poster Sessions 49. CELL BIOLOGY I 50. DISORDERS OF THE NERVOUS SYSTEM II 51. BEHAVIOUR II 52. EXCITABLE MEMBRANES & SYN. TRANSMISSION 53. OTHER SYSTEMS II 53A COMPUTATIONAL APPROACHES 75. ELECTRONIC POSTERS	**55. Plenary Lecture** - Berlucchi **GORDON HOLMES LECTURE** **Poster Sessions** 67. CELL BIOLOGY II 68. DISORDERS OF THE NERVOUS SYSTEM III 69. BEHAVIOUR III 70. DEVELOPMENT & PLASTICITY III 71. MOTOR SYSTEMS, SENSORY MOTOR INTEGR. III 72. ENDOCRINE & AUTONOMIC REGULATIONS 74. LATE POSTERS	12.00 12.30 13.00 13.30 14.00	
Symposia 43. STAR TRACK SYMPOSIUM 44. MECHANISMS OF NEUROPATHIES 45. TROPHIC FACTORS & RECEPTORS **Oral Presentations** 47. ION CHANNELS & TRANSMISSION 48. SENSORY SYSTEMS	**Symposia** 61. NEED FOR SYNERGY 62. FUNCTIONAL RECOVERY 63. FUNCTIONS OF THE AMYGDALA **Oral Presentations** 65. MOTOR SYSTEMS 66. COGNITION	14.30 15.00 15.30 16.00	
38. Plenary Lecture Grillner **VERTEBRATE NEURONAL NETWORKS**	**56. Plenary Lecture** Charnay **HINDBRAIN DEVELOPMENT** LEVI-MONTALCINI LECTURE	16.30 17.00	
Special Interest Cocktails		17.30 18.00 18.30 19.00 19.30 20.00	
Concert Utrechtsch Studenten Concert Beurs van Berlage		20.30 21.00 21.30 22.00	

1.01 CATECHOLAMINES: FROM GENE REGULATION TO NEUROPSYCHIATRIC DISORDERS

J. Mallet
Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, UMR 9923, C.N.R.S., F-91198 Gif-sur-Yvette, France

Abstract
The regulation of gene expression within neurons occurs not only during ontogenesis but also in the nervous system of the adult. More specifically, it has long been recognized that neurotransmitters such as catecholamines may alter the metabolism of post synaptic cells in addition to changing their electrical properties. Thus, neurons are endowed with the capacity to sense and integrate environmental changes. When such control mechanisms malfunction, neurological and psychiatric illnesses may result.

I will first discuss how studies of the regulation of tyrosine hydroxylase (TH), the rate limiting enzyme in catecholamine synthesis, have been used to elucidate specific adaptative responses in neurons. Then I will describe recent work linking manic depressive illness and schizophrenia to the TH gene locus; in particular, a rare allele of a microsatellite located in the TH gene was found exclusively in schizophrenic patients. Finally, I will discuss our findings, particularly in the context of Parkinson's diseases concerning *ex vivo* and *in vivo* gene therapy approaches for treatment of neurodegenerative disease.

2.01 CELL BIOLOGY OF Ca^{2+} SIGNALLING IN NEURONS AND NEUROSECRETORY CELLS.

Jacopo Meldolesi
Dept. of Pharmacology, Univ. of Milano, B. Ceccarelli and CNR Cytopharmacology Centers and DIBIT, Scientific Institute San Raffaele, Milano, Italy.

Intracellular Ca^{2+} signals result from the activation of multiple processes located both at the surface and within the cell. In the case of neurons and neurosecretory cells these processes can be very complex because of multiple reasons, including the geometrical complexity, the generation of in situ $[Ca^{2+}]_i$ rises and their evolution in dynamic phenomena, such as the oscillations and waves. Progress of cell biology in the field has yielded the first reliable high resolution information about the distribution of total Ca, investigated by electron spectroscopic imaging; the identification of the rapidly exchanging Ca^{2+} stores, with recognition of their molecular components; the discovery of whole classes of Ca^{2+} binding proteins of different affinity, located in the various intracellular compartments; molecular manipulations of individual proteins specifically located at the surface or within the cell, with ensuing fall out of information about properties and functions. All this information will be considered in a general framework, to reconstruct the homeostasis of the cation and correlate it to the running of Ca^{2+} dependent functions.

3.01 ATTENTION AND MEMORY STUDIED AT THE SINGLE-NEURON LEVEL IN THE MACAQUE MONKEY CORTEX.

Robert Desimone*, Laboratory of Neuropsychology, NIMH, Bethesda, MD, USA

Objects in the visual field must compete for limited processing capacity and control over behavior. In extrastriate visual cortex, this competition appears to take place among the different cell populations coding features of different objects in a scene. In part, competition is biased in favor of cells coding features of a particular object by bottom-up processes for figure-ground extraction and detection of novelty, which appear to be intrinsic to the visual cortex. In part, competition is also biased by top-down mechanisms that specify objects of current relevance to behavior. These mechanisms appear to involve an interaction of visual cortex with prefrontal regions involved in working memory. When a monkey is cued to find a target stimulus in a scene following a delay, prefrontal neurons coding features of the target are activated in a sustained fashion. Feedback from these cells biases neuronal responses in visual cortex in favor of the target stimulus, ultimately resulting in inhibition of cells coding features of distracting stimuli in the scene. Thus, as a result of biased competition in the cortex, relevant objects are "attended" and, more generally, acted upon by motor systems.

4. Symposium: Glia in neuronal regeneration

4.01 NEURONAL GROWTH-ASSOCIATED GENES RESPONSIVE TO CNS GLIA.

I.H.P. Skene*. Duke University, Durham, North Carolina 27710 USA.

The majority of adult neurons chronically suppress genes associated with developmental axon outgrowth, including genes coding for major growth cone components such as GAP-43. Re-activation of at least some of these genes appears to be required for neurons to become competent for regeneration after axon injury. In the PNS, suppression of the essential growth-associated genes depends primarily on the interaction of axon terminals with their targets. As a result, interruption of axons at any point along their length disrupts gene suppression and restores neuronal competence for regeneration. In the mammalian CNS, by contrast, lesions that leave a long proximal axon stump extending through CNS white matter fail to re-activate critical growth-associated genes, and the injured axons are unable to regenerate. Correlative studies suggest that suppression of growth-associated genes in these cases may be maintained by signaling cascades initiated by an interaction of glial cells with mature axons. In an effort to unravel these signaling pathways, we have begun to search for specific DNA response elements controlling the suppression of growth-associated genes in the mature CNS. Expression of the GAP-43 gene is tightly linked to successful regeneration throughout the CNS and PNS, strongly suggesting that this gene responds to the same signaling pathways that control neuronal competence for regeneration. We therefore have dissected the GAP-43 gene to identify DNA elements responsive to growth-controlling signaling cascades. Expression of reporter gene constructs in transgenic fish and mice has identified a 1 kb DNA fragment that can direct preferential activation of transcription in developing neurons, suppression of transcription in matureCNS neurons, and re-expression after CNS lesions that restore competence for regeneration. Much of this growth-associated regulation is mediated by a 386 bp DNA sequence containing a functional promoter. Gel-shift and mutational analysis shows that a small region of DNA downstream of this promoter contains multiple protein binding sites that cooperate to regulate transcription over a 10-fold range in post-mitotic neurons. The results indicate that signaling pathways converging on these DNA response elements may mediate critical aspects of growth-associated gene regulation in CNS neurons.

4.02 ANATOMICAL AND MOLECULAR PHENOMENA ASSOCIATED WITH THE INJURY AND REGROWTH OF RETINAL GANGLION CELLS IN ADULT RATS

A. Aguayo', D.Clarke, H.Friedmann, S.Mansour-Robaev, P. Kitlerova, H.Sawai, G.M.Bray Centre for Research in Neuroscience, McGill University, The Montreal General Hospital Research Institute, 1650 Cedar Avenue, Montréal, CANADA

Beginning 5 days after optic nerve (ON) transection the axotomized retinal ganglion cells (RGCs) undergo apoptosis at such a rapid rate that only 10% of normal survive by 2 weeks. We also observed that: 1) Most intact RGCs expressed the trkB neurotrophin (NT) receptor but a large proportion of these neurons co-expressed trkC. Truncated forms of trkB, lacking an internal tyrosine kinase domain predominated in ON glia. 2) A single intravitreal injection of BDNF or NT4 (5 µg in 5 µl BSA/PBS) at the time of axotomy spared all RGCs at one week and significantly increased the number of RGCs that survived at 2 weeks; similar effects were obtained with single injections given 4-6 days before to 5 days after axotomy. 3) A prolonged administration of these NTs extended the survival of some but not all of the RGCs. 4) The effects of repeated injections of NTs on RGC survival declined with time, 5) A powerful intra-ocular source of trophic support was detected after ON cut and denervation of the iris, a structure where mRNAs for all NTs and for CNTF were detected. Findings in the iris resembled patterns of NT expression observed after peripheral nerve (PN) injury but contrasted sharply with the very low levels of NTs detected in ON stumps, 6) Truncated trkBs droped immediately after cut but were upregulated after a week, coincidental with maximal RGC death. 7) A profuse but aberrant growth of RGC axons was observed near the optic disc of the treated animals.

NT-3 had only a small effect on RGC survival but stimulated axonal growth and caused a marked rise in GAP-43 expression 2 weeks after injection. Changes in GAP-43 levels after NT administration were not detected in uninjured RGCs, suggesting that axotomy-induced events are a pre-requisite for such a NT effect.

4.03 FACTORS AFFECTING AXONAL REGENERATION IN THE RAT SPINAL CORD.

Lisa Schnell*, Regula Schneider and Martin E. Schwab, Brain Research Institute, University of Zürich, August-Forel-Str.1, 8029 Zürich, Switzerland

After spinal cord hemisection in the rat lesioned corticospinal tract (CST) fibers show moderate sprouting around the lesion site but no long distance elongation distal to the lesion. The sprouting response was greatly enhanced by implants of embryonic (E 14-16) spinal cord tissue, whereas no growth of CST fibers into the transplants nor beyond the lesion site could be observed.

Local injections of NT-3 at the time of the lesion induced a similar increase in sprouting as the transplants. Injections of BDNF or NGF showed no or only a moderate effect. Again, in all these cases, elongation of the fibers was restricted to 0.5 - 1.0 mm beyond the lesion site. Only in the presence of the monoclonal AB IN-1 elongation of lesioned fibers over distances up to 22 mm within the intact spinal cord could be observed. This mAB IN-1 neutralizes the inhibitory properties of myelin associated proteins (NI-35/250). In animals with CST long distance regeneration a significant improvement of locomotor function like stride length and placing response reflexes could be demonstrated.

These results suggest a differential regulation for sprouting and elongation of lesioned CST fibers. Support from neurotrophic factors alone results in improved local sprouting but does not lead to long distance regeneration. We currently investigate the combined effect of neurotrophin and IN-1 application on the improvement of locomotor function.

4.04 Glia and Axonal Regeneration in the CNS of Fish, Frog and Lizards

C.A.O. Stuermer*, D. Lang, M. Bastmeyer, M. Wanner, M. Monzon-Mayor (1), M.E. Schwab (2). Univ. Konstanz (D), (1)Univ. Gran Canaria (S), (2) and Univ. Zürich (CH)

Success and failure of axonal regeneration are strongly influenced by the glia cell environment. We have compared the substrate properties of CNS myelin and oligodendrocytes of goldfish, Xenopus, and lizards, with those of rats, by monitoring axonal growth behavior in contact with these substrates and by examining axonal regeneration in vivo. Axons grew well on fish and on Xenopus optic nerve/tectum (ONT) myelin, and crossed oligodendrocytes. Axons failed to extend on oligodendrocytes and myelin of Xenopus spinal cord (SC) and lizard CNS. This and the presence of a glial scar correlates with the failure of axonal regeneration in the Xenopus SC in vivo. The growth permissive properties of fish and Xenopus ONT myelin and oligodendrocytes and the permissivity of scar forming cells correlate with successful regeneration in these systems. In lizards, however, a proportion of retinal axons grew across the lesion despite the presence of nonpermissive myelin and glial scars in the optic nerve. This regrowth seems to require several months.

Supported by Hertie-Stiftung, DFG (Stu 112/10), Boehringer-Ingelheim Fonds (D.L.), Swiss Nat. Science Found. (M.E.).

5.01 MOLECULAR GENETICS OF SPINAL MUSCULAR ATROPHY

S. Lefebvre, L. Bürglen, L. Viollet , P. Burlet, O. Clermont, A. Munnich and J. Melki* Unité de Recherches sur les Handicaps Génétiques de l'Enfant, INSERM U. 393, Hôpital des Enfants-Malades, 75743 Paris, France

Spinal muscular atrophy (SMA) is a common fatal autosomal recessive disorder characterized by degeneration of lower motor neurons, leading to progressive symmetrical limb and trunk paralysis associated with muscular atrophy.The childhood SMA are divided into acute (Werdnig-Hoffmann disease, type I), intermediate (type II) and juvenile forms (Kugelberg-Welander disease, type III) on the bases of age of onset and milestones of development. The gene for SMA has been mapped to chromosome 5q13.3 in a highly unstable region characterized by the presence of low copy repeats. Inherited and *de novo* deletions of the 5q13 region were observed in patientsand led to the identification of a duplicated gene, whose telomeric version, the survival motor neurone gene (SMN), is a SMA determining gene. The SMN has been found to encode a novel protein of 294 amino acids. These data form a base from which to explore the genotype-phenotype correlation, the biochemistry and cell biology of this disorder. These approaches should contribute to the understanding of the pathogenesis of SMA.

5.02 GENES IMPLICATED IN ALZHEIMER'S DISEASE

C. Van Broeckhoven. Laboratory of Neurogenetics. Born-Bunge Foundation, University of Antwerp (UIA), Department of Biochemistry, Universiteitsplein 1, B-2610 Antwerpen, Belgium.

Molecular genetic studies have identified 3 genetic loci for Alzheimer's disease (AD) i.e. the chromosome 21 (AD1) and chromosome 14 (AD3) loci for early-onset AD (EOAD, onset age < 60 years) and the chromosome 19 (AD2) locus for late-onset AD (LOAD, onset age > 60 years). The amyloid precursor protein (APP) gene at 21q21.2 was identified as the first AD1 gene based on the observation of 6 dominant base mutations. The mutations are located in or close to the βA4-amyloid fraction of APP, the major constituent of senile plaques in AD brains. Further, cDNA transfection studies have shown that APP mutations produce either more or longer βA4-amyloid and thus may be causative for AD pathology. However, APP mutations are with an estimated frequency of 5%, minor contributors to the EOAD etiology. The chromosome 14 locus AD3, on the other hand is responsible for approximately 70% of the familial EOAD cases. The actual AD3 gene defect is not yet known, but resides in a region of 3 Mb at 14q24.3. Two candidate genes located in this region were excluded as AD3 genes i.e. the cellular oncogene FOS and the dihydrolipoyl succinyltransferase (DLST) gene, based on sequencing data. A predisposing gene, AD2, was first identified for LOAD i.e. the apolipoprotein E (APOE) gene at 19q13.2. The APOE4 allele confers a significantly higher risk to LOAD in a dosage dependent manner with the risk being highest and onset age earliest in APOE4 homozygotes. The E2 allele (APOE2) on the other hand, seems to protect individuals from developing AD in late life. Also, in EOAD an elevated risk is associated with the APOE4 allele. However, the data obtained for the APOE2 allele is controversial suggesting a protective effect in some and an elevated risk in other populations. Additional studies are needed to determine the exact role of APOE in AD pathophysiology.

5.03 HUNTINGTON AND OTHER NEUROLOGICAL DISEASES DUE TO EXPANSION OF GLUTAMINE CODING CAG REPEATS.

J.L. Mandel*, D. Devys, G. Imbert, F. Saudou, Y. Trottier - IGBMC, BP 163, 67404 ILLKIRCH-STRASBOURG FRANCE

Huntington's disease (HD) is a dominant neurodegenerative disorder characterised by neuronal death in the striatum. It is caused by an expansion of a polyglutamine coding CAG repeat in a gene of unknown function. Normal alleles carry 6-34 CAGs, while HD alleles have 37 to 120 CAGs. This gene has a very wide pattern of expression that does not correlate with the localised neuropathology. A very similar mecanism has been found in four other neurological diseases: spinobulbar muscular atrophy (SBMA), spinocerebellar ataxia type 1 (SCA1) and type 3 (SCA3, or Machado-Joseph disease), and dentatorubro-pallidoluysian atrophy. They are all characterised by adult-onset neuronal death in selected but different regions of the nervous system, by an inverse correlation between length of CAG expansion and age of onset, and by a similar pattern of anticipation in succeeding generations (upon paternal transmission). However the proteins implicated in these five diseases show no common features apart from the polyglutamine tract. The function of only one of them is known, the androgen receptor implicated in SBMA (and several other transcription factors also carry polyglutamine tracts). The mecanism by which the expanded polyglutamine causes neuronal death is mysterious, but is clearly not a loss of function.

To study the HD gene product (huntingtin), we have developed monoclonal antibodies that detect huntingtin as a 350 kDa protein. In cells from HD patients, a doublet is detected corresponding to the mutated and normal protein. Huntingtin is present in the perikarya of many neurons, in neuropiles, and may be present in nerve endings. It is not detected in the cell nucleus, and is thus unlikely to be a transcription factor. Neural cell lines and transgenic mice that carry a mutated HD cDNA (73 CAGs, corresponding to a juvenile onset case) have been obtained and may provide cellular or animal models for HD.

5.04 FMR1 KNOCKOUT MICE: A MODEL TO STUDY FRAGILE X MENTAL RETARDATION

Ben A. Oostra[1], Cathy E. Bakker[1], Edwin Reyniers[2], Rob Willemsen[1], Rudy D'Hooghe[2], P.P.De Deyn[2], Coleta Verheij[1], Patrick Cras[2], and Patrick J. Willems[2].
[1] Dept Clin Genet, Erasmus, Rotterdam. [2] Dept Med Genet, Univ Antwerp, Belgium.

The fragile X syndrome is the most frequent form of inherited mental retardation in humans with an incidence of 1 in 1250 males and 1 in 2500 females. The clinical syndrome includes moderate to severe mental retardation, autistic behavior, macroorchidism, and facial features, such as long face with mandibular prognathism and large, everted ears. The molecular basis for this disease is a large expansion of a triplet repeat $(CGG)_n$ in the 5' untranslated region of the FMR1 gene. Due to this large expansion of the CGG repeat, the promoter region becomes methylated and the FMR1 gene is silenced.

About the physiologic function of FMR1 and the pathologic mechanisms leading to these symptoms hardly anything is known. Since the FMR1 gene is highly conserved in the mouse, we used the mouse to design a knockout model for the fragile X syndrome. These knockout mice lacking Fmrp have a normal littersize suggesting that FMR1 is not essential in human gametogenesis and embryonic development. The knockout mice show the abnormalities also seen in the functionally and anatomically affected organs of human patients. Mutant mice show a gradual development through time of macroorchidism. In the knockout mice we observed cognitive defects in the form of deficits in learning (as shown by the hidden platform Morris water maize task) and behavior, as shown in the exploratory behavior test and the motor activity test. Therefore this knockout mouse may serve as a valuable tool in studying the (patho)-physiological role of FMR1 in the fragile X syndrome, and may serve as a model to elucidate the mechanisms involved in macroorchidism, abnormal behavior, and mental retardation.

6. Symposium: Presynaptic release mechanisms

6.01 CALCIUM AND NEUROTRANSMITTER RELEASE.

G. Matthews* Department of Neurobiology & Behavior, State University of New York, Stony Brook, NY, 11794-5230, USA

Retinal bipolar neurons are non-spiking interneurons that release glutamate from ribbon-type synapses. Goldfish retina contains bipolar neurons with giant synaptic terminals (10-12 μm diameter) that are well-suited for patch-clamp analysis of presynaptic mechanisms. We have used capacitance measurements in these giant terminals to study the regulation of exocytosis and endocytosis. Activation of presynaptic calcium current induces a rapid increase in capacitance, corresponding to an initial fusion rate exceeding 10,000 per sec. The total size of this rapid-release pool is about 2000 vesicles. Exogenous calcium buffer inhibited the capacitance response, but a high concentration (5 mM) of a fast buffer (BAPTA) was necessary, suggesting that the calcium sensor for vesicle fusion is located within microdomains of high Ca near calcium channels. Both dialysis of buffered [Ca] via the whole-terminal patch pipette and flash photolysis of caged calcium also indicate that $[Ca]_i$ must exceed 10-20 μM to trigger an increase in capacitance in bipolar-cell synaptic terminals. Endocytosis is also regulated by calcium. Under normal conditions, capacitance after a brief depolarization returns to baseline with an exponential time constant of 1 to 2 sec. When resting [Ca] is elevated, recovery slows dramatically (half-inhibition at 500 nM) and stops altogether when internal calcium is > 1000 nM. The inhibition of recovery by elevated $[Ca]_i$ provides negative feedback of release by stopping the initial stage in vesicle recycling.

6.02 MECHANISM OF ACTION OF CLOSTRIDIAL NEUROTOXINS

H. Niemann, T. Hayashi, S. Yamasaki, and T. Binz. Department of Microbiology, BFAV, Paul-Ehrlich-Str.28, D72076 Tübingen, FRG.

The light chains of tetanus and of the seven botulinal toxins are zinc-dependent proteases that selectively cleave the synaptic proteins synaptobrevin, SNAP-25 or syntaxin. The three substrates form the core of an SDS-insoluble ternary fusion complex that exists in multiple isoform subsets in neuronal and nonneuronal cells mediating fusion of carrier vesicles with target membranes. We have studied the effects of proteolysis on the assembly and disassembly of the ternary fusion complex using exclusively recombinant polypeptides representing the cytoplasmically exposed domains of the three synaptic proteins. The L chains recognize and cleave α-helical domains with high coiled-coil forming propensity. Cleavage requires monomeric substrates and results either in the release of the interactive domain from the membrane or in products that are incapable of forming the SDS-resistant form of complexes. We further analyzed the structural requirements for binding of α-, ß-, γ-SNAP, and dissociation of the resulting complex with NSF. The role of individual domains of three proteins in binding of γ-SNAP is discussed. We show that the N-terminal domain of syntaxin, although dispensable for complex formation, plays a key role in the dissociation reaction.

DTIC QUALITY INSPECTED 3

6.03 Abstract not received

6.04 PROTEIN INTERACTIONS IMPORTANT FOR SYNAPTIC VESICLE EXOCYTOSIS V.O'Connor*, T. Dresbach, L. Pellegrini, W. De Bello, F. Schweizer G.Augustine and H.Betz, Max-Planck-Institut für Hirnforschung, 60528 FRG. Dept. of Neurobiology, Duke University, Durham, North Carolina 27710, USA.

Neurotransmitter release occurs via Ca^{2+} triggered fusion of synaptic vesicles (SV) with the presynaptic plasmamembrane (PM). The readily releasable pool of these vesicles are those that appear stably docked at the presynaptic active zone. *In vitro* studies indicate that an evolutionarily conserved protein network used for constitutive vesicle based intracellular protein transport also functions in sv fusion. In particular the ubiquitous ATPase N-ethylmaleimide sensitive fusion protein (NSF) and the soluble NSF attachment proteins (SNAPs) have been implicated in release because they can associate with a core complex containing the sv protein synaptobrevin and the PM proteins syntaxin and synaptosomal associated protein of 25 kDa (SNAP-25). When ATP hydrolysis is prevented the core complex forms a stable association with SNAP and NSF whereas hydrolysis of ATP by the associated NSF leads to complex disassembly. This disassembly may represent a biochemical correlate of fusion. We have characterized the squid homologues of the fusion complex and developed specific reagents to analyse its in vivo function. Several reagents; peptides, bacterially expressed proteins and neurotoxins, that interact with distinct components of the fusion complex, perturb neurotransmitter release when introduced into the presynaptic terminal of the squid giant synapse. Additional ultrastructural analysis of the perturbed terminals reveals that the fusion complex exerts an essential function on the post docking intermediates of sv fusion. Although our analysis also indicates a post docking role for the putative sv Ca^{2+} sensor synaptotagmin, we favour the idea that the function of this protein proceeds that of the fusion complex (O'Connor et al. Cell,76,785).

7. Symposium: Real time measures of human cognitive function

7.01 INVESTIGATING LANGUAGE COMPREHENSION WITH EVENT-RELATED POTENTIALS. P. Hagoort* and C. Brown. Max-Planck-Institut für Psycholinguistik, P.O. Box 310, NL-6500 AH Nijmegen, Nederland.

Language comprehension is a complex skill that can be fractionated into different subprocesses. One of these subprocesses is the assignment of a syntactic structure to the incoming string of words. As a result the listener or reader has determined which word(s) form the grammatical subject of a sentence, which the grammatical object, etc. Experimental results will be discussed which suggest that, in the context of language comprehension, a particular ERP-response is especially sensitive to syntactic processes. This Syntactic Positive Shift (SPS) is clearly different from the well-known N400-component, which is usually associated with the meaning of words and sentences. The SPS has been observed to syntactic violations, such as an agreement mismatch between the subject and the verb of a sentence (e.g., "The man smoke a cigar"). But it is also observed in so-called syntactically ambiguous sentences. Very often part of a sentence can be assigned more than one syntactic structure. For instance, in the utterance "The pope greets the priest and the monk...",the noun 'monk' can go together with 'priest' to form the object of the sentence (e.g., "The pope greets the priest and the monk at the annual meeting"). Alternatively it can start a new clause (e.g., "The pope greets the priest and the monk welcomes the cardinal"). Experimentally obtained SPS-effects in such syntactically ambiguous sentences will be discussed in terms of their significance for understanding language comprehension. In addition, results will be discussed of aphasic patients with a specific problem in assigning a syntactic structure to a sentence. These patients show an abnormal pattern of SPS-effects.

7.02 ELECTRICAL AND MAGNETIC STUDIES OF THE HUMAN MOTOR SYSTEM

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Topographic analysis and biophysical modeling of brain potentials and magnetic fields indicate focal activaties in the primary (MI) and supplementary motor (SMA) areas which precede and accompany the execution of voluntary movements. Contributions towards the understanding of the physiology of voluntary movements were made by modeling timing patterns and task-specific effects on MI- and SMA-activity. Unilateral movements are associated with bilateral activation of MI and SMA. Ipsilateral and contralateral MI-activity is excitatory and somatotopically organized. Bilateral MI-activity is present with mental simulation of the movement. MEG is not sensitive to magnetic fields of radial currents but is of particular value for modeling current flow in MI which mainly has a tangential orientation. By use of multi-channel, helmet-shaped MEG systems the duration of the studies on movement-related MI-activity has greatly been reduced. Results of EEG- and MEG studies will be reviewed and synoptically compared to results obtained by corticography.

Disorders of basal ganglia or cerebellum have effects on movement-related brain potentials: There is evidence for reduced disinhibition of thalamo-cortical input to the SMA in Parkinson's disease and for reduced movement-related cortical activity following cerebellar lesions.

7.03 SEQUENTIAL ACTIVATION OF HUMAN BRAIN STUDIED WITH MAGNETOENCEPHALOGRAPHY (MEG). M. Sams, Department of Psychology, University of Tampere, P.O. Box 607, 33101 Tampere, Finland

Compared with other modern human brain imaging techniques, MEG is characterized by good both spatial and temporal resolution. This makes it a useful means in studying brain mechanisms of neuromental functions varying rapidly in time and space.

We recently studied the brain activity when auditory and visual information are integrated in speech perception (Sams et al., Neurosci. Lett., 1991, 127, 141-145). Interestingly, when an auditory /pa/ syllable is dubbed to the videotaped face articulating /ka/, the auditory perception is modified and the subjects typically report hearing /ka/ or /ta/ (McGurk and MacDonald, Nature, 1976, 746-748). This persistent illusionary perception is strongly auditory in nature. When we presented infrequent deviant discordant pairings (auditory /pa/ together with visual /ka/) among frequent concordant stimuli (auditory and visual /pa/), the deviants elicited a specific MEG response, which was argued to be generated in the auditory cortex. Our conclusion was that visual information is able to modify the responsiveness of the auditory cortex. The experiments were made with a 24-channel neuromagnetometer, covering an area only of 12.5 cm in diameter above the auditory cortex.

We utilized rather similar stimuli and a 122-channel whole-head magnetometer in our new study. The larger coverage of the instrument allows more reliable and accurate localization of brain activity. The subjects were experienced lip readers. Now the concordant and discordant stimuli were also delivered equiprobably. The measured MEG signals were complex and showed a lot of individual variability. However, some subjects showed a distinct response to discordant stimuli in both conditions. The preliminary analysis suggests that the auditory cortex posterior to the source area for the 100-ms response (M100) is activated by the discordant stimuli, giving rise to the illusionary perception. The long latency of the response (onset clearly after M100) indicates that audiovisual integration of speech occurs at a rather late stage. This integration is reflected in the activity at or close to the auditory cortex.

7.04 EVENT-RELATED POTENTIAL STUDIES OF HUMAN MEMORY, Michael D. Rugg*, Wellcome Brain Research Group, School of Psychology, University of St Andrews, Scotland

Event-related brain potentials (ERPs) are an attractive means of studying human brain activity evoked during memory tasks because of their non-invasive recording methodology and their good time resolution. Furthermore, as the intracerebral generators of memory-related ERP effects become known, ERPs may offer a means of studying the time course and interaction of specific neural systems implicated in memory. This presentation will focus on recent ERP studies of recognition memory.

In a number of studies, ERPs evoked by correctly recognised items have been formed separately according to whether or not recognition was accompanied by the retrieval of the prior episode involving the item ('recollection'). This segregation was achieved by modifying the test phase of recognition memory tasks so that subjects first make a standard 'old/new' judgement, and then, for items judged old, a second judgement requiring knowledge about the context in which the item was experienced. Compared to items correctly judged new, ERPs to old items show several characteristic differences. These differences are larger, and in some cases are only present, in waveforms evoked by items for which information about the learning context can be recovered. The results of these studies offer strong support to 'dual-process' theories of recognition memory, and give insights into the time-course and possible neural underpinnings of retrieval from episodic memory.

8.01 THE LAMBERT-EATON MYASTHENIC SYNDROME: AN ANTIBODY MEDIATED DISORDER OF NEUROTRANSMITTER RELEASE

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The Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission characterised by a reduction in the nerve-stimulated quantal release of acetylcholine from the presynaptic motor nerve terminal. It is often found in association with a small cell carcinoma of the lung (SCLC). The disease is caused by IgG autoantibodies directed against the voltage-gated calcium channels (VGCCs) that control calcium ion entry following nerve-stimulated depolarisation.

We have developed a SCLC cell line derived from a patient with LEMS. This cell line showed a K^+-stimulated $^{45}Ca^{2+}$ influx, which was inhibited up to 80% by incubation in IgG purified from LEMS patients. The flux was inhibited similarly by the P/Q type VGCC neurotoxin antagonists, ω-AgaTx IVA and ω-CmTx MVIIC, but not by the N-type antagonist ω-CgTx GVIA.

We have recently developed an improved diagnostic assay for LEMS using ^{125}I-ω-CmTx MVIIC bound to VGCCs extracted from human cerebellum. Greater than 85% of clinically-definite LEMS patients were positive for the presence of anti-VGCC antibodies, defined as a titre >3SD above the mean of the healthy controls. All disease controls were negative.

We conclude that IgG autoantibodies to P/Q type VGCCs are likely to be the principle cause of the impaired transmitter release at the motor nerve terminals that characterises this syndrome.

8.02 Abstract not received

8.03 GLYCINE RECEPTOR SUBUNIT HETEROGENEITY: IMPLICATIONS FOR INHERITED MOTOR DISORDERS.

Cord-Michael Becker[1,2*], Cornel Mülhardt[1], Brigitta Saul[1], Wolfram Brune[2], Claudia Kling[1], Hans-Michael Meinck[2]. [1]Biochemisches Institut, Universität Erlangen-Nürnberg, Fahrstrasse 17, D-91054 Erlangen, [2]Neurologische Klinik, Universität Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany.

The strychnine-sensitive glycine receptor is a ligand-gated anion channel contributing to motor regulation by spinal cord and brain stem centers. Its adult isoform, $GlyR_A$, is an oligomeric protein composed of ligand-binding α1 and structural β subunits.

In mice and humans, hereditary motor disorders have been identified which, to varying degrees, mimick strychnine intoxication. The *spasmodic (spd)* mouse carries a recessive missense mutation of the α1 subunit gene (*Glra1*, Chr 11) diminishing the agonist affinity of the mutant receptor. In the *oscillator* mouse (*spa^{ot}*), a microdeletion within *Glra1* causes the complete loss of $GlyR_A$ being lethal at the age of 3 weeks. In the *spastic* mutant, the intronic insertion of a LINE-1 transposable element into the *Glyrb* gene (Chr 3) results in the aberrant splicing of β subunit transcripts and a consecutive reduction in $GlyR_A$ number. Hyperekplexia, a human disorder similar to the murine phenotypes, results from point mutations and an extended deletion within the *GLRA1* gene (Chr 5). The deletion produces a null mutation which, in contrast to the *oscillator* mouse, is tolerated in the affected child.

8.04 STRUCTURE AND FUNCTION OF CLC CHLORIDE CHANNELS: LESSONS FROM HUMAN INHERITABLE DISEASE

T. J. Jentsch*, K. Steinmeyer, C. Lorenz, M. Pusch.
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CLC voltage-gated chloride channels form a large gene superfamily with at least nine different members in mammals. At present, we know of two inherited human diseases associated with ClC channels: Myotonia (both the autosomal recessive Becker type as well as the dominant Thomsen type) with ClC-1, and a certain kidney disease (Dent's disease) with ClC-5.

ClC-1 is important for electrical muscle membrane stability. Its defect leads to repetitive action potentials resulting in myotonia (muscle stiffness). ClC-1 mutations cause myotonia both in the ADR mouse, as well as in humans. Recessive inheritance is due to loss-of-function mutations. Dominant mutations can be explained by dominant negative effects in a (homo)multimeric channel complex. Analysis of two human mutations predicts that a functional channel is probably a tetramer. Another dominant mutation leads to a large shift in the voltage-dependence of gating. Association of this subunit with the normal one alters the voltage-dependence of the multimeric channel. Thus, analysis of human mutations leads to important insights into the structure-function relationship of this channel class.

9. Symposium: "Suprachiasmatic nucleus", the mammalian biological clock

9.01 ORGANIZATION OF THE MAMMALIAN BIOLOGICAL CLOCK

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The mammalian circadian timing system consists of entrainment pathways, pacemakers and pacemaker projections to effector systems that exhibit circadian function. Photic entrainment is mediated by specific retinal components, photoreceptors and ganglion cells, that convey luminance information through a retinohypothalamic tract to the circadian pacemakers, the suprachiasmatic nuclei (SCN) of the hypothalamus and to the thalamic component of the system, the intergeniculate leaflet (IGL) of the lateral geniculate complex. The SCN is comprised of small, GABA-producing neurons. Retinal afferents to the SCN terminate in the ventrolateral portion of the nucleus, a subdivision in which GABA is co-localized with VIP or GRP in separate neuronal populations. This SCN subdivision also receives a dense serotonergic input from the midbrain raphe nuclei and a GABA-NPY projection from the IGL. The latter projection, the geniculohypothalamic tract, appears to integrate photic and non-photic input to modulate pacemaker function. The dorsomedial SCN contains neurons that co-localize GABA with AII or VP. Neurons in both SCN subdivisions produce dense intrinsic connections within the nucleus and project outside of it, predominantly to the anterior hypothalamus-subparaventricular zone, the paraventricular hypothalamic and thalamic nuclei, the retrochiasmatic area and the IGL. These regions, in turn, provide widespread projections to the cortex, basal forebrain, thalamus, hypothalamus and brainstem to provide a temporal regulation of the many functions under circadian control.

9.02 LIGHT RESPONSES OF THE SUPRACHIASMATIC NUCLEUS

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The suprachiasmatic nucleus is a dominant pacemaker in many species of mammals. The pacemaker is entrained to the environmental light-dark cycle via photoreceptors in the eyes. From retinal ganglion cells, two pathways project to the SCN, the retinohypothalamic tract and the geniculohypothalamic tract. Inside the SCN a subpopulation of cells is light-responsive. Multiple-unit recordings were performed in the SCN of freely-moving rats and the characteristics of the SCN's response to light was determined.

9.03 NON-PHOTIC RESPONSES OF THE CIRCADIAN CLOCK OF THE SUPRACHIASMATIC NUCLEI

M. Hastings. University of Cambridge, Dept. of Anatomy, Downing St. Cambridge CB2 3DY, U.K.

If the circadian oscillator of the suprachiasmatic nuclei is to function as a biological clock, it needs to be synchronised to external time. Under experimental conditions, light/ dark cues can be shown to be sufficient to effect entrainment in both nocturnal rodents and in Man. However, the temporal structure of our lives is more complex than a simple alternation between light and darkness, and recent studies have revealed the potent entraining effect of non-photic cues on the circadian system. This presentation will focus on the role of two non-photic cues which are able to reset the clock: arousal and melatonin. A variety of cues which arouse the individual can have a potent phase advancing effect, and a body of evidence now implicates serotonergic pathways as a mediator of this response. The pineal hormone melatonin can also be shown, when delivered in pharmacological doses, to advance the clock. This effect varies between species and developmental stage. The basis to this variation may reside in the pattern of distribution of melatonin receptors in various sub-divisions of the SCN, and in the signal transduction pathways to which they are linked.

9.04 CIRCADIAN RHYTHMS OF SPONTANEOUS NEURONAL FIRING WITHIN THE SUPRACHIASMATIC NUCLEUS

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The mammalian circadian pacemakers are situated in the suprachiasmatic nucleus (SCN). Extracellular neuronal discharges of individual SCN neurons monitored continuously throughout several circadian cycles in culture showed high and low firing rate levels with a periodicity of approximately 24 h. Sampling of the firing frequency of a large number of individual SCN neurons in acute slices showed high activity levels during the subjective day and low levels during the subjective night in vitro. In both preparations the SCN neurons were found to fire regularly and irregularly, while some remained silent; the latter group repeatedly responded to microiontophoretic application of glutamate. Glutamate pulses increased the activity of all SCN neurons, while GABA inhibited both the spontaneous and the evoked activity of the SCN. Although it has been well established that the isolated SCN can generate a circadian rhythm in the absence of external zeitgebers, the mechanisms underlying circadian rhythm generation within the SCN are not yet known.

Bos, N.P.A. and Mirmiran, M. Brain Res. 511 (1990) 158-162.
Bos, N.P.A. and Mirmiran, M. Brain Res. Bul. 31 (1993) 67-72.

10. Symposium: Hippocampal and neocortical microcircuits

10.01 NEOCORTICAL MICROCIRCUITS. Alex M. Thomson*, David C. West & Jim Deuchars. Dept. Physiology, Royal Free Hospital School of Medicine, London NW3 2PF.

Dual intracellular recordings from pairs of synaptically connected neurones and dye-filling in slices of adult rat neocortex are used to study local circuit synaptic interactions. To date, three broad classes of electrophysiologically and morphologically identifiable neurones and the connections between them have been studied: pyramids, fast spiking aspiny- and burst firing spiny- inhibitory interneurones. Excitatory connections from pyramid to pyramid display properties that are consistent between pairs of pyramids, but which differ profoundly from pyramid-interneurone connections. Pyramid-pyramid EPSPs are typically partially NMDA receptor mediated and display apparently presynaptically mediated paired pulse and frequency dependent depression. Pyramid-interneurone connections in contrast are typified by strong paired pulse and frequency dependent facilitation, apparently mediated presynaptically and appear to utilize predominantly non-NMDA receptors. To date, all the connections recorded in which one of these two broad classes of interneurone is presynaptic to a simultaneously recorded pyramid have resulted in IPSPs with a relatively rapid time course and a reversal potential close to rest. Preliminary evidence indicates that slow IPSPs in pyramidal neurones may result from repetitive activation of a separate group of interneurones.

10.02 RECURRENT SYNAPTIC CIRCUITS IN THE CA3 REGION OF THE HIPPOCAMPUS R. Miles+, T.F. Freund, A.I. Gulyás, K. Tóth and N. Hajós
+INSERM U261, Institut Pasteur, Paris, France and Inst. Exptl. Med., Academy of Sciences, Budapest, Hungary.

We have combined electrophysiological and morphological techniques to study the number and location of synapses involved in recurrent excitatory and inhibitory synaptic interactions in the CA3 region of guinea-pig hippocampus.

The number of synapses determines the style of synaptic function. Our data suggest that feedback excitation of CA3 inhibitory cells is often mediated by transmitter release from a single site. In material stained to reveal the axon of a single biocytin-filled pyramidal cell and the subset of parvalbumin containing inhibitory cells, most connections involved a single release site. In reconstructions of 4 pairs of synaptically connected pyramidal cells and inhibitory cells filled with biocytin, a single bouton was located with light microscopy and verified by EM. Finally amplitude distributions of spontaneous EPSCs and of miniature EPSCs in whole cell records from inhibitory cells, were often similar as expected if action potential dependent release involves a single site.

The location of synaptic terminals also affects the nature of a synaptic interaction. Different CA3 inhibitory cells innervate precise zones of pyramidal cell membrane. We have examined differences in post-synaptic actions of inhibitory cells which target either peri-somatic or dendritic regions. Amplitudes of IPSPs initiated by peri-somatic and dendritic inhibitory cells, were similar but dendritic IPSPs had slower kinetics. Dendritic and somatic inhibition exerted a differential control on post-synaptic activity. Somatic IPSPs, either unitary or focally induced, most efficiently suppressed repetitive firing of Na spikes when timed to co-incide with a pyramidal cell DAP. In contrast focally induced dendritic IPSPs were most effective in preventing discharge of broad presumed Ca-dependent dendritic spikes.

10.03 INHIBITORY MICROCIRCUITS AND THEIR STRUCTURAL CORRELATE

E.H. Buhl, MRC Anatomical Neuropharmacology Unit, Oxford University, Mansfield Rd., Oxford OX1 3TH, UK

Hippocampal and neocortical GABAergic interneurones are distinct due to the specificity of their synaptic output. They subdivide the surface of their postsynaptic targets into well-defined domains, often in precise conjunction with major excitatory afferent pathways. In *in vitro* slice preparations these local-circuit neurones have distinct membrane, firing and synaptic properties in which they differ from principal cells and, to some extent, from each other. Moreover, certain categories of interneurones may be activated in a feedforward manner, whereas others receive feedforward as well as recurrent synaptic input. With respect to their inhibitory input, recordings from synaptically connected pairs of interneurones show that they may be reciprocally connected and/or receive inputs from dissimilar types of interneurones.

Dual recording experiments reveal that several types of hippocampal and neocortical interneurones elicit short-latency fast IPSPs which are blocked by $GABA_A$ receptor antagonists. Hippocampal axo-axonic, basket, bistratified and neocortical basket and double-bouquet cells were found to mediate such fast IPSPs, thus corroborating the anatomically determined ubiquity of $GABA_A$ receptors. As a rule, GABAergic unitary IPSPs are mediated by >1 release sites, with electron microscopic counts of *all* identified synaptic contacts ranging from 2 to 15, therefore providing a safeguarding mechanism to minimise total failures of transmission.

Double recording experiments may be also used to assess the functional role of GABAergic interneurones. Both basket and axo-axonic unitary IPSPs can interact with intrinsic subthreshold membrane oscillations of concomitantly recorded hippocampal pyramidal neurones. By effectively entraining such membrane oscillations, unitary IPSPs can effect the suprathreshold properties of pyramidal cells. Using a theta-burst stimulation paradigm to activate single identified basket and axo-axonic cells, these can be shown to reliably phase-lock the firing of a postsynaptic pyramidal cell. Therefore, by virtue of their divergence, basket and axo-axonic cells may act as GABAergic devices to synchronise population activity.

10.04 SYNAPTIC PLASTICITY BETWEEN CELL PAIRS IN HIPPOCAMPAL SLICE CULTURES

S. M. Thompson*, D. Debanne, N. C. Guérineau, and R. A. McKinney
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The induction of various forms of short- and long-term synaptic plasticity at unitary synapses formed between pairs of intracellularly recorded hippocampal pyramidal cells in organotypic slice cultures will be described. Action potentials in a single presynaptic cell elicit responses in postsynaptic cells that were multiquantal, probably due to the formation of multiple sites of contact, and had amplitudes and waveforms comparable to those seen in acute hippocampal slices. When pairs of action potentials were elicited at short latency under control conditions, the paired-pulse ratio of unitary EPSCs was inversely related to the randomly varying quantal content of the first EPSC. Facilitation was observed when the quantal content was low, and depression when quantal content was high. Changing quantal content with various manipulations produced corresponding changes in the likelihood of facilitation and depression. Paired-pulse facilitation is ascribed to residual presynaptic Ca^{2+}, and lasts for roughly 500ms. Paired-pulse depression is ascribed to a depletion of readily releasable vesicles in the presynaptic axon, and this pool is refilled in 5s. Long-term potentiation (LTP) could be elicited by pairing single presynaptic action potentials with depolarization of the postsynaptic cell, but not by triggering bursts of high frequency presynaptic action potentials, suggesting that cooperative interactions are required for LTP induction at the synapses formed by a single cell. Long-term depression could be induced at previously potentiated synapses, in contrast, either by a train of low frequency presynaptic action potentials or by asynchronously pairing single presynaptic action potentials with depolarization of the postsynaptic cell. These results suggest that unitary synapses may undergo both potentiation and depression, and that the processes are mutually reversible.

10.05 SPECIALIZED INTERNEURONS IN CONTROL OF OTHER HIPPOCAMPAL INTERNEURONS.

A.I.Gulyas, L. Acsady, N.Hajos and T.F.Freund; Institute of Experimental Medicine, Hungarian Academy of Sciences, P.O.Box 67, Budapest, H-1450 Hungary

Functionally distinct subpopulations of hippocampal GABAergic interneurons can be identified on the basis of their neurochemical marker content. Light and electron microscopic analysis of calretinin (CR) and vasoactive intestinal polypeptide (VIP) containing neurons revealed a novel type of target selectivity. The postsynaptic targets of these cells were shown to be solely other GABAergic neurons. CR-immunoreactive cells can be found in all areas and layers of the hippocampus. Their dendrites and axons run primarily radially, cross several layers and frequently form dendro-dendritic and axo-dendritic contacts with other CR-IR elements. The cells form large clusters dendro-dendritically connected by regularly spaced zonula adherentia. Postembedding immunogold staining demonstrated that, CR-IR axons form symmetrical synapses solely on other GABAergic elements. Double immunocytochemistry identified the GABAergic target cells as VIP-containing basket cells and calbindin D28k-containing interneurons. Two subpopulation of VIP-IR cells were also shown to selectively terminate on other GABAergic cells. The first has dendrites in stratum lacunosum-moleculare, with a target selectivity for interneurons responsible for dendritic inhibition. The second group had a vertical dendritic tree with a bias towards str. lacunosum-moleculare, but their axons descended towards the str.oriens/alveus border and selectively innervated somatostatin/metabotropic glutamate receptor (mGluR1) immunoreactive interneurons. The possible role of these interneurons may include synchronization of inhibitory cell activity, and/or input-selective modulation of pyramidal cell excitability via disinhibition.

11. Oral Session: Learning and memory

11.01 NERVE GROWTH FACTOR AND CHOLINERGIC CONTROL OF LEARNING AND MEMORY PROCESSES IN DEVELOPING MICE

Gemma CALAMANDREI*, Laura RICCERI and Angela VALANZANO
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It has extensively been shown that Nerve Growth Factor (NGF) synthesized in hippocampus and cortex influences the neurochemical differentiation of basal forebrain cholinergic neurons of developing rodents. Moreover, recent behavioural findings have indicated that early administration of NGF affects behavioural responses under cholinergic control (such as suckling, locomotor activity, and spontaneous alternation in a T-maze) and markedly alters the response of immature animals to anticholinergic drugs. The involvement of CNS cholinergic pathways in learning and memory processes has suggested a role for NGF in cognitive functions. We investigated the effects of early administration of antibodies directed against NGF on the ontogeny of learning and retention capabilities of CD1 mice, using a passive avoidance learning task (PA). Neutralization of endogenous NGF by intracerebral anti-NGF treatment impaired learning and 24hr retention of a step-down PA task in 11- day old mice. Alteration of exploratory behaviour in the Hole Board test was also observed in antiNGF animals, while locomotor activity and age-typical response to scopolamine were unaffected. More extended treatment with antiNGF given systemically was found to impair 24 hr retention, but not acquisition, of a step-through PA task in 15 day mice. Mice undergoing the same treatment schedule were not impaired on day 21. Finally, analysis of choline acetyltransferase (ChAT) immunostaining in the septal area revealed significant differences between antiNGF-treated and control animals. Changes in the endogenous NGF levels at critical developmental stages appear to affect the maturation of learning and memory capabilities in altricial rodents.

11.02 NMDA RECEPTOR BLOCKADE INDUCES A TEMPORALLY GRADED AMNESIA FOR A WELL ESTABLISHED REACTIVATED MEMORY

Susan J. Sara,* Jean Przybyslawski & Tatiana Alexinsky. Institut des Neurosciences, Université P & M Curie, Paris, France.

Rats were trained in a radial maze which requires integration of distal spatial information contained in cues around the maze. Pretrial injection of the NMDA receptor antagonist, MK-801, at a dose which had no effect on overt behavior (.05mg/kg), markedly disrupted the well-trained. Surprisingly, the deficit persisted on subsequent drug-free trials 24h and even 48h later. Posttrial injections produced the same proactive effects on performance 24h later. A temporal gradient of efficacy of the drug was established by injecting rats at 5, 30, 60, 90, 120 or 180 min post trial. Only those rats whose MK-801 treatment was delayed for at least 120 min were able to perform the task normally 24h later. All other delays induced significant amnesia for the task, when the rats were tested 24h later. For some rats, several retraining trials were required to achieve pretreatment performance levels. Thus, it appears that activation of a well-established memory circuit triggers cellular events which depend upon NMDA receptors for up to two hours after reactivation. Retrieving a memory renders the trace labile, requiring reconsolidation. To what extent the entire postacquisition cascade of intracellular events is recapitulated each time a memory is reactivated is probably a function of the age and complexity of the memory and the amount of new information to be integrated into the circuit. These results provide physiological evidence that memory is a dynamic process undergoing continual reorganisation as a function of ongoing experience.

11.03 FACILITATION OF PASSIVE AVOIDANCE AND LEARNING IN PLACE PREFERENCE TEST AFTER SUBSTANCE P INJECTION INTO THE GLOBUS PALLIDUS.

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It has been shown that the globus pallidus (GP) is involved in sensorimotor integration, learning and memory processes. Electrolytic or neurotoxic lesions of the GP disturb avoidance learning and food rewarded T-maze learning in rats. After its injection into different brain regions, the role of undecapeptid substance P (SP) in positive and negative reinforcement has been demonstrated. Nevertheless, it is not known yet, whether SP elements of the GP affect learning and reinforcement. In the present experiments SP (10 ng or 100 ng in 0.5 µl) was injected into the GP in CFY rats. In separate groups of injected animals the learning performance was studied in a passive avoidance or a place preference paradigm. In the single-trial two-compartment passive avoidance situation SP was injected immediately after the conditioning trial and latency of re-entering to the shock-compartment was measured 24 h later. In the place preference test animals were injected with SP in the non-preferred compartment of the cage and times spent in the preferred and non-preferred compartments were measured 24 h later. SP injections of the GP resulted in a significant latency increase in the passive avoidance paradigm. In the place preference test rats spent more time in the compartment they were injected with SP. Effects were dose-dependent. The present results show that SP injection of the GP facilitates the retention of the avoidance behavior and acts as a positive reinforcer in place preference test.

11.04 BEHAVIORAL IMPAIRMENTS IN AGED RATS ARE TASK-DEPENDENT AND DIFFERENTIALLY MODULATED BY CHOLINERGIC DRUGS.

J. Stemmelin, C. Kelche, J.C. Cassel and B. Will*. LN2C, Université Louis Pasteur, URA 1939 CNRS, Strasbourg, France.

This experiment compared performances of 36 aged (24 months old) Long-Evans female rats in various behavioral tasks (beam walking, home-cage and open-field locomotor activity, spatial reference memory in a water maze and working memory in a radial arm maze [RAM]) with those of 12 adult (3 months old) rats. In the RAM test, we also assessed the effects of subthreshold doses of scopolamine (0.1 mg/kg, i.p), of physostigmine (0.05 and 0.1 mg/kg, i.p) and of tetrahydroaminoacridine (THA; 3 mg/kg, i.p). Compared to adult rats, old rats presented reduced beam walking scores, locomotor hypoactivity both in the home-cage and the open-field test, and drastic impairments in both water-maze and RAM tasks. In the water-maze task (but not in the RAM task), there were two sub-populations of old rats: one showed near normal learning (acquisition) and retention (probe trial) performances, whilst the other was impaired. In adult rats, the RAM performances were modified by neither drug treament. In contrast, in old rats, RAM performances were impaired by scopolamine, an effect that was slightly counterbalanced by physostigmine and completely compensated for by THA. It is concluded that 1) spatial working and reference memory capabilities are not necessarily impaired to a similar degree by ageing, 2) old rats present altered cholinergic functions as indicated by their sensitivity to a subthreshold dose of scopolamine, and 3) THA is more efficient than physostigmine to counterbalance the scopolamine-induced disruption in old rats.

11.05 MEDIAL TEMPORAL PATHOLOGY AND GLOBAL ANTEROGRADE AMNESIA DURING CHILDHOOD: THE EFFECTS OF AGE AT INSULT

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Chronic anterograde amnesia resulting from medial temporal damage sustained in childhood is a rare occurrence. We present the cases of two girls, both with profound amnesic syndromes, arising from damage sustained, in one case during birth, and in the other at the age of 9 years. Both cases showed impairment in the acquisition and long-term retention of declarative knowledge. Case BS, had a difficult birth, with a prolonged period of hypoxia. Throughout she has attended mainstream school with support, and has documented learning dificulties, which have been evident since the age of about 4 years. T2-relaxometry, a quantitative MRI technique that is used to assess hippocampal pathology, showed severe bilateral abnormalities. In contrast, case CF had normal development up until the age of 9 years, when she suffered a drug overdose, and subsequently developed temporal lobe epilepsy. Following this acute episode, it was noted that CF's personality, intellect, and, in particular, memory, had become substantially impaired. MRI indicate small hippocampi on both sides, with the left slightly smaller than the right, and white matter changes in the temporal lobe more severe on the right than the left. T2 relaxometry also revealed bilateral hippocampal abnormalities, more abnormal on the left than the right. Neuropsychological evaluations showed normal immediate memory, but impaired retention of both verbal and nonverbal material, in both girls. Our findings suggest that the diagnosis of global anterograde amnesia in these two children is associated with bilateral medial temporal pathology.

11.06 A SINGLE STRESSFUL SITUATION CROSS-SENSITIZES MICE TO THE PSYCHOSTIMULANT PROPERTIES OF COCAINE AND AMPHETAMINE

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The objective was to determine if single stress cross-sensitizes mice to cocaine and d-amphetamine. A confrontation between a resident and an intruder was selected as stressful situation because it represents a biologically relevant paradigm. The intruder received 20 bites in the resident's cage (attack period), and then was placed in a protective cage for 30 min (threat to attack period). For experiment I, separate groups of male CFW mice were either challenged with 40 mg/kg cocaine i.p. (COC group), or 6 mg/kg d-amphetamine (d-AMPH group) during days 2-10 after a single defeat, in order to study the time course of cross-sensitization. Locomotion was measured by a photocell motion detector 20 min after drug. For experiment II, several groups were tested: COC-treated after defeat (0, 5, 10, 20 mg/kg i.p.; DFC group), d-AMPH-treated after defeat (0, 1, 3, 6, 10 mg/kg i.p.; DFA group) and non-defeated controls separated into identical groups. Mouse behavior was videotaped and later analyzed by using ethological techniques. During experiment I, a significant increase in locomotion was found at day 7 after defeat in the COC group ($p < 0.01$), and at days 4 and 5 after defeat in the d-AMPH group ($p < 0.05$). The third-order formulas which fit the sensitization curve over time indicate that several endogenous neural systems might be recluted in both cases. During experiment II, ethoanalysis indicated that stereotypies and circling were significantly enhanced in the DFC group at intermediate doses ($p < 0.01$), and stereotypies increased in the DFA group at the 10 mg/kg dose ($p < 0.05$). In conclusion, the data revealed that single defeat cross-sensitizes mice to cocaine and d-amphetamine. The present data support the assumption that psychostimulants and stress interact at the neural level. *Supported by Spanish DGICYT grant 93-099 to E.F.E. and NIDA research grant DA02632 to K.A.M.*

11.07 FEMALES ARE MORE VULNERABLE TO THE PREDISPOSING TO DEPRESSION EFFECTS OF EARLY HANDLING.

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Early experiences exert profound and long lasting influences on the developing brain and thus affect CNS function throughout life. We exposed rats to neonatal handling from birth until day 22. When adult, the animals were tested for their ability to adapt to a repeated immobilization stress by assessing their deficits in body weight gain,feeding and open field behaviour. Exposure to early handling resulted in a statistically significant increase in the number of female animals that failed to adapt. Among males no such difference was observed. Animals that fail to adapt are considered to represent a model of depression. In the females early handling also resulted in decreased levels of 5-HT in the hippocampus and of DOPAC, 5HIAA and HVA in the hypothalamus. In contrast, in the experimental males 5-HT was increased in both the hypothalamus and the hippocampus and in the latter increases were also found in NE, DOPAC and DA. Our results suggest that the developing female brain is more vulnerable to the effects of maternal deprivation and early handling which predispose to depression.

11.08 VERBAL AND VISUAL MEMORY PROCESSING IN THE FRONTAL LOBE: A LONGITUDINAL FOLLOWUP-STUDY IN PATIENTS WITH FRONTAL LOBE DAMAGE.

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There is considerable debate regarding the role of the frontal lobe in memory processing. Findings in patients with frontal lobe damage have been inconsistent; this may be caused by variation in the *site* of the damaged frontal subregion (dorsolateral versus orbito-medial) and amount of *time* passed since the damage was acquired, as suggested by studies in monkeys. To investigate the influence of site and time on verbal and visual memory processing 12 patients with frontal lobe damage due to a tumor were assessed 3-5 weeks and 3 years post-neurosurgery. All patients gave consent to participate in the study. The damaged region was evaluated by two-dimensional 0.5 tesla T2-weighted spin-echo MRI (6 mm slices, 1.2 mm gab) or by CT (5 mm sections, 5 mm gab). In addition a 3-dimensional computer (3D) reconstruction of a 0.5 tesla T1-weighted gradient-echo 3D MRI (1.2 mm contiguous slices) with Gadolinium-DTPA was acquired 3 years postsurgery to accurately evaluate the the dorsolateral, medial and orbitofrontal damage in each patient individually. An improvement over time was found for verbal and visual memory, and in addition a differential improvement in verbal memory was observed in the patients with medial frontal damage and patients with orbitofrontal damage as compared to the patients with dorsolateral frontal damage. Thus both the damaged site and time passed since the damage influence memory processing in the human frontal lobe.

12. Oral Session: Neurodegenerative diseases

12.01 IS THERE A ROLE FOR Ca^{2+} IN ß-AMYLOID NEUROTOXICITY?

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Toxicity of ß-amyloid (Aß) is believed to be involved in neurodegeneration associated with Alzheimer's disease. Treatment of cultured rat hippocampal neurons with Aß 1-40 (1 μM) or the active fragment Aß 25-35 (1 μM) for 5 days reduced neuronal viability by approx. 40 - 50 %. Infection of the cultures with a recombinant, replication-defective adenovirus expressing the Ca^{2+}-binding protein calbindin D_{28K} (100 M.O.I.) greatly reduced Aß neurotoxicity compared to both control cultures or cultures infected with a replication-defective adenovirus expressing ß-galactosidase. However, treatments with the NMDA antagonist MK-801 (1 μM), the AMPA/kainate antagonist CNQX (1 μM), or tetrodotoxin (0.5 μM), agents known to inhibit glutamate- and synaptic activity-mediated rises in $[Ca^{2+}]i$, did not protect against Aß neurotoxicity. In case of MK-801 and tetrodotoxin, Aß neurotoxicity was actually potentiated. Moreover, exposure to Aß 25-35 (1 μM) for 24 or 48 hours did not influence basal $[Ca^{2+}]i$ as determined with FURA-2-based microfluorimetry. Similarily, NMDA- or Ca^{2+} ionophore-induced elevations in $[Ca^{2+}]i$ were not potentiated by pre-treatment with Aß 25-35. Morphological and biochemical characterization of Aß-induced neuronal degeneration suggested an apoptotic type of cell death, indicated by cell shrinkage, nuclear condensation, membrane blebbing and double-stranded DNA breaks visualized with the TUNEL technique. With respect to the protective effect of calbindin D_{28K} overexpression, we conclude that pathophysiological Ca^{2+} fluxes play an important role in Aß neurotoxicity. These Ca^{2+} fluxes appear to be associated with apoptotic rather than excitotoxic processes and could not be visualized by conventional FURA-2-based microfluorimetry.

12.02 DISTRIBUTION OF DNA DAMAGE IN ALZHEIMER BRAIN AS DETECTED WITH THE APOPTOSIS MARKER TECHNIQUE IN SITU END LABELING OF FRAGMENTED DNA.

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Differential accumulation of e.g., oxidative DNA damage has been proposed to underlie the spatio-temporal patterns of neuronal degeneration in Alzheimer's disease (AD), and may be explained by activity-dependent differences in DNA repair capacity. Earlier biochemical studies already indicated the involvement of DNA damage by demonstrating a twofold increase in DNA single strand breaks in AD cortex as compared to controls. In order to investigate the histological distribution of DNA damage in different brain areas, we applied in situ end-labeling (ISEL) on human brain. Although often used for detection of apoptotic cell death, ISEL in fact does not detect apoptosis itself but rather the associated DNA fragmentation. We, therefore, used ISEL in order to detect DNA strand breaks in tissue sections of cortex, locus coeruleus (LC), hypothalamus and hippocampus of control subjects and Alzheimer patients, matched for age and post mortem delay. We did not observe any apoptotic morphology in AD brain. Regarding the amounts of DNA damage present in occipital cortex, variable results were found, both between several cortical layers and also between individuals. The LC and hypothalamus appeared to be relatively spared, showing very little labeling. However, in the hippocampus in AD, strong labeling was found as compared to controls, displaying many positive neuronal nuclei and also microglia cells that were labeled throughout their cytoplasm. Our results suggest that this type of oxidative DNA damage, either primary or secundary, is involved in the degenerative changes in the hippocampus in AD. Brain material was obtained from the Netherlands Brain Bank (Coordinator Dr. R. Ravid).

12.03 INDUCTION OF ALZHEIMER-TYPE PATHOLOGY IN RAT BRAIN BY CHRONIC STIMULATION OF PROTEIN PHOSPHORYLATION

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Neurofibrillary tangles, neuropil threads and dystrophic neurites surrounding the amyloid cores of senile plaques, are made up by paired helical filaments (PHF), the principal component of the neurofibrillary degeneration (NFD) in Alzheimer's disease (AD). The extent of neurofibrillary degeneration found post mortem is a reliable pathological correlate of both duration and severity of AD. PHFs are composed of abnormally phosphorylated tau protein. As a result of this abnormal phosphorylation, PHF-tau is largely prevented from the efficient binding to microtubules which apparently leads to a destabilisation of microtubules, to an impairment of axonal transport and to cell death. There is hardly any degradation of PHF-tau in AD. Under in vitro conditions, PHF-like phosphorylated recombinant tau protein can be dephosphorylated by the protein phosphatase 2A. An impaired action of this phosphatase could, therefore, be involved in the induction of NFD in AD. In the present study, we have investigated the effects of chronic inhibition of phosphatase 2A by okadaic acid in rat brain on the phosphorylation of cytoskeletal proteins and the expression of the amyloid precursor protein (APP). Qualitative and quantitative changes in the phosphorylation pattern of cytoskeletal proteins were studied with immunocytochemistry, PAGE/Western blot and ELISA using a number of phosphorylation dependent antibodies. We observed a hyperphosphorylation of tau-protein which was associated with their redistribution from the axonal compartment into neuronal cell bodies, where they appeared as PHF-like immunoreactivity. Astrocytes showed a pronounced increase in APP immunoreactivity. The results demonstrate that Alzheimer-type changes of cytoskeletal protein phosphorylation, associated with changes in the expression and/or metabolism of APP can be induced in vivo by altering protein phosphorylation. The present experimental paradigm might, therefore, provide a tool to study molecular events leading to NFD and neuronal dysfunction as observed in AD. (Supported by the BMFT: 01 ZZ 9103-2.7)

12.04 THE HUMAN PERIRHINAL CORTEX. DISTRIBUTION OF CHOLINERGIC INNERVATION IN CONTROLS AND IN ALZHEIMER'S DISEASE.

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Decline in cholinergic innervation is a prominent feature of Alzheimer's disease (AD), which has been related to attentional deficits. Perirhinal cortex (PRC) is one of the cortical regions involved in some forms of memory. We have previously analyzed the normal architecture of PRC in the human brain and its changes in AD [Soc. Neurosci. Abstr.20:359,1994]. In the present study we prepared series of 50 µm sections from 6 controls and 6 AD cases that were perfused through the cerebral arteries. Sections were incubated with an antibody against choline acetyltransferase (ChAT; 1:500) and intensified with silver-gold. The distribution of ChAT-like immunoreactivity was exclusively found in fibers. The medial portion of PRC showed positive fibers around layer II and deep layer III. Often they formed clusters that extended across the upper layers. This pattern was extensive to the lateral portion of PRC, although staining was lighter in layer II. In both portions, ChAT-like immunoreactivity decreased in layers V and VI, although in some portions a tangential plexus in layer V was prominent. In AD cases, we found a substantial reduction in ChAT-like fibers in all portions of the PRC.

12.05 THE EFFECTS OF CABERGOLINE IN A PRIMATE MODEL OF PARKINSON

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The toxicity induced by MPTP manifests itself both in humans and monkeys with a Parkinson-like syndrome of akinesia, flexed posture, rigidity, tremors, loss of vocalisation and interest in food (Langston *et al*, 1983, Science, 219: 979; Burns *et al*, 1983, Proc. Natl. Acad. Sci. U.S.A. 80: 4546). We have previously reported that the D_2 dopamine agonist Cabergoline (CAB) restores motility in MPTP-treated monkeys when administered acutely at doses of 0.5 and 1 mg/kg (Carfagna *et al*, 1991, Abstracts Society For Neuroscience, 21st annual meeting, New Orleans, Louisiana, 424.3). This study evaluated the effects of repeated administration of CAB in MPTP-treated cynomolgus monkeys. Three monkeys received repeated administrations (6-29) of CAB at different doses both subcutaneously (*sc*, 0.1-0.5 mg/kg) and orally (*po*, 0.5-2 mg/kg) 12 or 47 days after MPTP (0.35 mg/kg; *iv* x 3 days). The behaviour of these monkeys was observed and scored. CAB administered either *sc* and *po* reversed the parkinsonian syndrome in the all monkeys. The minimal effective doses were 0.1 mg/kg *sc* and 2 mg/kg *po*. The effect was dose-dependent and long-lasting. Higher doses induced more intense and longer effects. Clear stimulation and moderate stereotypies without lingual diskinesia occurred only with higher dosages.The recovery of activity was followed by a relatively smooth wearing-off phase, which is different from the "on-off" effect described with l-DOPA treatment. In conclusion, CAB is a suitable candidate for therapeutic use in parkinsonism offering advantages over existing treatments.

12.06 THE EFFECT OF CHRONIC, HIGH FREQUENCY STIMULATION OF THE GLOBUS PALLIDUS (GP) IN PARKINSON'S DISEASE (PD).

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We are studying the therapeutic potential of chronic stimulation of the GP through stereotactically implanted Medtronic® electrodes in PD. At frequencies of 100-120 Hz and intensities of 1-3 V, GP stimulation is expected to lead to a functional block of pallidal function and mimic the effects of a pallidotomy. However, the effects can be reversed when stimulation stop and the surgical risk is smaller. In four patients we have documented: (1) beneficial effects on bradykinesia, rigidity and tremor using the UPDRS; (2) improvement in a timed walking task and the grooved pegboard task; (3) accelerated simple hand and foot reaction time; (4) improvement in a delay response and a serial reaction time task; and (5) enhanced cortical excitability assessed by transcranial magnetic stimulation. These effects appear to be bilateral, although they are more marked for the hemibody contralateral to the stimulated GP. There have been no negative effects on mental status. However, at low GP stimulation frequencies (5 to 25 Hz) we have documented worsening of performance as compared with the unstimulated condition. The effects of GP stimulation have been sustained for the first three months of follow-up. There have been no complications. Consistent with the notion of cortical hypoexcitability in PD and current models of basal ganglia-cortical circuitry, activation of GP through low frequency stimulation leads to functional worsening while the presumed depolarization block at high frequency GP stimulation results in functional improvement. Chronic GP stimulation holds promise as a therapeutic tool in PD and provides a unique insight into the physiology of the cortico-basal ganglia loops.

12.07 MANUAL TRANSPORT ANALYSIS FOR PHYSIOLOGICAL ASSESSMENT OF MOTOR PERFORMANCE IN PARKINSON'S DISEASE

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Manual transport of objects in the surrounding space are basic motor activities of daily life which are dependent on motor control mechanisms at different CNS level. These functions are disordered in Parkinsons's Disease, for instance in transportation of food during eating. We have analysed motor performance in manual transport acts since 10 years in order to develop physiological clinical methods to measure motor performance and assess motor disorders.

Computer assisted opto-electronic cameras permit precise and truly objective measurements of free human movements. We have developed standardised test movements and software for automatic analysis, the Posturo-Locomotor-Manual program making opto-electronic movement analysis to an independent, sensitive and affordable standard clinical method for assessment of movement disorders. In Parkinson's Disease, the normal co-ordination profile of the P, L, and M phases into a smooth movement with bell shaped speed curves is fragmented, indicating a deficient preplanning of motor programs.

A method for analysis of the finger precision grip measuring grip and load forces, which is essential for manual transport acts such as lifting a glass or picking strawberries, has been developed (Johansson R & Cole K, Curr. Opin. Neurobiol. 2:815-23, 1992). A perfect coordination of grip in patients with Parkinson's disease falsified the hypothesis of a general motor planning disorder in PD.

It is suggested that the co-ordination of postural, locomotion and manual reaching movements of the PLM test is dependent on the basal ganglia, while the finger-precision grip seems to be under direct cortical control.

12.08 ANTISENSE "KNOCKOUT" OF CNS DOPAMINE RECEPTORS.

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We are pioneering the new technology of antisense "knockout" to block CNS dopamine receptor function. In contrast to classical pharmacological antagonism which operates by drug binding to receptors, antisense oligodeoxynucleotides bind to receptor-coding mRNA and stop the production of receptor protein. Why is this new technology of critical importance? Advances in molecular biology have found that dopamine, as well as most other neurotransmitters, has multiple receptor subtypes, each coded by a distinct gene. Since such receptor "families" are closely related structurally, drugs often do not discriminate between them and bind to all members of the family, producing a range of functional effects. This is the case for the 5 members of the "D_1" and "D_2" dopamine receptor families. We are using antisense oligodeoxynucleotides *in vivo* to block the production of each dopamine receptor subtype selectively in order to determine their behavioral and neurophysiological functions. For example, a 3 day intraventricular infusion of an antisense oligodeoxynucleotide corresponding to the 5'-terminus of the D_2 receptor mRNA resulted in a >50% decrease in rat striatal D_2 receptors and a 70% loss in the nucleus accumbens. In contrast, D_1, muscarinic M_1 and $5HT_2$ receptors were unaffected. D_2 receptor knockout reliably induced catalepsy, a behavior previously associated with decreased D_2 receptor activation. Spontaneous locomotor activity was also significantly reduced. Locomotor activation by the non-selective D_2 agonist, quinpirole, was inhibited by over 75%. In contrast, grooming behavior stimulated by a D_1 agonist was unaffected. Apomorphine's ability to inhibit dopamine neuron firing via autoreceptors was also abolished suggesting that D_2 receptors, in part, mediate this important regulatory role. The specific sequence of the oligodeoxynucleotide was essential because an oligo with the same nucleotide content but in random sequence was inactive. Results of D_3 and D_4 receptor antisense treatments will also be discussed. Antisense strategies give hope not only for clarifying receptor mechanisms but also for producing new and perhaps better therapeutic agents.

13.01 POLYNEURAL INNERVATION IN THE HUMAN FETUS.

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Innervation of human muscles starts around the 6th week of gestation. It is well known from animal studies mainly in rats, that muscle fibres are innervated polyneurally at early stages. Up to 8 axons may terminate upon one single end plate in the soleus muscle of the rat and this polyneural innervation is replaced by mononeural innervation until the 16th postnatal day. The significance of polyneural innervation at first, and the selective retraction of supernumerous terminals most probably is to ascertain a proper matching between the properties of motoneurons and their muscle fibres.

Polyneural innervation also occurs in the human at early stages of development. However, it is not known when regression to mononeural innervation takes place. Therefore, we studied innervation patterns in the psoas muscle of human fetuses between the 15th and 45th weeks postmenstrual age (PMA). The subjects died because of abnormalities, most likely not interfere with muscle or spinal cord development. Innervation patterns of the muscle fibres were studied by means of a combined silver and acetylcholinesterase staining. Numbers of axon endings were counted and motor endplates (acetylcholinesterase-positive spots) were measured. At 15th weeks PMA, 3 axons on the average terminate upon 1 motor endplate. This value decreases to around 2 at 25 weeks PMA and 1.40 at 45 weeks PMA. In the latter case, mononeural innervation was observed in major parts of the muscle leaving a few circumscribed regions with polyneural innervation. We conclude that regression of polyneural innervation in the psoas muscle of the human infant starts before birth and continues after term age.

13.02 CHANGING EXPRESSION OF PARVALBUMIN DURING DEVELOPMENT OF THE LOWER CERVICAL SPINAL CORD AND FOLLOWING CORTICAL LESION IN THE IMMATURE RAT.

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Parvalbumin (PV) is one of a number of Ca^{2+} binding proteins whose expression appear related to neuronal activity and/or growth related processes *[1]*. We have studied expression by immunohistochemistry using a specific monoclonal antibody (Sigma), during post-natal development of the lower cervical spinal cord, which receives extensive innervation from the sensorimotor cortex *[2]*. The effect on PV expression of lesioning this region of the cortex unilaterally 7 days post-natally (P7), the onset of corticospinal synaptogenesis, was also assessed.

Three waves of expression are apparent. 1) From P0-7 staining was strong in large sensory afferents with staining of varicosities around motoneurones, in the intermediate grey and just lateral to the central canal. Staining gradually disappeared from distal portions of these axons between P7-21 only to remain in dorsal roots and columns thereafter. 2) From P10 a proportion of neurones in laminae VII and VIII stained positively and more intensely, reaching a maximum around P18 then declining until fewer, faintly stained neurones remained. 3) From P18 staining of neurones in the dorsal horn increased consisting of a band of small neurones and processes in laminae II and III and neurones in the medial part of laminae V and VI. The cortical lesion, without producing a gross motor deficit, had significant effects upon PV expression on the contralateral side of the spinal cord, that is, the side the lesioned pathway would have innervated. It almost completely abolished staining in ventral horn neurones at P14, and in laminae V and VI between P22-29 also reducing staining in laminae II and III at this time. This suggests that a functioning corticospinal pathway has a significant influence on the development of spinal cord neurones.

References. 1) Solbach S & Celio MR (1991) Anat Embryol 184:103-124.
2) Curfs MHJM et al (1994) Dev Brain Res 78:182-190.

13.03 MAP-KINASE BLOCKAGE BY 2-AMINOPURINE INHIBITS OUTGROWTH OF AXONS IN CULTURED, ADULT MOUSE SUPERIOR CERVICAL GANGLIA AND SCIATIC NERVES.

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When a peripheral nerve is injured there is a rapid increase of transcription factors such as c-jun and c-fos, which probably regulate the synthesis of regeneration-related proteins. However, the mechanism(s) leading to their up-regulation is not known. Mitogen activated protein kinase, MAP-K, has been suggested to be involved in the conversion of external receptor stimuli to the onset of various intracellular events. The kinase is activated by numerous hormones, growth factors and other extracellular factors leading to the up-regulation of transcription factors including c-jun. It is therefore possible that MAP-K is involved also in peripheral nerve regeneration, but knowledge about MAP-K in regenerating nerves is still limited.

Here, we show by immunohistochemistry that MAP-K is present in neurons of both superior cervical ganglia (SCG) and dorsal root ganglia of the adult mouse. Furthermore, in both preparations MAP-K immunoreactivity is markedly increased in neuronal cell bodies during outgrowth of new axons. Also the latter structures were immunoreactive for MAP-K. We then used the purine analouge 2-aminopurine (2-AP), which is a kinase inhibitor acting on MAP-K, to look for effects on nerve regeneration. At a dose of 2 mM, 2-AP strongly inhibited outgrowth of axons from SCG cultured in matrigel as well as outgrowth of axons within crush injured sciatic nerves. The inhibition is likely not a result of toxic effects since neither protein synthesis nor axonal transport were affected.

The present results suggest that MAP-K is involved in the early stages of peripheral nerve regeneration.

13.04 REGENERATION OF IDENTIFIED SEPTOHIPPOCAMPAL PROJECTION NEURONS IN VITRO.

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Previous studies have suggested that septohippocampal neurons degenerate following axotomy. However, prelabeling of septal cells by injection of retrograde tracer into the hippocampus prior to axotomy revealed many prelabeled cells even after long survival times following axon transection by lesion of the fimbria-fornix. Here we demonstrate that axotomized septohippocampal neurons may not only survive but regenerate an axonal process.

We have prepared slice cultures of identified septohippocampal projection neurons that were retrogradely labeled by hippocampal injection of the retrogradely transported tracer Fast Blue prior to slice preparation. These septal cultures were co-cultivated with slices of hippocampus. After an incubation period of two weeks, a second retrogradely transported tracer (Latex beads coupled to Lucifer Yellow) was injected into the hippocampal co-culture. Among single-labeled cells (either labeled with Fast Blue or Latex beads) a few double-labeled neurons were observed in the septal cultures. The presence of single Fast Blue-labeled cells indicates that these neurons had already innervated the hippocampus when their axons were cut for culture preparation. Neurons only labeled with Latex beads demonstrate that a septohippocampal projection has formed in vitro. Double-labeled cells indicate that these identified septohippocampal projection neurons did not only survive axotomy caused by culture preparation, but were able to regrow an axonal process in vitro and innervate a co-cultured hippocampal slice.

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13.05 REACTIVE GLIOSIS IN FETAL AND NEONATAL RATS

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Our goal was to investigate the reaction of the fetal and neonatal brain to lesions and the possibility of the development of brain tracts through the area lesioned.
The embryos were exposed with the corresponding segment of uterus horn, 2 mm long paramedian sagittal incisions were performed with a sterile blade through the uterine wall into the developing cortex and then the embryos were repositioned into the abdominal cavity. The pups were usually born on the 23rd day of pregnancy. Similar telencephalic lesions were performed on neonatal animals, too.
The animals were sacrificed at one day, one week, two week, three week or one month of age or, sometimes, immediately after operation. Parallel vibratome sections were processed for immunohistochemistry against either vimentin or glial fibrillary acidic protein or neurofilament protein. To investigate the myelination in the developing corpus callosum, semithin sections were prepared.
No glial reaction characteristic for the adult rat brain was found after fetal lesions. The development of corpus callosum was complete although retarded. The axonal connection between the hemispheres was demonstrated by *Phaseolus* tracer. The myelination gradually progressed during the first lifemonth. In neonatal rats, a strong glial reaction developed in two weeks. In contrast to the gliosis of adult rats, however, the glial rection of the early postnatal brain almost disappeared during the next week. Fiber ingrowth but no considerable regeneration of corpus callosum was observed.

13.06 GAP JUNCTION COUPLING BETWEEN IMMATURE NEOCORTICAL PYRAMIDAL NEURONS: ELECTROTONIC EFFECTS AND REGULATION BY NEUROTRANSMITTERS

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During the early postnatal period neurons in rat neocortex are extensively coupled via gap junctions. In view of possible interactions with developing chemical synapses we investigated to what extent gap junctions affect electrotonic cell properties of developing neurons and whether junctional permeability is regulated by modulatory afferents to the neocortex.
Layer II/III pyramidal cells in coronal slices of rat prefrontal and frontal cortex were recorded on postnatal days 3 to 18 using either the whole cell blind patch technique or conventional microelectrodes. To asses the extent of gap junction coupling neurons were filled with the tracer neurobiotin. Intracellular acidification by weak organic acids, resulting in a 64 % decrease in dye-coupling, was used to study the effects of gap junction closure on electrotonic parameters. In the majority of neurons tested a reversible increase in input resistance by 22-300 % and a decrease in electrotonic length by 5-49 % was observed. Voltage responses to transient current injections resembling a synaptic potential were on average increased by 149 %. Already at early developmental stages the rat neocortex is invaded by a number of neuromodulatory afferents which might regulate gap junctional conductance under physiological conditions. A significant reduction in dye-coupling was observed after preincubation of slices in dopamine, serotonin or the ß-adrenergic agonist isoproterenol and after stimulation of cAMP-dependent protein kinase (PKA).
Our results indicate that gap junctions significantly influence the electrotonic structure of immature pyramidal neurons and thus the efficacy of synaptic potentials. Modulatory afferents activating PKA-mediated connexin phosphorylation might contribute to the regulation of junctional conductance during cortical development.

13.07 **TRANSPLANTATION OF SCHWANN CELLS INTO THE INTACT AND LESIONED ADULT RAT STRIATUM : IMPACT ON C-JUN RESPONSE OF SCHWANN CELLS.** *,1,2,E.Vaudano 3B.Finsen, 1P.Reid, 1A.R.Lieberman and 2S.P.Hunt. 1 Dept. of Anatomy, UCL, WC1E 6BT London, UK; 2Div. Neurobiology MRC LMB, CB2 2QX Cambridge, UK, 3Dept. Anatomy, Odense Univ., 5000 Odense C, Denmark.

Adult CNS neurons regenerate their axons if provided with a growth permissive substrate such as Schwann cells (SCs) transplanted into the brain, although this regeneration is always very limited when compared with PNS regeneration. SCs "activated" following denervation, or grown in vitro, express high levels of the transcription factor c-jun. We have shown that c-jun is rapidly downregulated in SCs implanted into the intact brain. This might be due either to the presence in the CNS of an active inhibitor of c-jun expression, or to the lack of one or more factors necessary to maintain the c-jun response. After PNS injury there is a massive invasion of the lesioned nerve by macrophages which secrete interleukin I which is known to induce c-jun expression. The lesion inflicted on the CNS by the transplantation of SCs is followed by a much more limited macrophage reaction, which in itself may be inadequate to maintain c-jun expression. The intensity of the reaction of brain macrophages can be greatly enhanced by lesioning the target brain area prior to grafting, We have compared c-jun expression in SCs implanted into the adult rat striatum one week after: 1) implant in the intact striatum; 2) implant into the striatum previously excitotoxically lesioned; 3) implant into the striatum previously lesioned with 6OHDA. We find c-jun expression as well as extensive migration (and possibly proliferation) of SCs implanted into the excitotoxin lesioned striatum, which also displays an intense brain macrophage and glial reaction, compared with a very limited c-jun response and migration in the SCs implanted into the intact or 6OHDA lesioned striatum (where the micro-macroglial responses are much weaker) supporting the hypothesis that glial cell reactions and the brain macrophage reaction in particular play a critical role in regulating the c-jun response in SCs implanted into the brain.

13.08 THALAMIC INNERVATION OF TRANSPLANTS OF EMBRYONIC PARIETAL OR OCCIPITAL NEOCORTEX PLACED INTO THE PARIETAL CORTEX OF NEWBORN RATS. Afsaneh EBRAHIMI-GAILLARD*, José GUITET and Michel ROGER. CNRS: URA 1869, Département des Neurosciences, Université de Poitiers, 86022 Poitiers, France.

It has been established that transplants of embryonic occipital cortex placed into the parietal cortex of newborn rats have the capacity to form barrels (Schlaggar and O'Leary, Science, 1989, 252: 1556), probably as a result of an invasion of the transplants by host ventrobasal (VB) thalamic afferents. In this study, we examined the VB input of transplants of parietal or occipital embryonic (E16) origin placed into the parietal cortex of newborn hosts. Four months after grafting, anterograde (PHA-L) or retrograde (CTB) tracers were injected respectively into the host VB or into the transplant. Our results indicate that following injection of PHA-L into the VB a large number of labeled fibers and terminals were seen in transplants of parietal origin. These labeled fibers were frequently arranged in "clusters" within the transplants. In marked contrast, practically no labeled fibers were found in transplants of occipital origin. Following injection of CTB into transplants of parietal origin a large number of cells were labeled in the ipsilateral VB. By contrast, following injection of CTB into transplants, of occipital origin, very few cells were labeled in the ipsilateral VB. Our results indicate that ventrobasal thalamic afferents are not likely to invade transplants of occipital origin. Consequently, VB afferents are probably not capable of organizing barrels in a "foreign" piece of cortex.

14. Poster Session: Neurotransmitters, modulators, receptors I

14.01 MELANOCORTIN MC_4 RECEPTORS MEDIATE α-MSH INDUCED EXCESSIVE GROOMING BEHAVIOR R.A.H. Adan*, J. Oosterom, J.H. Brakkee, J.P.H. Burbach and W.H. Gispen. Rudolf Magnus Institute for Neurosciences, P.O.Box 80040, 3508 TA Utrecht, The Netherlands.

Melanocortins have various physiological actions on the brain. The cloning of melanocortin (MC) receptors opened new avenues to study the effect of these neuropeptides on the nervous system. We here investigated the activity of peptides derived from adrenocorticotrope hormone (ACTH) on cloned MC_3, MC_4 and MC_5 receptors in vitro and correlate these with central effects of melanocortins in vivo. ACTH 4-9(NH)$_4$ was the core sequence of ACTH able to activate these receptors. Furthermore, γ-melanocyte-stimulating hormone (MSH) displayed selectivity for the MC_3 receptor, whereas [D-Phe^7]ACTH 4-10 more efficiently activated the MC_4 receptor than the MC_3 receptor. Two peptides, [D-Arg^8]ACTH(adrenocorticotrope hormone)-(4-10) and [Pro^{8,10},Gly^9]ACTH-(4-10), antagonized the action of α-MSH on the melanocortin MC_4 and MC_5 receptors, but not the melanocortin MC_3 receptor. [Ala^6]ACTH-(4-10) inhibited the α-MSH activation of the melanocortin MC_3 and MC_5, but only weakly antagonized the activation of the melanocortin MC_4 receptor. [Phe-I^7]ACTH-(4-10) antagonized the melanocortin MC_3, MC_4 and MC_5 receptors equally well. These antagonists were also tested to block a behavioral response induced by α-MSH. α-MSH-induced excessive grooming behavior in rats was inhibited by [Phe-I^7]ACTH-(4-10), [D-Arg^8]ACTH-(4-10) and [Pro^{8,10},Gly^9]ACTH-(4-10), but not by [Ala^6]ACTH-(4-10). This, together with the activity of MC peptides on grooming behavior published previously, suggests that α-MSH-induced excessive grooming behavior is mediated by melanocortin MC_4 receptors.

14.02 REVERSE TRANSPORT BY CLONED CATECHOLAMINE TRANSPORTERS IN SUPERFUSED COS-7 CELLS. Ernst Agneter*, Helmut Drobny, Harald Reither, Ernst A. Singer and Christian Pifl Institute of Pharmacology and Institute of Biochemical Pharmacology, University of Vienna, A-1090 Vienna, Austria

The cloned human dopamine transporter (DAT) or noradrenaline transporter (NAT) were transfected in COS-7 cells, the cells were loaded with ^{3}H-dopamine or ^{3}H-noradrenaline and superfused in microchambers. Reverse transport was induced by replacement of sodium or chloride in the superfusion medium by lithium or isothionate. These manipulations of the superfusion buffer induced an increase in efflux of the catecholamines. Different uptake inhibitors were examined for their ability to modify the ion evoked release. 10 µM cocain and 0.3 µM mazindol blocked the efflux induced by zero chloride from cells transfected with DAT or NAT and the efflux induced by zero sodium from cells transfected with NAT. The efflux from DAT tranfected cells induced by lowering of extracellular sodium was only blocked by cocaine or mazindol if 5 mM sodium remained in the superfusion buffer. 0.1 µM desipramine blocked the zero chloride induced release from NAT transfected cells. Desipramine inhibited the efflux from NAT expressing cells evoked by lowering of extracellular sodium to a higher extent if 5 mM sodium remained in the medium as compared to the complete removal of sodium. Desipramine did not affect ion induced release from DAT transfected cells on any condition. Reverse transport by catecholamine transporters did not only show selectivity versus uptake inhibitors but also versus substrates. Whereas the ion induced efflux from DAT transfected cells was markedly reduced if cells were loaded with ^{3}H-noradrenaline instead of ^{3}H-dopamine, the efflux from NAT transfected cells was larger if the cells were loaded with ^{3}H-dopamine instead of 3H-noradrenaline.

In conclusion, the reverse transport of catecholamines can be studied in superfused cells transfected with the cDNA of the DAT or NAT. These experiments can give insight into the mechanism of uptake inhibition in particular.

14.03 EFFECT OF OXIDATIVE STRESS ON GLUTAMATE RECEPTORS AND IN $[Na^+]_i$ IN CULTURED CHICK RETINA CELLS. P.Agostinho*, C.B. Duarte, C. R. Oliveira. Center for Neurosciences of Coimbra. Dept. Zoology, University of Coimbra 3049 Coimbra Codex Portugal.

Retina is a structure of the CNS, highly susceptible to oxidative damage because of the high rate of oxygen consumption and increased content of polyunsaturated fatty acids. Cultures of retina cells constitute a good neuronal model, because they contain almost every neurotransmitter known, but glutamate and GABA predominate.

Reactive oxygen species have been shown to induce the release of endogenous excitatory amino acids (EAA), mainly glutamate, which is increasingly implicated in neurotoxicity. It is generally accepted that toxicity of EAA is mediated through the activation of NMDA and non-NMDA receptors.

In the present study we analysed the effect of ascorbate/Fe^{2+}-induced oxidative stress on glutamate receptors in cultured chick retina cells. The activation of NMDA and non-NMDA receptors can raise the intracellular Na^+ concentration, and thus stimulate the release of GABA. Therefore, we used specific glutamate receptor agonists to stimulate the release of [^{3}H]GABA in control cells and in cells submitted to oxidative stress. The results show that maximal responses to Kainate and AMPA are not different in control and peroxidized cells, whereas the EC50s determined for peroxidized cells are significantly lower than those determined under control conditions. The maximal responses for NMDA are significantly higher for peroxidized cells. In cells submitted to oxidative stress an increase in the resting intracellular Na^+ concentration is observed, due to the activation of glutamate receptors.

This work has been supported by JNICT (Portuguese Research Council)

14.04 PRODUCTION AND CHARACTERIZATION OF A SPECIFIC 5-HT1B RECEPTOR ANTIBODY. D.[1]Aït-Amara*, J. [2]Chauveau, J. [2]Benfares, R. [3]Hen and L. [1]Segu. [1]CNRS-URA 339, 33405 Talence Cedex; [2]Immunotech S.A, BP 177F, 13276 Marseille Cedex 9, France. [3]Center for Neurobiology and Behavior, 10032 New York, USA.

Serotonin is a neuromodulator which influences several physiological functions by interacting with multiple receptor types. To understand the role of the serotonin 1B receptor type (5-HT1B) it is determinant to know its subcellular distribution. We have therefore generated specific antibodies directed against the mouse 5-HT1B receptor.

A synthetic peptide corresponding to the sequence (26-45) of the 5-HT1B receptor, was coupled to BSA with glutaraldehyde, and injected to rabbits. Sera from the fifth immune bleed were precipitated by ammonium sulfate and affinity-purified using the synthetic peptide antigen.

In ELISA analysis the precipited antisera detected the free and the coupled peptide with hight titers. Immunoblot analysis of membranes prepared from transfected cells expressing the 5-HT1B receptor, revealed an immunoreactive 50 kDa band with the precipited antibodies. This immunoreactive band disappeared when the antiserum was pre-absorbed with the synthetic peptide. No immunoreactivity was observed with the membranes of non transfected cells. When membranes prepared from the substantia nigra of mouse brain, which is the structure of the brain with the highest density of 5-HT1B receptors, were tested in immunoblot, precipited antisera detect the 50 kDa band but produced background level. This band of 50 kDa was not labeled with membrane preparation from cerebellum which contains a very low concentratio of 5-HT1B receprors. These results indicate that by immunoblot this antibody recognizes specifically the 5-HT1B receptor.

In radio-immunohistochemitry on brain section, affinity-purified antibodies give the same distribution obtained with 5-HT1B ligand's, except in he superficial layer of the superior colliculus and in the dorrsal subiculum which are not labeled by the antibodies.

14.05 CCK mRNA IS ELEVATED IN PAG AND FRONTAL CORTEX FOLLOWING CHRONIC MORPHINE ADMINISTRATION

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Much evidence suggests that cholecystokinin (CCK) interacts with opioid transmission in pain mechanisms (Michveych et al,. 1982) and affects CCK peptide levels in brain regions such as hypothalamus (Faris et al,. 1986) and periaqueductal grey (PAG). Increased levels of CCK following acute and chronic morphine administration could be achieved either by increased biosynthesis of the peptide and/ or its decreased release. In order to investigate this mechanism further we measured the effect of chronic morphine administration on CCK mRNA levels in different brain regions (frontal cortex, temporal cortex, PAG, locus coeruleus and thalamus). Analysis of CCK mRNA was carried out by slot-blot analysis and quantitated relative to β-tubulin mRNA. Parallel analysis of Go mRNA was carried out to test the specificity of the response. Daily morphine (morphine sulphate, 10 mg/kg i.p.) administration for 5 days induced a substantial increase in CCK mRNA content in PAG (188%) and frontal cortex (54%). No significant differences in CCK mRNA concentration were observed in temporal cortex, locus coeruleus and thalamus following repeated treatment with morphine. Naloxone administration on the 5th day did not completely reverse the increase in CCK mRNA in PAG. CCK mRNA was significantly elevated (105%) compared to saline controls after morphine withdrawal but at a reduced level compared to chronic morphine treatment. These results indicate that chronic morphine administration elevates CCK mRNA levels in parallel with peptide levels in a region specific manner. The effect of chronic morphine administration was specific for CCK mRNA and levels of other mRNAs, e.g. Goα mRNA in PAG were not affected by this treatment. These results indicate the importance of the PAG as a site for opioid CCK interactions.

Miceveych PE et al. (1982) Brain Res 250, 283-289
Faris PL et al (1986) Brain Res 367, 405-407.

14.06 *N*-METHYL-D-ASPARTATE (NMDA) RECEPTORS IN RAT HILAR NEURONS.

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NMDA-subtype glutamate receptors (NRs) are composed of different subunits named NR1 and NR2A-D which combine in different oligomers with distinct Mg^{2+} sensitivity, kinetics and pharmacological properties. Using the whole-cell mode of the patch-clamp technique in acute slices of the juvenile hippocampus (P11-P16) we compared the functional properties of NRs in hilar neurons and granule cells. I-V relations were obtained by clamping the neurons continuously to holding potentials (V_h) between -100 and 100 mV before, during and after the bath application of NMDA (50 μM, 1 mM Mg^{2+}, 10 μM glycine). The NMDA-induced current reversed at -0.1 ± 1.4 mV (mean ± S.D.; n=32) in hilar neurons and -1.9 ± 0.8 mV in granule cells (n=4). The V_h at which the maximal inward current amplitude (I_{max}) was reached was -34.2 ± 7.2 mV in hilar neurons (n=31) and -30.0 ± 8.2 mV in granule cells (n=4), respectively. To estimate the strength of the Mg^{2+} block of the NRs the current at a V_h of -80 mV (I_{-80}) was divided through the I_{max} yielding a value for the degree of the negative slope of the I-V relation of the NMDA-activated current. This ratio was 0.31 ± 0.05 in granule cells, while in hilar neurons a wide range from 0.01 to 0.84 (mean ± S.D.: 0.43 ± 0.20) was found suggesting the presence of more than one NR population. This was also suggested by the action of D-APV on the NMDA-(100 μM) induced current in hilar neurons displaying IC_{50}s between 3 and 12 μM (n=4). Spermine showed no or only weak effects on the NMDA-induced current in hilar neurons depending on the glycine concentration (10 μM glycine: 105 ± 11% of the control, n=5; 0.3 μM glycine: 120 ± 23%, n=5). These data suggest the expression of NRs with a lower Mg^{2+} sensitivity in a subpopulation of juvenile hilar neurons as compared to granule cells. In addition, NRs present on some hilar neurons show a pharmacological profile previously described for recombinant NRs assembled from NR1 and NR2C/D subunits.

14.07 DIFFERENTIAL DISTRIBUTION OF METABOTROPIC GLUTAMATE RECEPTOR mRNA IN RAT LUMBAR SPINAL CORD NEURONS.

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There is mounting evidence that AMPA, NMDA and kainate subtypes of the glutamate ionotropic receptor are involved in mono- and polysynaptic noxious and non-noxious neurotransmission in the spinal cord. Metabotropic glutamate receptors (mGluR) are supposed to be required for the development of spinal hyperexcitability produced by inflammatory and mechanical hyperalgesia. *In situ* hybridization with subtype specific oligonucleotides detected marked differences in abundance and distribution of mRNA encoding the mGluR1 to mGluR7 receptor subtype. The mGluR1, -3 and -4 mRNA were expressed throughout all laminae of the spinal cord, with mGluR1 and -3 being slightly concentrated in the superficial dorsal horn. mGluR2 mRNA showed a specific expression in very low abundance in occasional cells of all laminae. In the dorsal horn mGluR5 mRNA was preferentially located in neurons of laminae I to III, while mGluR7 mRNA was concentrated in laminae I and II. In the ventral horn, mGluR1, -3 and -4 mRNA were present in motor neurons, with the mGluR1 subtype gene being either highly expressed or totally missing in directly neighbouring neurons. Serial sectioning through single motor neurons permitted the detection of co-localized expression of ionotropic and metabotropic receptor subtype genes. For instance, NMDAR1 and GluR-B mRNA were found highly expressed in all motor neurons, no matter whether mGluR1 was or was not co-expressed. The differential distribution of mGluR receptor mRNA in the spinal cord suggests an inter-regional heterogeneity of mGluR receptor function. Together with a differential co-localization with ionotropic glutamate receptor subunits and peptidergic receptors this may help to understand the local circuitry of nociceptive transmission and activity-dependent plasticity in the spinal cord.

14.08 GLUTAMATE-LIKE IMMUNOREACTIVITY IN ASCENDING SPINAL AFFERENTS TO THE RAT PERIAQUEDUCTAL GREY. AN IMMUNOELECTRON MICROSCOPIC STUDY.

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Peripheral stimuli and periaqueductal microinjections of substances acting at excitatory amino acid receptors can elicit responses that form part of an integrated defence behaviour. L-glutamate is an endogenous agonist of such receptors and has been suggested to play a neurotransmitter role in ascending spinal afferents to the PAG. However, morphological experiments have not yet been carried out to demonstrate the localization of glutamate in the spinoperiaqueductal pathway (SPP). To investigate whether glutamate is contained at high levels in synaptic terminals of the SPP, an anterograde tract-tracing method in combination with immunocytochemistry was used in the present study.

Nineteen adult Sprague-Dawley rats (230-280 g) received large injections of 10% HRP-WGA into the lumbar enlargement of the spinal cord. Three to five days later, the animals were perfusion-fixed with 0,1 M phosphate-buffered 1% formaldehyde and 2.5% glutaraldehyde. Anterogradely transported peroxidase was visualized with TMB/tungstate-DAB/cobalt (Weinberg and van Eyck, 1991) and glutamate-like immunoreactivity was studied at the electron microscopic level by means of a highly specific monoclonal anti-glutamate antibody (mAb 2D7; Liu et al., 1989) and a postembedding immunogold procedure.

Axon terminals of SPP neurons contained round clear synaptic vesicles and made asymmetrical synaptic contacts on dendrites. Quantification of glutamate-like immunoreactivity, as assessed by gold particle densities over diverse tissue profiles, revealed high levels of glutamate in synaptic terminals of the SPP.

These findings support a neurotransmitter role for glutamate in the spinoperiaqueductal pathway.

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14.09 KINETIC MODULATION OF ^{3}H-STRYCHNINE INTERACTION WITH SPINAL CORD MEMBRANES.

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Glycine is the main inhibitory transmitter in the spinal cord. The glycine receptor complex is coupled to chloride channels and contains binding sites for glycine and the antagonist strychnine. The binding site for this antagonist seems to be located in the channel or quite near to it, so it may be hypothesized that channel kinetics may be approached by performing binding kinetic experiments with [^{3}H]strychnine. The present communication deals with steroid and antagonist regulation of [^{3}H]strychnine binding kinetics. To this end, association and dissociation of [^{3}H]strychnine to rat spinal cord membranes, in the presence and absence of the studied compound, was investigated. Results show that [^{3}H]strychnine association is retarded by 2 μM 3-α-hydroxy-16-imino-5-ß-17-aza-androstan-11-one (RU 5135) and by 20 μM 3-[2'-phosphonomethyl[1,1'-biphenyl]-3-yl]alanine(PMBA), while it is accelerated by 100 μM cyanotriphenylborate (CTB). Progesterone, deoxycorticosterone and pregnenolone, all three at 100 μM concentration, have no effect on the association. [^{3}H]Strychnine dissociation is retarded by 2 μM RU 5135 as well as by 20 μM PMBA, while it is accelerated by 100 μM CTB. Deoxycorticosterone (100 μM) has no effect on dissociation. Present results add new evidence to the fact that RU 5135, PMBA and CTB are able to modulate the glycine receptor.

14.10 THE 5-HT_{1A} RECEPTOR AGONIST FLESINOXAN DEPRESSES 5-HYDROXYTRYTAMINE LEVELS IN THE MEDIAN RAPHE NUCLEUS (MRN) OF THE FREELY MOVING GUINEA PIG.

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It has recently been suggested that extracellular 5-HT sampled with a microdialysis probe in the rat MRN is of cytoplasmic origin and is not influenced by the presence of 5-HT_{1A} receptor agonists such as 8-OH-DPAT (Adell et al., 1993). In these experiments we have measured 5-HT in the MRN of the guinea pig and reassessed this hypothesis.

In 30 experiments basal 5-HT levels were 2.8 ±0.3 pg/20 min sample. Alterations in 5-HT levels are expressed as % of basal (100%) values. The 5-HT levels were stable over a 6 hour period and were not influenced by injections of 0.9% physiological saline (n=6). Addition of tetrodotoxin (1 μM) to the dialysis fluid for a period of 60 min reduced 5-HT levels to 19 ±3% (n=3). Flesinoxan (0.3-3 mg/kg i.p.) dose-dependently reduced 5-HT levels. At 3 mg/kg the peak reduction in 5-HT levels (to 32 ±4%, n=4) occurred within 40 min; complete recovery was not observed within a 6 hour period. Flesinoxan (0.01-1 μM) introduced via the dialysis probe also reduced 5-HT levels (to 44 ±5%, n=4 at 1 μM). The 5-HT_{1A} receptor antagonist WAY 100635 (0.1 mg/kg i.p) did not alter 5-HT levels in 4 experiments although at this dose the reduction in 5-HT levels induced by flesinoxan (0.1 μM) was significantly reversed from 68 ±4% (n=5) to 88 ±8% (n=5) of basal values ($P<0.05$, Paired t-test).

In contrast to the suggestion of Adell et al. (1993), these results would suggest that the 5-HT level in the MRN is under neuronal control and sensitive to 5-HT_{1A} receptor stimulation.

Adell A. et al. (1993) J. Neurochem 60: 1673.

14.11 TOLERANCE TO KETAMINE INDUCED BLOCK OF SPREADING DEPRESSION TRANSFERS TO MK-801 BUT NOT TO AP5. A. Rashidy-Pour[1], Z. Motaghedlarijani[1] and J. Bures*, [1]Dept. Physiol., School Med. Sci., Tarbiat Modarres University, Tehran, Iran and Inst. Physiol., Acad. Sci., Prague, Czech Republic.

Blockade of cortical spreading depression (SD) by repeated injections of the NMDA antagonist ketamine (KET) declines due to rapid development of tolerance. The specificity of this effect was examined in 31 rats in which slow potentials of SD waves evoked from occipital cortex were recorded in parietal cortex with a computerized polygraph. Five KET injections (50 mg/kg, i.p.) were applied at 60-75 min intervals. The first one blocked SDs elicited at regular 15 min intervals for 30 min at the near and for 60 min at the far electrode. SD blockade induced by subsequent KET injections gradually weakened and was not detectable after the 5th injection. MK-801 (2.5 mg/kg) failed to block SD in rats with marked KET tolerance, but suppressed SD for more than 2h without KET pretreatment. KET tolerance did not prevent SD blockade in a cortical area superfused with 10^{-3} mol/l AP5. It is concluded that repeated doses of KET may change the NMDA receptor conformation at a site shared by both KET and MK-801. Supported by grant MZCR 7141.

14.12 EFFECTS OF ACUTE COCAINE TREATMENT ON D1 DOPAMINE RECEPTOR.

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Effects of cocaine on D1 dopamine receptors in cortex and striatum were studied under different experimental conditions including chronic, acute and 48 hours withdrawal cocaine treatment. Saturation kinetic studies were carried out by using membrane binding techniques. The D1 antagonist [^{3}H] SCH 23390 (8 to 0.06 nM) was used as a radioligand and the non-specific binding was defined using (+)-butaclamol (1 µM). In order to preclude binding to 5-HT$_2$ sites, 40 nM mesulergine was used.

Significantly lower Bmax values were found in striatum of acutely treated animals when compared to those of the remaining groups while significantly higher Bmax values were found in cortex of acutely treated animal when compared with those of the remaining groups. No differences were found in affinity between cortex and striatum under any of the conditions studied. These data support the idea of a quick response and adaptation of these receptors to cocaine intake as well as a differential response in different dopaminergic systems by mechanisms of "up-regulation" and "down-regulation".

This work has been partially supported by a grant from DGICYT PM91-0058 and FISS 92/0136. María Adoración Candelas is a fellowship of the University of León.

14.13 MODULATION OF $[Ca^{2+}]_i$ BY HIGH-AFFINITY KAINATE RECEPTOR ACTIVATION IN THE HIPPOCAMPUS: ROLE OF VOLTAGE-SENSITIVE Ca^{2+} CHANNELS

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We have recently identified a functionally active presynaptic high-affinity kainate receptor which modulates the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in synaptosomes from the rat hippocampal CA3 subregion (Neurocsi. Lett.185:83. 1995). The receptor is activated by kainate (EC_{50}=0.86 µM), AMPA (EC_{50}=43.04 µM) or domoic acid ((EC_{50}=0.22 µM), and the effects of the agonists are antagonized by CNQX. The effect of kainate on the $[Ca^{2+}]_i$ is not observed in an NMG medium (Na^+ absent), which suggests that the receptor is not permeable to Ca^{2+}. In Na^+ medium, the increase in $[Ca^{2+}]_i$ was inhibited by blockers of the voltage-sensitive Ca^{2+} channels (VSCC), suggesting a contribution of the VSCC to the influx of Ca^{2+} following kainate receptor activation. Thus, the $[Ca^{2+}]_i$ signal obtained in response to kainate relative to the control values was inhibited to 80.4±3.1 % by ω-conotoxin GVIA (ω-CgTx GVIA) (0.5 µM), to 75.3±3.6 % by ω-agatoxin IVA (ω-Aga IVA) (100 µM), whereas ω-CgTx GVIA plus ω-Aga IVA inhibited to 57.3±3.6 % of the control value, indicating that the effects of the two toxins are additive. On the other hand, ω-CgTx MVIIC (100 µM) did not show inhibition additional to that of ω-Aga IVA alone. Thus, we conclude that two main types of VSCC are activated following presynaptic kainate receptor activation: the N-type VSCC (sensitive to ω-CgTx GVIA) and the P- or Q-type VSCC (sensitive to either ω-Aga IVA or to ω-CgTx MVIIC). (Supported by JNICT, Portuguese Research Council).

14.14 IDENTIFICATION OF A NEW COMPONENT OF THE AGONIST SITE OF THE NICOTINIC α7 HOMOOLIGOMERIC RECEPTOR. Pierre-Jean Corringer*, Jean-Luc Galzi, Jean-Luc Eiselé, Sonia Bertrand, Jean-Pierre Changeux and Daniel Bertrand. Neurobiologie Moléculaire, URA CNRS D1284, Institut Pasteur, 25 rue du Docteur Roux, 75724 Paris Cedex 15, France. Département de Physiologie, Centre Médical Universitaire, 1211 Geneva 4, Switzerland.

The acetylcholine binding sites of the *Torpedo* nicotinic receptor is build up by domains of α subunits (principal binding component) and non-α subunits (complementary binding component). In homooligomeric receptors such as α7, each subunit potentially contains both components of the binding site. Comparison of protein sequences suggests that residues γTrp55 and δTrp57 of *Torpedo* receptor labelled by d-tubocurarine correspond to residue Trp54 of chick α7. This residue was mutated in the α7-V201-5HT3 homooligomeric chimaera, which possesses the N-terminal domain of α7, displays α7 nicotinic pharmacology, and for which both equilibrium binding studies and electrophysiological recordings could be carried out in parallel. We found that replacement of Trp 54 by a Phe, Ala or His, causes a progressive increase both in binding affinity and in responses (EC_{50} or IC_{50}) for acetylcholine, nicotine and dihydro-β-erythroidine, without significant modification in α-bungarotoxin binding. Except for Gln 56, comparatively small effects are observed when the other residues of the 52-58 region are mutated into alanine. These data support the participation of Trp 54 in ligand binding, providing evidence for a new "complementary component" of the α7 nicotinic binding site.

14.15 EFFECTS ON HEART RATE MEASURED BY TELEMETRY IN A FEARFUL SITUATION.

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Resident aggression by Long Evans Outbred male rats, was used as a fear stimulus for Wistar Kyoto intruder rats. Intruders were implanted with transmitters (TA11CTA-F40, Data Sciences Int., USA) to measure ECG, temperature and locomotion. Behavioral responses were also recorded. We followed four experimental procedures. In all, the intruders were measured in their home cage during a 60 minute control period before and a 30 minute control period after exposure.

1) The intruder was placed into the residents cage for a 10 minute encounter followed by a 20 minute period in which the intruder was alone in the residents cage. Heart rate increased by ± 35% (n=4), but declined to 50% of the increase, when the resident was removed from the cage. The increase was not only caused by increased locomotion. 2) After 4 weeks the same intruders were again exposed, but without physical contact (i.e. the intruder was placed into a wire cage in the residents cage). Heart rate increased by ± 40%, (n=4), but again rapidly declined as in 1. 3) Naive intruders were placed in the residents cage for 30 minutes, without a resident. Heart rate increased by ± 25% (n=4). 4) After 1 week the same intruders as in 3. were used in a protocol described under 2. Heart rate increased by ± 25% (n=4), but declined when the resident was removed from the cage.

The protocols in which there is no actual physical encounter with the resident (2. and 4.) give a reproducable and stable increase in heart rate. To assure the same level of increase the resident should remain present. This procedure will be used to investigate the effect of anti-panic drugs on heart rate and behavior simultaneously.

14.16 CHARACTERISATION AND MAPPING OF OPIOID RECEPTORS IN BRAIN TISSUE AND IN PRIMARY CULTURES BY MONOCLONAL ANTIBODY OF KAPPA-2-SUBTYPE SPECIFICITY

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The majority of published data can be rendered to kappa-1-subtype opioid receptors e. g. pre-synaptic regulation of transmitter release. The recent molecular cloning results did not solved the problem of kappa-1 and kappa-2 receptor subtypes, because pharmacologically the cloned receptors belong to the kappa-1 subtype.

Our laboratory developed a monoclonal antibody (mAb) with established kappa-2 subtype selectivity (KA8, IgG1,k) (J. Neurochem. 56, 1991, 1887). The mAb shows some agonist character, it can effectively displace opioid ligands in radio assays in frog and in chick brain (Neuroscience 58, 1993, 459). Double immunocytochemistry by this mAb and proper cell-markers showed kappa-opioid receptor-like labelling (κ-2-ORLI) on developing neurons and type-2 astrocytes in primary cultures of chick, rat and human by light and electron microscopy. K-2-ORLI was marking neuronal and astroglial plasma-membrane, ribosomes and polyribosomes, sometimes in close vicinity to the membrane. In neurons κ-2-ORLI was present in dendrites to be associated with micro tubules and in synaptic specializations always post-synaptically.

These results show that kappa-2-opioid receptors may play function in developing and adult neurons and glial cells, however, this can be different from that of the kappa-1-opioid receptors with established pre-synaptic localisation, contrary to the post-synaptic, extra-synaptic and glial expression of kappa-2-opioid receptors presented here. To know this function, however, needs further studies.

14.17 **CALCITONIN GENE-RELATED PEPTIDE (CGRP) AND THE NICOTINIC ACETYLCHOLINE RECEPTOR (nAChR) IN THE PRIMATE PREFRONTAL CORTEX AND IN MEYNERT'S BASAL NUCLEUS.** B. Csillik*, J. Nemcsok, P. Rakic, P. Goldman-Rakic, B. Chase and E. Knyihar-Csillik. Bay Zoltan Institute for Biotechnology, P.O.Box 2337, H-6726 Szeged, Hungary; Section of Neurobiology, Yale University, New Haven, CT, USA; Dept. Biology, Univ. Nebraska, Omaha; NE, USA; Dept. Clin. Neurology, Albert Szent-Györgyi Med. Univ. Szeged, Hungary

Microstructural correlation between CGRP and nAChR was studied in the macaque with light- and electron microscopic immunohistochemical techniques in order to disclose the possibility of a functional linkage similar to that described by Changeux *et al* in the neuromuscular junction. We used a polyclonal antibody (Amersham) to visualize CGRP, two monoclonal antibodies (mAb74.25 and mAb35) to detect the α-subunit of CGRP, and biotinylated α-bungarotoxin (BTX) to reveal BTX-binding proteins. We found a close microtopographical correlation between CGRP-immunoreactive varicous axons and sites of nAChR, both in the prefrontal cortex and in the basal nucleus. Distinct differences between the localization obtained with biotinylated BTX and the two monoclonal antibodies suggest pleiotropy of the nAChR. In addition, in the prefrontal cortex we found a widespread system of CGRP-immunoreactive interneurons, mainly stellate and granular cells , driven by assymmetrical axo-dendritic and axo-somatic synapses and establishing symmetrical axo-dendritic and axo-somatic synapses with pyramidal cells. It is concluded that the micro-topographical relations do not exclude the possibility of a functional linkage between CGRP and nAChR and, that intense CGRP innervation of the prefrontal cortex, provided by a species-specific system of autochthonous CGRP neurons may contribute to the exceptional efficiency of cholinergic innervation of this area, probably related to the mechanism of working memory.

14.18 DISTRIBUTION OF NADPH-d POSITIVE CELLS IN THE HIPPOCAMPUS FOLLOWING NEONATAL X-RAY IRRADIATION INDUCED GRANULE CELL LOSS. B. Czéh[1]*, A.Czurkó[2] and L. Seress[1] Institutes of Physiology[1] and Institute of Behavioral Sciences[2], University Medical School of Pécs, H-7643 Pécs, Szigeti ut 12. Hungary

Nitric oxide (NO) is a novel neuronal messenger, which has been proposed to play a role in CNS development, plasticity, and neurotoxicity. Nitric oxide synthase (NOS) which produces NO from arginine can be detected by NADPH-diaphorase (NADPH-d) histochemistry. NADPH-d positive cells form a subpopulation of GABAergic neurons and are known to be resistant to injury, such as hypoxia or status epilepticus.

Neonatal X-ray irradiation drastically reduces granule cell population in the dentate gyrus, without a significant effect on the pyramidal cells of Ammon's horn. We have found that most NADPH-d positive cells survive irradiation which destroyed 40% of the granule cells. However, 50% of NADPH-d positive cells were lost in those animals where only 20% of granule cells remained. Thus, in the dentate gyrus, the number of surviving NADPH-d positive cells is related to the degree of granule cell degeneration. A further analysis is necessary to describe the axonal arborization of the remaining inhibitory cells. This model allows a detailed examination of whether the target cell loss or the loss of afferents is critical for the survival of local circuit neurons in the hippocampus. The findings will be discussed in connection with possible roles of NO producing cells in neurodegenerative diseases.

14.19 THE INFLUENCE OF PROPRANOLOL AND ORCIPRENALINE ON STRESS-INDUCED ANALGESIA

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It is well known that the stressfull events course analgesia. The aim of this study was to examine the role of ß-adrenergic receptors in stress-induced analgesia.

The experiments were performed on male Wistar rats aging 3 to 4 month. The analgesia was measured by a tail-flick method (bulb 48W). Sterss was induced by unescapable electric footshock lasting 10 min. Saline, propranolol (2 mg/kg) and orciprenaline (2 mg/kg) were injected ip 15 min before stress.

In controls, the maximal analgesic effect were found 20 min after stress. Reaction time returned to control values one hour after stress. In propranolol treated animals, stress-induced analgesia was significantly reduced 20 and 40 min after stress. Compared to the control, orciprenaline significantly enhanced the stress-induced analgesia 40 min after stress. Stress caused the functional engagement of pineal gland. In orciprenaline treated animals occured the signs of high stimulated activity of pineal gland, while in propranolol treated animals the signs of activity supresion could be seen. We concluded that ß-adrenergic receptors are involved in stress-induced analgesia and this is in a part mediated through the pineal gland.

14.20 SEROTONIN INCREASES STRIATAL DOPAMINE RELEASE IN VIVO BY TWO DISTINCT MECHANISMS: INVOLVEMENT OF DOPAMINE UPTAKE SITES AND 5-HT$_4$ RECEPTORS. P. De Deurwaerdère*, N. Bonhomme, G. Lucas, M. Le Moal and U. Spampinato, Université de Bordeaux II, INSERM U. 259, Domaine de Carreire, 33077 Bordeaux Cedex, France.

In the present study we investigated in vivo the mechanisms by which serotonin (5-HT) enhances striatal dopamine (DA) release by using intracerebral microdialysis. A probe (CMA11/3mm) was implanted into the right striatum of halothane anesthetized rats and perfused with an artificial CSF (NaCl 145, KCl 2.7, $CaCl_2$ 1.2, $MgCl_2$ 1 mM, pH=7.4) at a constant flow rate of 2µl/min. After a stabilisation period (90 min), 15 min fractions were analysed by HPLC-ECD. Drugs were locally applied by means of the microdialysis probe.

1, 3 and 10 µM 5-HT increased extracellular DA in a concentration-related manner by about 65, 190 and 440% respectively. Such effects were reduced by 50% either in the presence of 1 µM tetrodotoxin (TTX) or when Ca++-ions were removed from the artificial CSF. The DA uptake blocker nomifensine (0.1 µM) significantly lowered (~50%) the increase in DA outflow induced by 3 µM 5-HT. Furthermore, 1 µM nomifensine coperfused with 1 µM TTX abolished the increase in DA outflow produced by 1 and 3 µM 5-HT and strongly reduced that induced by 10 µM 5-HT. In addition, 1 µM GR125487, a potent and selective 5-HT$_4$ receptor antagonist, was able to decrease by about 50% the effect induced by 1 µM 5-HT, whereas it had no action in the presence of TTX.

These data demonstrate in vivo the existence of two components in the facilitatory control of striatal DA outflow exerted by 5-HT: the first one, Ca++ and TTX-insensitive, is related to DA uptake sites; the second one, Ca++/TTX-sensitive, is mediated by a postsynaptic mechanism involving 5-HT$_4$ receptors.

14.21 DEXAMETHASONE PREVENTS EEG AND BEHAVIOURAL EFFECTS INDUCED BY CENTRALLY ADMINISTERED ß-ENDORPHIN IN RABBITS. A. Di Giannuario *, S. Pieretti, A.Capasso [1], L. Sorrentino [1] & A. Loizzo. Laboratory of Pharmacology, Istituto Superiore di Sanita', and [1] School of Pharmacy, Univesity of Salerno, Salerno Italy.

We recently evidenced that dexamethasone prevented epileptiform bursting induced by the selective agonist for mu opioid receptors, DAMGO in rat hippocampal slices. Thus in the present study we firstly studied the electroencephalographic (EEG) and behavioural effects induced by intracerebroventricular (i.c.v.) administration of ß-endorphin in rabbits, in the presence and absence of the selective mu antagonist ß-funaltrexamine (ß-FNA) and the selective delta antagonist naltrindole (NTI) (administered i.c.v., both at 20 nmol, respectively 20 hr and 15 min before ß-endorphin). Finally the influence of dexamethasone on ß-endorphin effects was investigated. Under pentobarbital anesthesia, male "Fauve de Bourgogne" rabbits were implanted with a cannula for i.c.v. drug administration, and cortical and hippocampal electrodes for the EEG recording session. ß-endorphin (30 nmol,i.c.v.) induced EEG nonconvulsive limbic seizures, EEG background and behavioural alterations. Both ß-FNA and NTI prevented ß-endorphin-induced limbic seizures while only ß-FNA antagonized tardive EEG and behavioural alterations induced by ß-endorphin. Dexamethasone prevented ß-endorphin-induced effects when administered intravenously (3 mg/kg, i.v.) 30 min before. Dexamethasone inhibition was blocked by a protein synthesis inhibitor cycloheximide, injected i.v. (12 mg/kg) 90 min before dexamethasone. Our results suggest that dexamethasone influence on mu-delta opioid receptor activation may be mediated by a protein synthesis mechanism.

14.22 PHARMACOLOGICAL IN VITRO CHARACTERIZATION OF GUANIDINOSUCCINIC ACID AS AN ENDOGENOUS N-METHYL-D-ASPARTATE RECEPTOR AGONIST. M. Diltoer*, M. Chowdhury, Ph. Lebrun, M. DeRidder, R. D'Hooge, P. DeDeyn, F. Colin and J. Manil. Lab. Neurophysiology, Vrije Universiteit Brussel (VUB) Laarbeeklaan 103, B-1090 Brussels, Belgium.

Guanidinosuccinic adid (GSA), an endogenous metabolite accumulating in cerebrospinal fluid of uremic patients, has close chemical relationship with L-aspartic acid and N-methyl-D-aspartate (NMDA). Therefore GSA may be involved in the development of symptoms of uremic encephalopathy as memory loss and convulsions.

We investigated *in vitro* the effects of tonic application (40 minutes) of GSA on the field potentials of pyramidal neurons in the CA1 region of 300 µM slices of rat hippocampus, evoked by stimulation of the Shaffer collaterals.

GSA mimiced the effects of NMDA. GSA (62.5 and 125 µM), induced a dose dependent long-term potentiation of the response (GSA-LTP) antagonized by D-AP5, MK801 and a high extracellular Mg^{++} concentration. GSA-LTP occluded the high frequency stimulation LTP (HFS-LTP). At 250 µM and higher GSA induced epileptiform discharges and depression of the responses through membrane depolarization which was nevertheless followed by a GSA-LTP after washout. At 1 mM GSA, a slow spontaneous recovery from depression of the AMPA-response was observed due to a slow desensitization of the NMDA-receptors. Glycine at 10 µM potentiated the effect of GSA and 7-Cl-kynurenic acid antagonized dose dependently the effect of GSA.

We concluded that occlusion of HFS-LTP by GSA-LTP may contribute the memory deficits and that GSA-LTP can facilitate convulsions both observed in uremic encephalopathy.

14.23 INFLUENCE OF IONIZING RADIATION AND RADIOPROTECTOR WR-2721 ON THE BRAIN CATECHOLAMINES CONTENT IN RATS.

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Ionizing radiation elicits a variety of behavioral decrements. Radioprotector WR-2721 also produces behavioral toxicity reducing motor activity and aggravating rather than attenuating radiation-induced performance decrements. Recently, we have shown that behavioral effects of WR-2721 might be a consequence of its depleting action on brain catecholamines content. The aim of this study was to establish the changes in the content of brain dopamine (DA) and noradrenaline (NA) in irradiated (9 Gy of γ-rays), unprotected rats vs those protected by WR-2721 (300 mg/kg ip, 20 min before irradiation). The brain catecholamines content was determined at 4 hrs, and at 1, 2, 3, 4, 5, 7 and 15 days after irradiation. It was shown that in the first 24 hrs after irradiation significant decrease in both DA and NA brain content was noticed only in rats pretreated by WR-2721. Such changes in the radiation-only group were observed not before two days after irradiation. In the further postirradiation course decrease in brain catecholamines was more pronounced in unprotected vs WR-2721-protected animals. Moreover, in the group pretreated by WR- 2721 normalization of brain catecholamines content occured on the day 4 after irradiation, and in the unprotected group three days later. These results suggest that known behavioral decrements in the irradiated animals protected by WR-2721, in the first hours after irradiation, might be a consequence of brain catecholamines depletion caused by the protector alone.

14.24 THE SEROTONERGIC INNERVATION OF THE VISUAL LAYERS OF THE MATURE AND DEVELOPING RAT SUPERIOR COLLICULUS. I.Dori*[1], A.Dinopoulos[1] and J.G.Parnavelas[2], Dept.Anat., Sch.Vet.Med., Univ.Thessaloniki, Thessaloniki 54006, Greece[1], Dept.Anat., Univ.Coll.London, London WC1E 6BT, U.K.[2]

The serotonergic innervation of the mature and developing rat superior colliculus (SC) was examined with light and electron microscope immunocytochemistry. At birth, serotonin (5-HT)-immunoreactive fibers were mainly distributed in the deep layers. The superficial, visual, layers were only sparsely innervated. In the subsequent weeks, the density of the 5-HT innervation increased and the adult pattern was attained by the end of the third postnatal week. Electron microscopical analysis of the visual layers showed that 5-HT-containing axonal varicosities formed predominantly symmetrical synaptic contacts, mainly with dendritic shafts, throughout postnatal life. Preliminary counts showed that the proportion of labeled varicosities forming synapses increased from birth until the end of the first week, but then declined markedly in the subsequent two weeks. Exuberant synapses formed by 5-HT axons during development is not a feature unique to the SC. There is now evidence that such synapses occur also in other brain areas of the rat, as well as in other species. Similar changes of the 5-HT system in other brain areas have been associated with neuronal maturation, which implies that 5-HT may participate in the morphogenesis of the rat SC.

14.25 INVOLVEMENT OF NMDA AND AMPA TYPE GLUTAMATE RECEPTORS IN SEGMENTAL SPINAL REFLEXES; AN ANALYSIS IN RATS.

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Effects of different competitive and non-competitive excitatory amino acid (EAA) antagonists were tested on various ventral root reflex components in spinal rats, in order to determine the involvement of EAA receptor subtypes in the spinal reflex transmission. The applied drugs were: CPP and MK-801 as NMDA antagonists; NBQX and GYKI 52466 as AMPA/kainate type antagonists. The studied reflex components were: the monosynaptic- (MSR), the disynaptic- (DSR) and the polysynaptic (PSR) reflex potential (up to the poststimulus time of 10 ms) as well as the late asynchronous ventral root reflex discharge (RD, 10-500 ms poststimulus time) recorded from the L_5 ventral root after stimulation of the L_5 dorsal root by single shocks. PSR and RD components evoked by train of five stimuli were also studied. In contrast with previous suggestions, i.e. that NMDA receptors would mediate PSR and AMPA/kainate receptors would mediate MSR, we have found that both subtypes are involved in generation of all components. Although there were some relative differences in antagonist sensitivities of various components, AMPA antagonists could abolish completely all the studied reflex components while NMDA antagonists, which inhibited slightly also the MSR, yielded only partial inhibition of all of them. In conclusion, AMPA receptors play a fundamental while NMDA receptors play a supplementary role in the spinal reflex transmission. Contribution of NMDA receptors gains more importance in the case of longer latency components and train stimulation, hence it seems to be dependent on firing patterns rather than on specific pathways.

14.26 OPIOID REGULATION OF THE SENSORIMOTOR CORTEX ACTIVITY UNDER SATIETY AND FOOD DEPRIVATION.

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We focused our work to study neuronal activity of sensorimotor cortex during neuropeptide beta - endorphine microiontophoretic application in hungry and satiated rabbits. The results obtained showed that in the group of satiated rabbits most of the neurons (85.8%) had a frequency of activity up to 10 imp/s, with an average variation coefficient of interimpulsive intervals of 107%. Beta-endorphine inhibited 39.3% and activated 17.8% registered neurons. The increase of discharges regularity was registered in 35.7% and its decrease in 25% of neurons. In the group of hungry rabbits (72 hours) we observed the increase of both, frequency and average variation coefficient of interimpulsive intervals. In this conditions beta-endorphine inhibited 32.2% and activated 9.7% neurons. The increase of discharges regularity was registered in 32.2% and its decrease in 25.8% neurons. The obtained results showed that sensorimotor cortex is involved in detection of examined functional states, which is partly realized through the opioid mechanism.

14.27 IN VITRO AND IN VIVO ACTIONS OF PROMETHAZINE SULFOXIDE.

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Promethazine sulfoxide (PS), the main metabolite of promethazine, was chemically synthesized and crystallyzed. Alternatively, PS was obtained with a nearly quantitative yield as a product of promethazine and hydrogen peroxide in a peroxidase-catalyzed reaction. PS is able to inhibit such a reaction which was followed spectrophotometrically, luminometrically, polarographically and potentiometrically. PS, unlike promethazine, is devoid of antioxidant effect on rat brain synaptosomes, has no photosensitizing effect and exhibits a neuroleptic effect slightly lower but not significantly different from that of promethazine. We were able to work out a mechanism for the peroxidase-catalyzed sulfoxidation of promethazine which involves a strong oxygen consumption and the production of intermediate cation radical species (phenazathionium and promethazine singlet).

The present results may contribute to the understanding of the neuroleptic action of phenothiazines and, in particular, to that of promethazine whose sulfoxidation is inhibited by ascorbic acid and reduced glutathione. PS also appears to act as an oxidizing agent which can replace hydrogen peroxide in peroxidase-catalyzed reactions.

14.28 KAINATE RECEPTOR SUBUNITS GLUR6 AND GLUR7 IN GLIAL CELLS OF THE ADULT WHITE MATTER.

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Glutamate, the major excitatory neurotransmitter of the brain, activates a family of receptors which has been classified into four major classes, namely AMPA- and kainate-preferring, NMDA and metabotropic receptors. Glial cells, like neurons, possess non-NMDA receptors which may be involved in brain signaling. We have recently shown that astrocytes of the adult white matter express AMPA receptors (Matute and Miledi, 1993, Proc. Natl. Acad. Sci. 90:3270-3274). Here, we describe the presence of kainate-preferring receptor subunits in astrocytes and oligodendrocytes of the *corpus callosum*, *fornix* and *optic nerve* from the adult bovine brain. Vibratome sections of the three areas were processed for conventional immunoperoxidase techniques using a monoclonal antibody that recognizes GluR5, GluR6 and GluR7 subunits (Pharmingen). To identify GluR5/6/7 immunoreactive glial cells, we used double labeling experiments with antibodies to glial fibrillary acidic protein and to 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) as astrocyte and oligodendrocyte cell type markers respectively. GluR5/6/7+ astrocytes had a stellate or elongated shape and displayed many radial processes, while GluR5/6/7+ oligodendrocytes formed tiers of rounded cells, a typical feature of interfascicular oligodendroglia. A large subpopulation of CNPase+ cells showed immunoreactivity to GluR5/6/7 antibody whereas almost all astrocytes were labeled. To elucidate which of the three kainate receptor subunits recognized by the GluR5/6/7 antibody were indeed expressed in the areas studied, we carried out RT-PCR analysis using specific oligonucleotide primers. The results showed that GluR6 and GluR7, but not GluR5, receptor subunits are present in glial cells of the white matter. Taken together, these findings indicate that astrocytes and oligodendrocytes in the adult brain express GluR6 and GluR7 kainate-preferring receptor subunits and thus, they provide further evidence for the molecular diversity of glutamate receptors in glial cells. Supported by D.G.C.Y.T (grant PM92-244). J.M.G.-B. holds a graduate student fellowship from the Gobierno Vasco.

14.29 SIMULTANEOUS MODULATION OF SEROTONIN, DOPAMINE AND NORADRENALINE RELEASE IN FRONTAL CORTEX OF FREELY-MOVING RATS BY THE NOVEL 5-HT_{1A} RECEPTOR LIGAND, S 15535.

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Inasmuch as cortical monoaminergic transmission is implicated in disorders of mood, we examined the influence of the novel, selective 5-HT_{1A} receptor ligand, S 15535, upon the release of dopamine (DA), serotonin (5-HT) and noradrenaline (NE) in the frontal cortex of single, awake rats. Rats were implanted (AP: + 2.2, L: ± 0.6, DV: - 0.2) with a guide cannula and 5 days later a CMA/11 probe (4mm length, 0.24 mm O.D.) was positioned and perfused at 1 µl/min with Ringers' solution. Twenty µl samples were diluted with 20µl of phase (NaH_2PO_4: 75 mM, EDTA: 20 µM, $C_{10}H_{21}SO_3Na$: 1mM, MeOH: 17.5%, TEA 0.01%, pH: 5.70) and analysed by HPLC with a column (hypersil, 5 µm, C_{18}, 150x4.6 mm) thermostated at 45°C and a coulometric detector (ESA 5014, E_1 = - 90mV and E_2 = + 280mV). The D_2- agonist, apormorphine (0.63 mg/kg, s.c.) and the D_2- antagonist, haloperidol (0.63), respectively, *decreased* and *increased* DA release and the α_2- agonist (+)-medetomidine (0.16) while the α_2- antagonist, RX 821,002 (0.63), respectively *diminished* and *augmented* NE release. The 5-HT_{1A} antagonist, WAY 100,135 (10.0) did not modify release of 5-HT, DA or NE whereas the 5-HT_{1A} agonist, 8-OH-DPAT (0.16), decreased levels of 5-HT and increased those of DA and NE. S 15535 (5.0), which acts as an agonist and antagonist at pre- and post-synaptic 5-HT_{1A} sites, respectively, reduced the release of 5-HT, and increased the release of DA and NE. This increase in DA and NE release was mimicked by the 5-HT uptake inhibitor, fluoxetine (10.0), which also increased 5-HT release. In conclusion, cortical DA, NE and 5-HT release is controlled by D_2-, α_2- and 5-HT_{1A}-autoreceptors, respectively, the latter of which show low tonic activity. The ability of S 15535 to simultaneously decrease 5-HT release yet enhance that of DA and NE may be related to its distinctive profile of anxiolytic and antidepressant properties.

14.30 DISCRIMINATIVE STIMULUS PROPERTIES OF ELTOPRAZINE

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Eltoprazine has been developed for its anti-aggressive properties. Previous studies have shown that these effects are probably mediated via 5-HT_{1A} and 5-HT_{1B} receptors, but it was not possible to antagonize eltoprazine's behavioral effects. Recently, new putative 5-HT_{1A} and 5-HT_{1B} receptor antagonists have been developed. In a drug discrimination procedure we tested whether these compounds are able to antagonize the stimulus properties of eltoprazine, and also tested compounds with known affinity for 5-HT_{1A} and 5-HT_{1B} receptors. Rats were trained in a two lever operant procedure to discriminate eltoprazine (1.0 mg/kg p.o.) from water. Eltopra-zine generalized to the 5-HT receptor agonists batoprazine, 1-(1-naphthyl)piperazine (1-NP) and 1-(3-chlorophenyl)piperazine (mCPP). Moreover, these drugs increased response rates, indicative of 5-HT_{1B} receptor activation. The 5-HT_{1A} receptor agonist flesinoxan only partially substituted and reduced response rates profoundly, suggesting that 5-HT_{1A} receptors are of minor importance in the eltoprazine cue. The putative 5-$HT_{1A,1B-,1D}$ receptor agonist GR46611 did not generalize to eltoprazine, and the putative 5-$HT_{1B,1D}$ receptor antagonist GR127935 did neither substitute for nor antagonize the eltoprazine cue. Alprenolol partially antagonized, but methiothepin, mCPP and the selective 5-HT_{1A} receptor antagonist WAY-100635 failed to antagonize eltoprazine. These results show that the stimulus properties of eltoprazine are probably mediated by 5-HT_{1B} receptors, however, it is still not possible to completely antagonize this 5-HT_{1B} cue.

14.31 MOLECULAR PHARMACOLOGY OF THE RAT SYNAPTIC VESICLE MONOAMINE TRANSPORTER (rVMAT2)

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Two distinct transport activities participate in synaptic transmission by classical transmitters. The first one is located in the presynaptic plasma membrane and takes up released transmitter from the synapse aiding to terminate the action and recycling of neurotransmitter. In contrast, the other transport activity involves the storage of neurotransmitter into synaptic vesicles. Only recently it has been possible to characterize at molecular level the structure of these transporters. The nucleotide sequence of the isolated cDNA predites a protein with 12 transmembrane domains, acting as a H^+ amine exchanger, using the inwardly acidic pH gradient generated by the ATPase to drive uptake. Recently it has been presented the characteristics, distribution and pharmacology of the human synaptic vesicle monoamine transporter (hVMAT2) with high similarity to the rat brain synaptic vesicle monoamin transporter (rVMAT2) -88% of nucleotide identity-. Besides the high homology of the sequences identified, there are several interesting changes between boths. In order to investigate the effect of the mismatch between the human and the ratVMAT2 in their pharmacological profile, rVMAT2 was functionally identified and characterized either in striatal synaptosomal preparations and after transfection of pCDNAI/-rVMAT2 into COS-7 cells. [^{3}H]TBZOH binding showed up specific binding, saturable and of high affinity when we compare with control experiments. The rank order of [^{3}H]TBZOH for different substrates followed the previous stablished order for the hVMAT2, that is 5HT > dopamine > norepinephrine > histamine. These results demonstrate that there is not difference in the potency of various substrates to inhibit the binding of [^{3}H]TBZOH neither striatal synaptosomal preparations nor transfected COS cells and confirm the no relevance of the mismachts in their sequences.

14.32 EFFECT OF EXCITATORY AMINO ACID RECEPTOR AGONISTS ON THE RELEASE OF THE NITRIC OXIDE PRECURSOR ARGININE FROM RAT CEREBELLAR SLICES.

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Arginine (Arg), the nitric oxide (NO) precursor, has been found to be released following stimulation of the white matter in cerebellar slices (Hansel et al., 1992) and stimulation of sensory afferents in rat thalamus in vivo (Do et al., 1994). NO synthesizing enzymes, NO precursor and metabolites (citrulline and argininosuccinate) are reported to be localized in different cells (in cerebellum: granule and basket cells for NO synthase and Bergman Golgi epithelial cells for Arg), suggesting a considerable shuttling of NO intermediates. The Arg release may represent its transfer between two cellular compartments, in order to supply NO synthase with its substrate. To investigate the mechanism involved in this shuttling of Arg, released materials from cerebellar slices and cortical astrocytes which were preincubated with [^{3}H]-Arg were analyzed for labelled and endogenous amino acids. In cerebellar slices, glutamate (500µM), AMPA and kainate (100µM) increased significantly the extracellular level of labelled Arg, an effect which could be inhibited by CNQX. Furthermore, it was unaffected by NMDA (100µM), whereas tACPD (100µM) gave rise to a delayed Arg increase. Moreover, in astrocyte cultures, an 80% increase in exogenous Arg concentration was also induced by 500µM glutamate and 300µM AMPA. NMDA (300µM) had no effect.
These results support the involvement of non-NMDA and metabotropic receptors, probably located on glial cells, in the increase in extracellular Arg concentration which is occuring upon selective pathway stimulation both in vitro and in vivo. It could thus be proposed that NO transmission and NO synthesis may be based on the transfer of Arg from glia to neurons which is dependent on activation of excitatory amino acid receptors on glial cells.

14.33 PEPTIDERGIC INNERVATION OF SKIN IN RETT SYNDROME

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Rett syndrome (RS), a severe neurological disorder limited to females, is related to the degeneration of a few neuron systems within specific brain regions. However there are several clinical symptoms such as hypoalgesia, distal hypotermia and trophic disturbances of the skin at the distal ends which suggest an involvement of the peripheral nervous system (PNS) also. Peptidergic nerve fibers in the skin, are involved in functional roles such as nociception, cutaneous blood and sweat production. Therefore an immunocytochemical study has been carried out in order to reveal any pathological change in the density and distribution of peripheral nerve fibers immunoreactive (IR) for several peptides (SP,CGRP,NPY), in the skin of patients with RS. An indirect immunofluorescence method was employed on cryostat sections of diagnostic skin biopsies from patients (9 cases - average age 8 years) with classical RS (stage II - III) and from autistic patients (10 cases - average age 7 years).used as controls. The relative number of IR nerve fibers for each antigen was assessed, subjectively by two observers unaware of the patients groups, and graded arbitrarily in relation to epidermis, dermis, blood vessels, sweat glands, hair follicles in the skin. The IR nerve fibers were dramatically reduced in the skin from all patients with RS but not in control skins:, These findings show that peptidergic nerve fibers of sensory and autonomic origin are dramatically reduced in the skin of patients with RS and can explain the sensory and autonomic disturbances present in the advanced stages of syndrome. In the same time.the involvement of the PNS, in the syndrome is also confirmed.

14.34 **CHANGES IN THE EXPRESSION OF γ_{1L} AND γ_{1s} $GABA_A$ RECEPTOR SUBUNITS IN THE AGING RAT BRAIN.**

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Aging-related alterations in both protein and mRNA expression of γ_{2s} and γ_{2L} $GABA_A$ receptor subunits have been observed in several rat brain areas . Subunit-specific antibodies to γ_{2s} and γ_{2L} as well as a riboprobe to the large intracellular loop of γ_2, which recognizes both γ_{2s} and γ_{2L} mRNAs, in conjunction with a computerized image analysis system were used* for quantitative immunocytochemistry and *in situ* hybridization. In addition, specific oligonucleotide probes to γ_{2s} or γ_{2L} mRNA were used for quantitative dot blot hybridization. A large increase in the number of heavily immunostained neurons with anti-γ_{2L} antibody was detected in the cerebral cortex (113%) and subiculum (89%) of old rats. No significant aging-related change in γ_{2L} mRNA was observed in the cerebral cortex. However, γ_{2s} immunostaining was decreased (12%) as well as the expression of γ_{2s} mRNA (9-24%) in the cerebral cortex of old rats. In the cerebellum, aging-related decreased expression of both γ_{2s} (24%) and γ_{2L} (23%) peptides was also accompanied by decreased expression of γ_{2s} (16-38%) and γ_{2L} (24%) mRNAs respectively. The most important decrease of γ_{2s} (48%) and γ_{2L} (20%) proteins was revealed in the molecular layer of the cerebellum. The observed aging-related changes in the expression of $GABA_A$ receptor subunits might lead to altered $GABA_A$ receptor subunit composition.

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14.35 **POSTNATAL DEVELOPMENT OF THE AMPA GLUR2/3 RECEPTORS IN RAT VISUAL CORTEX.** I. Gutiérrez-Ibarluzea*, J.L. Mendizabal-Zubiaga, E. Arana-Arri, C. Reblet and J.L. Bueno-López. Department of Neurosciences. University of the Basque Country. E-48940 Leioa, Bizkaia, Spain.

Excitatory amino acid receptors play a critical role in neurogenesis, and in developmental and adult synaptic plasticity. The non-N-methyl-D-aspartate receptors seem to be related to the dendritic and axonal outgrowth and to the synaptogenesis, at least in hippocampal circuits. Herein, we report the patterns of immunoreactivity of the AMPA GluR2/3 receptor subunits in the rat visual occipital cortex during the postnatal development.

Wistar rats, from postnatal day 0 (P0) to fifteen weeks (P85) were perfused through the heart with 4% buffered paraformaldehyde and 0,2 % picric acid and their brains were cut with cryotome in 50 µm coronal sections. The sections were then immunocitochemically incubated using a well-established monoclonal antibody against the AMPA-glutamate receptor subunits GluR2/R3. In a first step, from P0 to P7, the immunoreactivity did not exhibit the laminar distribution showed at P13 similar to that in the adult. In addition, the immunoreactivity was not circumscribed to the neuronal somata and proximal dendrites as in the adult. However, the horizontal somata cells of the deepest part of layer VI showed an intense immunoreactivity which began at P4/P7 and continued till the adulthood. In a second step, from P7 to P10 the big somata cells of layer V began to show a conspicious immunoreactivity and the adult staining pattern became more and more defined. Finally, at P13 the laminar distribution of the immunoreactivity was similar to that in the adult.

Thus, we found differences in the immunoreactivity against the AMPA-glutamate receptor subunit GluR2/R3 during the postnatal development in the rat visual occipital cortex. Indeed, there seems to be an inside-out pattern in that immunoreactivity.

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14.36 **REDUCTION OF SHUTTLE-BOX DEFICIT BY (-)DEPRENYL**

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Dopamine receptor agonists have been reported to be effective in depression states of experimental animals induced by inescapable foot shocks. They have reversal effect on the shuttle-box deficit in the learned helplessness paradigm.

(-)Deprenyl the only selective inhibitor of MAO-B enzyme widely used in clinical practice in the treatment of Parkinson's disease facilitates the nigrostriatal dopaminergic tone and it has reducing effect on the number of cortical beta-adrenoceptors similarly to the action of most putative antidepressants. The effect of (-) deprenyl on reduction of escape failure was examined in doses 0,25 mg/kg and 1 mg/kg sc. treatment on 5 consecutive days. The significant anti-depressant activity of (-)deprenyl in daily dose 1 mg/kg sc. was achieved in learned helplessness paradigm of rats, without increasing the number of intersignal reaction.

14.37 PROPERTIES OF AMPA RECEPTORS EXPRESSED IN CULTURED CEREBELLAR GRANULE CELLS. N.J. Hack*, A. Borgdorff, W.J. Wadman and R. Balázs. Netherlands Institute for Brain Research and University of Amsterdam, Amsterdam, The Netherlands.

The survival of immature cerebellar granule cells *in vitro* is promoted by excitatory amino acids (EAAs). With maturation the cells become vulnerable to EAAs, especially to NMDA and kainate, by 9 days *in vitro*. In the same time, the sensitivity to AMPA remained very low and was due to the characteristic desensitisation of the AMPA receptor since cyclothiazide (a blocker of receptor desensitisation) rendered cells vulnerable to AMPA. However, even under these conditions, AMPA induced only 30% cell loss at 9 DIV (vs 80% KA toxicity). However, vulnerability increased further reaching a maximum by 16 DIV (65% cell loss). Since cellular responses to AMPA depend so dramatically on the maturational stage of granule cells we investigated whether the increase in AMPA induced toxicity between 9 and 16 DIV was related to developmental changes in AMPA receptor properties and/or density. Assessing $^{45}Ca^{2+}$ influx with fura-2 $[Ca^{2+}]_i$ imaging we characterised pharmacologically the cellular responses to AMPA. Indirect routes of Ca^{2+} entry activated by AMPA contributed significantly to the $^{45}Ca^{2+}$ influx, these included NMDA receptors, voltage sensitive calcium channels and Na^+/Ca^{2+} exchange. However, nearly one fifth of the total $^{45}Ca^{2+}$ influx remained unaccounted for and this estimate was similar under Na^+ free conditions. This observation suggested that a proportion of the Ca^{2+} flux passes through the AMPA receptor proper. We observed no difference in $^{45}Ca^{2+}$ influx upon AMPA receptor activition between 9 and 16 DIV. However, the imaging data showed a dramatic increase in $[Ca^{2+}]_i$ following AMPA receptor stimulation at 16 DIV compared with 9 DIV, suggesting that a decrease in the ability of cells to maintain Ca^{2+} homeostasis contributes to the increase in vulnerability with age.

14.39 **EFFECTS OF GLYCINE ANTAGONISTS - ACTING AT THE STRYCHNINE-INSENSITIVE GLYCINE RECEPTOR - IN THE INFERIOR COLLICULUS**

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Glutamate and aspartate are the major excitatory transmitters within the ascending auditory system. In the inferior colliculus (IC) acoustically induced excitation is predominantly mediated by NMDA- and non-NMDA-receptors (Faingold et al., Hear. Res. 1989) while glycine has inhibitory effects.

Since the NMDA-receptor complex comprises several modulatory sites we were interested whether antagonists, acting at the strychnine-insensitive glycine recognition site of the NMDA-receptor, affect acoustically induced excitation in the central nucleus of the IC.

In the present study multibarrel electrodes were used for extracellular recordings and iontophoretic application of 5,7-dichlorokynurenic-acid, ACEA 1021 and (+)HA-966. All three antagonists reduced acoustically induced excitation although to different extents. 5,7-dichlorokynurenic-acid was the most effective compound. It reduced acoustically induced excitation by 83% at an ejection-current of -120 nA. ACEA 1021 reduced acoustically evoked responses by 68% at the same current. (+)HA-966 reduced acoustically evoked excitation only at ejection-currents higher than -80 nA.

In summary, glycine-antagonists reduced acoustically induced excitation which indicates a contribution of NMDA-receptors to acoustically evoked excitation. In addition, 5,7-dichlorokynurenic-acid and ACEA 1021 were reported to be potent and selective glycine antagonists. Therefore the failure to completely block acoustically induced excitation further indicates that the response is NMDA- and non-NMDA-receptor mediated. Furthermore, we conclude that glycine exhibits a dual role in the IC: on the one hand by acting on the NMDA-receptor in mediating excitation and on the other hand as an inhibitory transmitter.

14.40 HYPOTHALAMIC APPLICATION OF NITRIC OXIDE INDUCES RELEASE OF CENTRAL VASOPRESSIN AND CORTICOTROPIN RELEASING FACTOR. T.F.W.Horn*, F.E.Bloom and J.Raber, The Scripps Research Institute, 10666 N. Torrey Pines Rd., La Jolla, CA 92037, U.S.A.

Nitric oxide (NO) may modulate the central and peripheral release pattern of Arginine Vasopressin (AVP) and Corticotropin releasing factor (CRF). However, recent studies with various NO-donor substances or NO-synthase inhibitors by differing routes reported contrary effects of NO on AVP release. Therefore we investigated the direct effect of NO-containing perfusion buffer (gassed with 5% NO/95% N_2) on AVP and CRF release from hypothalamic slices in an *in vitro* superfusion paradigm (samples collected at 15-min intervals). After a 90-min wash period, the first 15-min control sample was taken and the perfusion buffer switched to NO-containing medium for two consecutive sample periods followed by a final control period. This sampling procedure was repeated after 30 min. NO induced a significant increase in AVP-release during both NO-pulses. CRF release was increased during the second pulse of NO only. The effect was blocked in the presence of 10 mM cobalt chloride, indicating the involvement of Ca^{2+} or 50 µM dandrolene, an inhibitor of intracellular calcium mobilization. Hemoglobin (100 µg/ml) acting as a NO-scavenger abolished the effect of NO on both, AVP and CRF. The NO-induced AVP release is not required for the later changes in CRF since the same delayed effect of NO was seen in AVP- deficient Brattleboro rats. Furthermore, microdialysis with NO containing medium within the paraventricular (PVN) and supraoptic nucleus (SON) of urethane-anaesthetized rats and subsequent analysis of the perfusates for AVP was performed to confirm these results *in vivo*. 30-min microdialysis samples from both, PVN and SON displayed increased levels of AVP during perfusion with NO-containing medium as compared to control perfusions. Our data provide the first direct evidence that NO can act locally as a positive modulator of central AVP release. (Supp. by MH47680, HFSPO, DAAD)

14.41 LONG TERM EXPOSURE TO GLUTAMATE RECEPTOR AGONIST AND ANTAGONIST ALTERS THE SUSCEPTIBILITY OF HIPPOCAMPAL SLICE CULTURE TO EXCITOTOXIC DAMAGE. B. Jakobsen* and J. Zimmer, PharmaBiotec, Dept. of Anatomy and Cell Biology, University of Odense, Denmark

Glutamate is the predominant excitatory neurotransmitter in the mammalian central nervous system. The physiological responses to glutamate are mediated by several different receptor subtypes that are characterised by their individual preferential responses to different glutamate agonists. Experimental data indicate that glutamate receptors are involved in the ontogenetic development of neurons and the activity-dependent synaptic plasticity of the adult brain. Excessive activation of NMDA, kainate acid (KA) and α-amino-5-hydroxy-methyl-4-isoxazole propionic acid (AMPA) receptors are, however, also implicated in the pathophysiology related to acute and chronic brain injury.

In the present study long term treatment of rat hippocampal slice cultures by glutamate receptor ligands was used to explore inducible changes in receptor mediated neurotoxicity

Hippocampal tissue from 5 day old rats was cut into 350-µm-thick slices, embedded in a plasma-thrombin clot on a glass coverslip and cultured by the roller-tube methoed, which preserve the normal basic connective and cellular organisation of the cultured tissue.

When 4 weeks old cultures were acutely exposed to a high dose of KA (3µM), there was a selective loss of the CA3 pyramidal cells. If, however, similar cultures were exposed from day 4 and onwords until 4 weeks in vitro to a low dose of KA (2µM) (which does not normally cause neuron loss) an acute high dose of KA had no apparent toxic effect. A similar long term treatment of the cultures from day 4 with the competetiv KA/AMPA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX), reversed the situation. Now even the low dose of KA resulted in a significant loss of CA3 pyramidal cells. The susceptibility of the cultures to KA could also be changed by hyperthermia. Cultures are normally cultured at 36•C, but can survive temperatures of 41-42•C. At this temperature even the low dose of KA did, however, kill CA3 pyramidal cells. When mature cultures first were exposed to the high temperature and then 5 days later exposed to an acute high dose of KA, they did, however, become resistant.

It is concluded that the sensitivity of hippocampal neurons to the glutamate agonist KA, are modifyable by chronic long time exposure to low doses of KA and NBQX and by high temperatures.

14.42 THE EFFECTS OF DOPA BLOCKING AND STIMULATING AGENTS ON GASTRIC STRESS-ULCER FORMATION IN RATES

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Dopaminergic and adrenergic regulations perhaps play important role in mechanisms of stress-ulcerations in rat glandural stomach.
The present study examines the effects of central and peripheral dopaminergic agonists and antagonists on gastric stress-ulcer formation in rats induced by electrical unescapable foot-shock.
Male Wistar rats were intraperitonealy injected 15 minutes after beginning of the stress by apomorphine (1mg/kg), metoklopramid (10mg/kg),dopamine (20mg/kg) and domperidone (10mg/kg). Apomorphine markedly reduced number of lesions (erosions and petechiae), $p<0.01$ and lesion area (ulcus index is significantly lower UI=0.1±0.6), compared with untreated group (UI=5.75 ±1.25), $p<0.01$. On the other hand , metoklopramid does not showay difference in lesion from control group.
Dopamine reduced number of gastric lesion ($p<0.01$) and lesion area (UI=0.18±0.15),compared to untreated group (UI=5.72±1.25), $p<0.01$. Domperidone does not produce or induce stess ulcer effects.
The results of this study suggest that apomorphine effect on stess-ulcer formation might be responsible for prevention of gastric lesion, modulated through mechanism that involve dopa respectors in CNS.
Ulceroprotective effect of dopamine is probably result of increasing in mucosal blod flow.

14.43 QUANTITATIVE MORPHOLOGY OF LHRH- IMMUNOREACTIVE NEURONS IN THE NERVUS TERMINALIS AND CNS OF THE BIG BROWN BAT, *EPTESICUS FUSCUS***

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Five big brown bats (3m, 2f) ranging from juvenile to adult animals (cryotome and cryostat sections) were investigated with the methods of immunocytochemistry (Sternberger 1974).

Within the Nervus terminalis (N.t.), variation of LHRH cell number was moderate (range 56-129; average: 68); there were about twice as many spindle-shaped cells as irregular cells. In the brain, the degree of variation was about the same as in the N.t. (range: 528-1.047; average: 713); however, the spindle-shaped cells were 3.5 times as numerous as the irregular cells.

In the nervous system as a whole, there were only minor differences between left and right (averages: 350 [left] and 332 [right]). There was no significant difference between both sexes and no obvious numerical trend during postnatal ontogenesis. On an average, the postnatal big brown bat exhibits 780 LHRH-ir cells within the N.t. and forebrain, which is distinctly more than in the mole rat (Jastrow et al., this volume) and much more than in the mouse (Schwanzel-Fukuda et al. 1987) and the musk shrew (Dellovade and Rissman 1994). It should be noted that, within the Nervus terminalis of mammals, the LHRH-ir cells represent only one neuron population, which shows marked regression in parallel to the establishment of the brain-pituitary-gonadal axis during the late fetal period.

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14.44 DIRECT MASS ANALYSIS OF NEUROPEPTIDES IN SINGLE NEUROENDOCRINE CELLS

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Neuropeptides are synthesized in the form of larger prohormones, from which they are proteolytically cleaved, further modified and stored in secretory granules, untill they are released in response to depolarization. In the present study, we introduced the use of matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) to detect neuropeptides directly in single identified neurons in the brain of the pond snail *Lymnaea*. We studied the peptide profiles of two giant neurons involved in regulation of respiration and heart beat. Mass spectra of these neurons showed, besides peptides previously identified by molecular biological and peptide chemical methods, several unidentified peaks, representing putative peptides. We verified this finding by using conventional peptide chemical techniques and showed that the unidentified peaks represent post-translational modifications of known peptides, as well as novel peptidergic co-transmitters.
Subsequently, the use MALDI mass analysis was explored for obtaining direct peptide fingerprints of single vertebrate neuroendocrine cells and tissues. As a model, MALDI mass analysis was directly performed on pieces of neuro-intermediate lobe and on single melanotrope cells of the rat pituitary. Using this extremely fast procedure, we identify about 20 peptides, including N-terminally acetylated, C-terminally amidated and phosphorylated species. *In toto*, these peptides account for almost the entire lengths of proopiomelanocortin, propressophysin and prooxyphysin. Moreover, the spectral fingerprints of single melanotrope cells and neuro-intermediate lobes not only provide qualitive confirmation, but also contain semi-quantitive information contained in the ratios in which certain peptides are synthesized. For example, di-acetyl αMSH is the most abundant form of processed αMSH, followed by mono-acetyl αMSH and αMSH at 4x and 6x lower levels respectively.
These experiments demonstrate that MALDI-MS forms a new and valuable approach to the study of biosynthesis and processing of bioactive neuropeptides in individual neurons and neuroendocrine cells of both invertebrates and vertebrates.

14.45 GLUTAMATE-EVOKED CURRENTS IN ACUTELY DISSOCIATED NEURONS FROM THE RAT MEDIAL PREOPTIC NUCLEUS

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The membrane currents evoked by fast application of glutamate were studied in acutely dissociated neurons from the medial preoptic nucleus of the rat. The whole-cell currents were measured under voltage-clamp conditions by the use of the perforated-patch technique. At negative membrane potentials, all studied neurons responded to a brief (20 - 100 ms) pulse of 1 mM glutamate with a fast inward current, reaching a peak within 20 ms and showing a subsequent roughly exponential decay (time constant about 20 - 30 ms). More than 50 % of the neurons studied showed, in addition, a more slowly decaying (time constant about 0.3 - 0.4 s) current component. The latter component showed strong outward rectification and was preferentially detected at positive membrane potentials. Both current components showed a reversal potential close to +10 mV (with presumably physiological ion concentrations used). The AMPA-receptor antagonist NBQX (10 µM) blocked the fast current component, but did not significantly affect the slow current component. AMPA (1 mM) evoked currents with properties similar to those of the fast current component evoked by glutamate. NMDA (1 mM) evoked currents with properties similar to those of the slow current component evoked by glutamate. In conclusion, the results suggest that the soma region (including dendrite bases) of medial preoptic neurons express glutamate-activated ion channels of the AMPA-receptor type as well as of the NMDA-receptor type.

14.46 S-NITROSOGLUTATHIONE IS ENDOGENOUS IN RAT CEREBELLUM

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The form in which the diffusable and short-lived messenger nitric oxide (NO) is stored, delivered and transported in CNS has not been directly studied. Based on the strong reactivity of NO for thiols and on the presence of cysteine and glutathione at the mM level intracellularly and µM level extracellularly (Zängerle et al., 1992), we have investigated whether S-nitrosothiols (RSNO), i.e. S-nitrosocysteine and/or S-nitrosoglutathione (GSNO) may be the potential "package" form in which NO could be stored.

We have optimized an extraction method which avoids partial degradation of RSNO and developed a sensitive and selective analytical method based on reversed phase HPLC combined with multiwavelength detection and on-line absorption spectrum which allows to quantify RSNO at a level of 150-300 pmol. In experiments in which cerebellar slices from 8-10 days old rats were incubated with radioactive [35S]-cysteine and extracted, a radiolabelled peak corresponding to GSNO has been detected. Its identification was confirmed by spiking with reference compound. Indeed, labelled cysteine was taken up and incorporated into glutathione and GSNO. Moreover, the endogenous compound eluting at the retention time of GSNO was chemically characterized by micro HPLC coupled to continuous flow-fast atom bombardment mass spectrometry: its fluorenylmethyloxycarbonyl-derivative has a mass spectrum identical to that of authentic GSNO. The use of the same technique and deuterated GSNO as an internal standard will allow us to determine the endogenous concentration of GSNO. The packaging of NO in form of GSNO might serve to facilitate its transport, prolong its life and target its delivery to specific effectors. Furthermore, the formation of GSNO may provide a means to control the toxicity of the free radical NO·.

14.47 NMDA RECEPTORS HAVE CRUCIAL ROLE IN THE APOMORPHINE-INDUCED SENSITIZATION.

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We studied the aggressive behaviour induced by repeated treatment with apomorphine, a dopamine agonist (0.5 mg/kg s.c. twice daily, 10 days), in rats. The first signs of defensive aggressiveness appeared on the third day of apomorphine treatment and were generally seen on the 7th day. Aggressivness induced by a challenge dose of apomorphine (0.5 mg/kg s.c.) on the 11th day was antagonized by haloperidol (0.05 and 0.1 mg/kg i.p.) and clozapine (10 mg/kg i.p.). An antagonist of N-methyl-D-aspartate (NMDA)-gated channels, dizocilpine (MK-801), also blocked the aggressive behaviour at 0.25 and 0.5 mg/kg i.p. but caused ataxia. When dizocilpine (0.25 mg/kg i.p.) and apomorphine were coadministrated for 10 days, aggressive behaviour did not develop. At 0.025 mg/kg i.p., dizocilpine even accelerated the appearance of apomorphine-induced aggressive behaviour, which manifested on the 3rd day in all rats. In separate study, a 7-day treatment with dizocilpine (0.25-1 mg/kg i.p.) of rats, sensitized by a prior 10-day apomorphine treatment, did not reverse the established aggressive behaviour. In binding studies neither density nor affinity of striatal dopamine D_2 receptors was changed by acute or chronic apomorphine treatment. Acute apomorphine did not change [^{3}H]-MK-801 binding in the rat brain. However, in rats treated for 10 days with apomorphine, the number of NMDA-gated channels in open state was increased in the frontal cortex and hippocampus. In these rats, a challenge dose of apomorphine (0.5 mg/kg s.c.) normalized the increased number of [^{3}H]-MK-801 binding sites in the frontal cortex.

In conclusion, repeated treatment with apomorphine seems to modify the function of dopamine D_2 receptors without affecting their number or affinity to [^{3}H]-spiperone. The increased number of NMDA-gated channels in open state appears to be related to this alteration of dopamine D_2 receptors. This poorly characterized phenomenon seems to be the main reason for the development of apomorphine-induced aggressive behaviour.

14.48 BRAIN ISCHEMIA REPERFUSION INJURY ALTERS THE PROPERTIES AND FUNCTION OF CHLORIDE CHANNELS. Izabela Kołądkiewicz*, Marek Samochocki, Małgorzata Chalimoniuk, Joanna Stroszнajder. Lab of Cellular Signalling, Medical Research Centre, Polish Academy of Sciences, 3 Dworkowa street, PI-00784 Warsaw, Poland

Properties and function of chloride channels were investigated by determination of association and dissociation kinetics of specific chloride (Cl^-) channel ligand [^{35}S]tert-butylbicyclophosphorothionate (TBPS). These studies were carried on in the absence and the presence of $GABA_A$ agonist (muscimol) using synaptic plasma membrane (SPM) from the hippocampus and the cerebral cortex isolated 4 and 30 days after 5 min of bilateral occlusion of both common carotid arteries in gerbils. Furthemore, muscimol (20-100μM) stimulated $^{36}Cl^-$ uptake into synaptoneurosomes was determined. It was found that the half-life of fast phase of [^{35}S]TBPS dissociation which corresponds to an opening time of receptor-dependent Cl^- channel, was significantly decreased in the hippocampal SPM 4 days after arteries occlusion in the presence of muscimol. However, 30 days after ischemia, in spite of this modification of Cl^- channel, the half-life of fast phase of [^{35}S]TBPS dissociation was significantly lower in the brain cortex SPM, in the presence and absence of muscimol. These results suggest a decrease of opening time also the other Cl^- channels, not connected with $GABA_A$ receptor. Moreover, 30 days after ischemia, a significant lowering of GABA-activated Cl^- uptake in the presence of 50-100μM muscimol was observed. Among processes which occur during ischemia and which potentially may induce modification of the Cl^- channels properties and function, the action of unsaturated fatty acids, peroxides and pH were taken into consideration. It was found that all of them modified the GABA-operated chloride channel function. Our results demonstrate that the properties and function of Cl^- channels were affected by ischemia-reperfusion injury. These alterations may be responsible for the lower hyperpolarization ability of $GABA_A$ receptor complex.

14.49 Abstract withdrawn

14.50 SUBTYPE-SELECTIVE ANTAGONISM OF $GABA_A$ RECEPTORS BY FUROSEMIDE. E.R. Korpi*, T. Kuner, P.H. Seeburg and H. Lüddens. Biomedical Research Center, Alko Group Ltd, POB 350, FIN-00101 Helsinki, Finland, and Laboratory of Molecular Neuroendocrinology, Center for Molecular Biology, Heidelberg, Germany

A great number of compounds affect inhibitory γ-aminobutyric acid$_A$ ($GABA_A$) receptors, none of them showing strict receptor subtype specificity. We have now found that furosemide, but not bumetanide, another Cl^-/cation transporter blocker, specifically antagonizes GABA-inhibition of $GABA_A$ receptor-associated convulsant binding sites labelled by [^{35}S]TBPS in cerebellar, but not in cerebrocortical or hippocampal membranes. Autoradiographic experiments localized the GABA antagonism by furosemide to cerebellar granule cell layer. Using membranes from human embryonic kidney 293 cells expressing recombinant $GABA_A$ receptor subtypes, we found that granule cell-specific α6β2/3γ2 receptors, but not α6β1γ2 or the widely-expressed α1β2γ2 receptors, can be uniquely antagonized by furosemide. Electrophysiologically studied GABA responses of Xenopus oocytes expressing α6β2γ2 receptors were potently, rapidly and reversibly antagonized by furosemide. Furosemide appeared to interact noncompetitively with the receptor complex via a novel recognition site that allosterically regulates the Cl^- ionophore. As the first subtype-selective $GABA_A$ receptor antagonist, furosemide should facilitate studies on cerebellar physiology. It might serve as a lead structure for the development of additional subtype-selective $GABA_A$ ligands.

14.51 DEVELOPMENT OF NON-NMDA SITES IN CHICK CEREBELLUM.
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[^{3}H]ABCPA a novel photoaffinity ligand was used for labelling non-NMDA sites in chick cerebellum. Electrophoretic analysis with SDS-PAGE revealed two major radioactive bands of 45(P1) and 33.5(P2) KDA.

P1 is completely absent at E13. Low amounts of this protein are present at E17 and a rapid increase follows until P15. The inhibition of binding of [^{3}H]ABCPA by 2mM kainic acid in all ages studied was in the order of 70%. P2 is already present at E13 and a small increase follows until E17 when it reaches plateau levels. Inhibition of [^{3}H]ABCPA binding by 2mM of KA is in the order of 20% in all ages studied. Binding of [^{3}H]ABCPA in both proteins and in all ages studied was completely inhibited by 2mM CNQX.

14.52 EFFECT OF L-GLUTAMATE ON HIGH-AFFINITY CHOLINE TRANSPORT SYSTEM IN RAT HIPPOCAMPAL SYNAPTOSOMES
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Prague Psychiatric Centre, Czech Republic

The effects of L-glutamate (GLU) on the high-affinity choline uptake, the specific binding of (3H)hemicholinium-3 ((3H)HCh-3) and the activity of Na^+,K^+-ATPase were investigated in hippocampal synaptosomes of young male and female Wistar rats. 100 mM GLU significantly decreased the high-affinity and low-affinity choline uptake, the specific as well as the nonspecific binding of (3H)HCh-3 and the activity of Na^+,K^+-ATPase in comparison with control samples. Kinetic analysis revealed a change in Vmax and Bmax rather than in Km and Kd. Damage of presynaptic cholinergic nerve terminals by GA via its effect on the release of arachidonic acid was discussed.

14.53 DISTRIBUTION OF $GABA_B$ RECEPTORS IN THE BASAL GANGLIA AND THALAMUS OF THE RHESUS MONKEY

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$GABA_B$ receptors have been implicated in several neurological conditions yet their characteristics in the primate brain have not been fully established. In this study we analysed the distribution pattern and binding properties of $GABA_B$ receptors in certain thalamic and basal ganglia nuclei of Macaca mulatta using [^{3}H]GABA quantitative autoradiography (Neuroscience, 20:365-83, 1987). The data were compared to earlier findings in the rat (Neuroscience, 20:365-83, 1987). In addition to high binding density in sensory thalamic nuclei, as previously shown in the rat, high binding density was also observed in association nuclei such as the MD, LD, LP and Pulvinar. Interspecies differences between other thalamic nuclei were also noted. In the basal ganglia, the highest binding density was observed in the caudate, in contrast to the findings in the rat where the globus pallidus displayed the highest density. In monkey, the globus pallidus and substantia nigra pars reticularis displayed moderate binding densities, whereas in the subthalamic nuclei it was not detectable. Differences in anatomical organization may the underlying reason for the apparent interspecies differences in $GABA_B$ receptor binding.

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14.54 DAMAGE OF FROG RANA TEMPORARIA CEREBELLUM MOLECULAR LAYER INDUCED BY GLUTAMATE IN VITRO.
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This report is related to the problem of toxic influence of disbalance of excitatory aminoacid mediators on neuronal nets.

It was observed by electronmicroscopical and morphometrical methods that elevated concentration of L-glutamate (1mM) induced pathological changes in cerebellum molecular layer (after 2h of incubation): swelling of glial cells (GlC), boutons (B) and spines (S) in synapses of Parallel fibres on Purkinje cells (PF-PC), decrease of their active zones, desynaptization - disconnection of boutons and spines (vacant boutons), dark spine degeneration.

The swelling of GlC, B and S is the consequence of the presence of glutamate transporters in GlC, PC and granular cells, /1/. Dark spine degeneration and decrease of active zones in PF-PC-synapses is explained by pathological influence of elevated concentration of L-glutamate on protein synthesis, /2/. These mechanisms are the basis of many deseases, such as: epilepsy, neurotrauma and others.

/1/. NEURON, 1994, v.13, 713-725; /2/. DOKLADY AKADEMII NAUK RAN, 1993, v.333, 127-130.

14.55 MOLECULAR CLONING AND CHARACTERISATION OF THE HUMAN $mGlu_3$, $mGlu_5$ AND $mGlu_6$ RECEPTORS
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Glutamate receptors in the mammalian CNS are categorised as ionotropic or metabotropic receptors. Seven rat metabotropic receptor sequences have been published and allocated to three main groups, based on pharmacological preferences and sequence homologies (Nakanishi, 1994, Neuron 13: 1031). In CHO cells, group I receptors ($mGlu_1$ and $-_5$) positively couple to phospholipase C, while receptors of groups II ($mGlu_2$ and $-_3$) and III ($mGlu_4$, $-_6$ and $-_7$) negatively couple to adenylate cyclase. Sequences for the human $mGlu_2$ and $-_5$ receptors have recently been described (Flor et al., 1994, Eur. J. Neurosci. (Suppl. 7), Abst. 47.01; Minakima et al., 1994, Biochem. Biophys. Res. Commun. 199: 1136). We here report the cloning of cDNAs encoding three human metabotropic receptors, $hmGlu_3$, $-_5$ and $-_6$, one from each group. These were obtained from human brain and retina cDNA libraries by homology screening using radiolabelled fragments of the rat $mGlu_1$ and $-_4$ receptors. The deduced amino acid sequences are 846, 1180 and 866 residues in length, respectively, and display ~95% homology to the published rat sequences. *In situ* hybridisation on human brain sections revealed that $hmGlu_3$ mRNA is widely expressed and $hmGlu_5$ mRNA is strongly expressed in the hippocampus, but no $hmGlu_6$ mRNA is expressed. PCR analysis showed that, as in the rat, $hmGlu_6$ mRNA is virtually restricted to the retina. In CHO cells stably expressing $hmGlu_5$ receptors, glutamate raised intracellular [Ca^{2+}] (detected by aequorin luminescence), while in cells expressing $hmGlu_3$ and $-_6$ receptors glutamate lowered the forskolin-elevated intracellular cAMP concentration. L-CCG-1, quisqualate and L-AP4 were, respectively, the most potent agonists at the $mGlu_3$, $-_5$ and $-_6$ receptors, in agreement with published studies on the corresponding rat receptors. The pharmacological preferences and coupling mechanisms of these receptors are currently under study.

14.56 MECHANISMS OF THE PRESYNAPTIC ACTION OF NICOTINIC AGONISTS IN MOUSE THALAMUS.
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Miniature GABAergic inhibitory postsynaptic currents (mIPSCs) were recorded in relay cells in slices of the dorsal lateral geniculate nucleus (DLG) of mouse in the presence of 10µM CNQX and 300nM TTX. Micromolar concentrations of the nicotinic agonists nicotine, DMPP, ABT418 and carbachol in the presence of atropine increased the frequency of mIPSCs in 61/145 cells. DMPP (10µM) induced a mean increase in mIPSCs frequency of 4.0±2.9 fold (n=56) whithout altering the amplitude distribution. The increase in frequency could be blocked by the nicotinic antagonist dihydro-β-erythroidine (1µM). The GABA-A antagonist SR-95531 blocked all mPSCs in the absence and in the presence of nicotinic agonists.

Relay cells in the DLG receive a GABAergic input from axon terminals and from interneuron dendrites. The ventro-basal thalamus (VB) does not contain interneurons. Yet, DMPP (10µM) increased the mIPSCs frequency in 6/11 cells in VB, indicating that this effect is not a specific property of interneurons dendrites.

The presynaptic effect of nicotine was dependent upon extracellular calcium since it was suppressed in low calcium extracellular medium (4/4 cells). It remained unchanged in the presence of the high-voltage-activated calcium channel blocker cadmium (50µM) but was significantly reduced by the low-voltage-activated calcium channel blocker nickel (50µM). This indicates that the presynaptic action of nicotinic receptors is due, at least in part, to the activation of low-voltage-activated calcium channels and possibly also to a direct calcium influx through the nicotinic receptors present in the axon terminals.

14.57 THE EFFECT OF NICOTINIC AGONISTS ON THE RELEASE OF SEROTONIN IN RAT HIPPOCAMPUS.
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In the present study we investigated the effect of different nicotinic agonists (dimethylphenylpiperazinium-iodide (DMPP), nicotine, cytisine, lobeline, and epibatidine) and antagonists (mecamylamine and dyhidro-ß-erythroidine) on the release of [^{3}H]5-HT from hippocampal slices. The nicotinic agonists DMPP, lobeline and electrical field stimulation released [^{3}H]5-HT from the hippocampus; other nicotinic agonists, such as nicotine, cytisine, and epibatidine, had no effect. The effect of DMPP and lobeline was $[Ca^{2+}]_o$-independent and tetrodotoxin-insensitive. In Ca^{2+}-free medium DMPP was still able to release tritium from the hippocampus, while the stimulation-evoked release of [^{3}H]5-HT was abolished. Ca^{2+} channel blockers (cadmium, ω-conotoxin GVIA and nifedipine) could not modulate the effect of DMPP. Because of the dual character of the action of DMPP and lobeline, we investigated the effect of an ion channel modulator, flufenamic acid (FFA), on the release of [^{3}H]5-HT. FFA, at a concentration of 100 µM, inhibited the effect of DMPP and lobeline to release 5-HT from hippocampal slices. The effect of DMPP and lobeline to enhance the release of [^{3}H]5-HT from the hippocampus was most likely mediated via nAChRs in part, while another source of the 5-HT-releasing property of DMPP may be the activation of ion channels.

14.58 Abstract withdrawn

14.59 ACUTE VS DELAYED EFFECTS OF NALOXONE ON SPATIAL MEMORY IN RATS.
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Three groups of rats were injected with naloxone (1 or 4 mg/kg) or saline. Four weeks later, each group was given the second injection of 1 mg/kg naloxone or saline, and used in response to a spatial change test with long retention interval (20 min). No acute effect of naloxone was found; the drugged and control rats performed on a chance level. By contrast, the delayed naloxone effect was reflected by different proportions of responses to spatial change in groups receiving different doses of naloxone in the first injection. The 1 mg, 4 mg, and saline groups showed 80%, 38%, and 40% of responses to spatial change, respectively ($p < .05$, χ^2 test). The same rats were exposed for the second time to the same spatial test in undrugged conditions. The pattern of responses to spatial change revealed an interaction of the delayed effects of the first and the second injections of 1 mg/kg naloxone and saline. The dose of 4 mg/kg given in the first injection caused a chance level performance in the repeated spatial test, regardless of the dose in the second injection. These results point to long-lasting and dose dependent effect of the initial blockade of the opioid system.

14.60 NEUROTRANSMITTER MECHANISM OF DELTA-SLEEP INDUCING PEPTIDE ADAPTIVE ACTION UNDER EXPERIMENTAL AUDIOGENIC EPILEPSY

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Delta-sleep inducing peptide (DSIP) is well known as a powerful adaptation - promoting agent tested in conditions of various stress types: cold, psychoemotional, hypo- and hyperoxic. It is also shown that DSIP injection leads to supression of generalized epileptic activity. Nowadays a great number of researches links the mechanism of realizing polyfunctional, prolonged, stressprotective effectes of delta-sleep inducing peptide (DSIP) with its modulation influence on synaptic transmission. The monoamines take part in development of epileptyform activity . In this connection the DSIP influence on the rat brain cortex, thalamic, hypothalamic and hyppocampal adrenaline, noradrenaline, DOPA, dopamine and serotonin level under normal and experimental audiogenic epilepsy was studyed by HPLC.

It has been found, that a single intraperitoneal DSIP injection (12 µg/100 g body weigh, 1 hour befor placing the animals into the stress condition) to "sensitiv" rats increased latent period of epileptic convulsions appearence and prevented spontaneous epileptic activity development in group of "unsensitiv" rats due to creation of optimal ratio between monoamines in brain structures.

14.62 CANNABINOID AND PROTEIN KINASE-MEDIATED MODULATION OF GABA TRANSMISSION IN THE BASAL GANGLIA.

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Cannabinoid receptors are found in high concentrations in the output regions of the basal ganglia. Decreased GABAergic transmission in these regions is thought to contribute to the symptomatology of Parkinson's disease. We have investigated the effect of cannabinoid receptor activation on GABA uptake in the globus pallidus using WIN 55,212-2 and Δ^9-tetrahydrocannabinol (Δ^9-THC). WIN 55,212-2 and Δ^9-THC caused a concentration-dependent decrease in [^{3}H]-GABA uptake into pallidal slices. Protein kinase A activation using : a) forskolin (100µM) resulted in a 220% increase in GABA uptake into pallidal slices, b) SpcAMP (100µM) caused a 313% increase in [^{3}H]-GABA uptake. This effect was reduced (35% decrease) by simultaneous incubation with 50µM WIN 55,212-2. The same concentration of WIN 55,212-2 also decreased forskolin-stimulated accumulation of cAMP into globus pallidus slices (34.4% decrease). Additionally, protein kinase C inhibition with chelerythrine chloride (3-100µM) caused up to 80% decrease in [^{3}H]-GABA uptake whereas PKC activation with (-)indolactam V caused a 48% increase in GABA uptake. Both results would suggest actions of PKA an PKC on the GABA transporter. WIN 55,212-2 may act to decrease GABA uptake by decreasing PKA activity. *In vivo*, experiments were conducted using the reserpine-treated rat model of Parkinson's disease. Although without locomotor effect on its own WIN 55,212-2 (0.1mg/kg) potentiated the anti-parkinsonian effect of (0.3mg/kg) apomorphine in a significant manner. In the case of Parkinson's disease, modulation of GABA transmission by cannabinoids could be beneficiary and further characterization of this effect could lead to new therapeutic strategies.

14.63 IMMUNOHISTOCHEMICAL CHARACTERIZATION OF CAJAL-RETZIUS NEURONS FROM HUMAN PREFRONTAL CORTEX AND VISUAL CORTEX.

R. Martín*, M. Megías, A. Peñafiel, A. Gutiérrez and A. de la Calle. Dpt. Cellular Biology, University of Málaga, 29071-Málaga, Spain.

The Cajal-Retzius cells, basic neuronal elements of cortical layer I, are the first one to appear during cortical development. Recently, it has been found that these neurons use γ-aminobutiric acid (GABA) as a neurotransmitter. The existence of these neurons in human adult brain is still a matter of controversy. We have studied the morphological features of Cajal-Retzius neurons in prefrontal and visual cortical regions from old human brains using calcium-binding proteins immunocytochemistry, which define different GABAergic subpopulations, and NADPH-d histochemistry.

The human brains were obtained at autopsy from patients with no history of neurological or psychiatric diseases. *Post mortem* delay ranged from 7-15 hr. The brains were prefused *ex situ* with cold 4% paraformaldehyde, 0.5% glutaraldehyde in 0.1M PB via the basilar artery, suspended by the basilar artery in the same fixative for 20 hr and cut into 1 cm coronal blocks. Vibratome sections (50µm) were obtained and processed with the immunohistochemical PAP method using anti-parvalbumin, anti-calbindin or anti-calretinin antisera or with NADPH-d histochemical technique.

Cajal-Retzius neurons containing parvalbumin, calbindin or calretinin were detected throughout cortical layer I. In addition, Cajal-Retzius cells NADPH-d positive were observed. All of these neurons were large and showed different morphology: horizontal, pyriform or irregular.

14.64 LOCALIZATIONS OF THE α SUBUNIT OF Gi_2-PROTEIN IN NEURONS OF THE LATERAL SEPTAL NUCLEUS OF THE MOUSE.

B. Martín-Clemente*, P. Sánchez-Blázquez, J. Garzón and A. Fairén. Instituto Cajal, Avenida del Doctor Arce 37, E-28002 Madrid (Spain).

We investigated the possible synaptic localization of the $Gi_2\alpha$ subunit in the septal region of the mouse, using a rabbit polyclonal antiserum against a thyroglobulin-conjugated, synthetic 11-aminoacid internal fragment of $Gi_2\alpha$ (which comprises the residues 115-125 of the cDNA predicted sequence of this protein). IgGs purified by affinity chromatography immunolabeled a single band of 39 kDa in Western blots (Sánchez-Blázquez *et al.*, 1993). CD/1 adult male mice were processed for electron microscopic immunohistochemistry using a standard ABC protocol. In the septal region, the immunoreactivity localized to neurons and glial cells of the septohippocampal nucleus and the intermediate part of the lateral septal nucleus, while diffuse immunoreactive puncta occurred within these nuclei and also within the vertical limb of the diagonal band of Broca. In neurons, the immunoreaction product distributed within the perikarya and proximal dendrites and spared the nuclei. Immunoreactivity localized to membranes of the Golgi apparatus, intracytoplasmic vesicles and mitochondria and, in addition, to endoplasmic reticulum, to nuclear and plasma membranes and to dendritic microtubules. In the plasma membrane, the distribution of the immunoreaction product was patchy and showed a conspicuous relationship to postsynaptic densities of asymmetrical synapses. In the septum, we observed no immunoreaction localized to presynaptic terminals. Since not all postsynaptic densities were labeled, we postulate a selective association of Gi_2 protein to characteristic types of synapses, whose nature is currently under investigation.

14.65 PROTEIN KINASE C- MEDIATED INHIBITION OF THE GLUTAMATE TRANSPORTER BY ARACHIDONIC ACID.

D.F.Lundy and G.J.McBean*, Department of Biochemistry, University College, Belfield, Dublin 4 , Ireland.

Preincubation of purified synaptosomes from rat brain with arachidonic acid (ARA) showed a potent dose-dependent inhibition of D-[^{3}H]aspartate transport (for example, 10µM ARA reduced the level of transport to 5% control), compared to co-incubation of the synaptosomes, in which case 10µM ARA reduced transport to 80% of control. Removal of calcium ions from the incubation medium further increased the level of inhibition of transport by ARA.

Incubation of the synaptosomes with 100nM staurosporine for 50 minutes prior to the addition of ARA completely blocked the inhibition of transport when ARA was pre-incubated (10 minutes), but not when it was co-incubated. The inhibition of D-[^{3}H]aspartate transport observed in the presence of the calcium ionophore (A23187), was also reduced in the presence of 100nM staurosporine. Other fatty acids, for example, linolenic and arachidic acid, showed minimal inhibition of D-[^{3}H[aspartate transport when pre-incubated for 10 minutes prior to the start of the transport assay, even up to a concentration of 50µM. The methylated analogue of ARA, which does not activate protein kinase C, was neither as effective as ARA in inhibiting the glutamate transporter, nor was its activity blocked in the presence of staurosporine. Further analysis of the mechanism of inhibition of the gluamate transporter by ARA has revealed that inclusion of a phosphatase enzyme also prevents the inhibitory action on ARA on D-[^{3}H]aspartate transport.

These results suggest that ARA either directly, or indirectly, inhibits the activity of at least one type of glutamate transporter by a mechanism that involves activation of protein kinase C, leading to phosphorylation of the glutamate transport protein.

This work was supported by the Irish Health Research Board.

14.66 TWO PROMINENT CALRETININ-IMMUNOREACTIVE PLEXUSES IN HUMAN VISUAL CORTEX.

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We used a calretinin-antiserum to study the location of neurons and terminal plexuses containing calretinin in the human visual cortex, area 17. The calretinin immunoreactive cells were mainly concentrated in layers II and III, wich agrees with Glezer et al. (1992). They decreased in number from layer IV to VI. In layer I positive neurons appeared which had the Cajal-Retzius morphology. Most of the calretinin-immunoreactive neurons were bitufted with vertical orientation, although some of them were multipolar. Neurons located in layer II-VI usually gave rise an apical prolongation that could be follow up to superficial layers. There were two main fields with prominent calretinin-immunorreactive plexuses: one located in layer I and the other in layer V-VI. In layer I the immunoreactive fibres displayed an horizontal orientation. Thin and thick varicosities run parallel to the pial surface. In layer V there were a immunoreactive plexus with thinner terminals than in layer I. In order to situate this plexus in layer V accurately, we did parvalbumin- and calretinin-immunocytochemistry in consecutives vibratome sections. There was a delimited palvalbumin-immunoreactivity field located in layer IV which represents thalamic afferents, both in human and monkey visual cortex (Blüemcke et al., 1990). Parvalbumin- and calretinin-immunoreactive plexuses did not overlap. The calretinin-positive terminals in layer VI were not as numerous as in layer V. Numerous calretinin-immunoreactive fibres could be seen in the white mater.

14.67 **DOPAMINERGIC INNERVATION OF FOREBRAIN AREAS RELEVANT TO LEARNING IN THE DOMESTIC CHICK**

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Several forebrain in the domestic chick, including the medio-rostral neostriatum/ hyperstriatum ventrale (MNH), the lobus parolfactorius (LPO) and parts of the dorsocaudal neostriatum (Ndc), are involved in auditory filial imprinting. Since we have recent evidence that dopamine (DA) may play a modulatory role in auditory imprinting, we investigated the dopaminergic innervation of these forebrain areas at the light-, confocal-laser-scanning- and electronmicroscopical level. To elicit the sources of dopaminergic input onto MNH, LPO and Ndc, we combined retrograde tracing with DA- immunohistochemistry (IHC) using fluorescence detection systems. In order to identify dopaminoceptive neurons in these areas we performed double-label immunohistochemistry using antibodies against DARPP-32 and tyrosine hydroxylase (TH). DA- ir fibers were found in moderate densities in the MNH and Ndc and in high densities in the LPO. Combined DA- IHC/tracing experiments revealed that the majority of the dopaminergic input onto the MNH and Ndc arose from the area ventralis (AVT), whereas the LPO was mainly innervated from the substantia nigra. Combined TH- and DARPP-32- IHC demonstrated that catecholaminergic terminals are closely related to DARPP-32 positive neurons. In the MNH and Ndc catecholaminergic fibers formed predominantly basket- like terminals arround the somata and dendrites of neurons expressing DARPP-32. The majority of TH- and DA- ir synaptic profiles in MNH and Ndc is symmetric.

Our results indicate that the general organisation of dopaminergic afferents to the avian telencephalon shows a multitude of striking similarities to the mesostriatal and mesocortical DA- system in mammals.

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14.68 CATECHOLAMINERGIC FIBERS INNERVATE THE VENTRICULAR WALL AND THE CHOROID PLEXUSES OF THE HEDGEHOG CNS.

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Immunocytochemistry with antisera against noradrenaline (NA) and dopamine (DA) was used to reveal the distribution of catecholaminergic (CA) fibers in the ventricular system of the hedgehog *Erinaceus europaeus*. Light microscopic examination of immunocytochemically stained sections showed that NA- and DA- fibers are unevenly distributed along the ventricular wall, both supraependymally and subependymally, and in the choroid plexuses. Supraependymal fibers, occasionally recognized to originate from subependymal fibers, were found to run at various angles before terminating freely in the ventricles. In the lateral ventricles, CA fibers were in general more abundant in the ependyma lining gray matter. The ventricular surface of the lateral septal nucleus was moderately innervated by both types of CA fibers, whereas the ependyma lining the caudate nucleus was richly supplied by DA- and devoid of NA- axons. In the ventral wall of the posterior horn, ependymal zones exhibiting increased density of NA- and sparse DA- fibers were found to be separated by a zone with low NA- and increased DA- fiber densities. The ependyma of the third ventricle exhibited an uneven moderate to high innervation density. Dense CA innervation was observed in the ependymal wall of the ventral half of the cerebral aqueduct. The ependyma of the floor of the fourth ventricle displayed numerous NA- but fewer DA- fibers, whereas the velum medullare showed a moderate number of NA - but no DA- axons.

The choroid plexuses exhibited moderate number of NA- and sparse DA- axons. Of the circumventricular organs, the subfornical organ and the vascular organ of the stria terminalis displayed a great number of NA- but few or sparse DA- axons. Profusely innervated by CA immunostained fibers was found to be the median eminence.The subcommissural organ was devoid of CA axons and the area postrema displayed only few CA fibers.

14.69 EVIDENCE FOR THE PRESENCE OF NEUROTENSIN RECEPTORS ON ASTROCYTES.

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There is good evidence that the tridecapeptide neurotensin which was isolated from bovine hypothalamus may act as neurotransmitter or neuromodulator in the mammalian central nervous system (CNS). We have been interested to investigate whether in addition to neurones, astrocytes also possess receptors for neurotensin. The cellular localization of binding sites for ^{3}H-neurotensin and its nonpeptide receptor antagonist ^{3}H-SR-48692 was studied in explant cultures of rat neocortex, striatum, brain stem and spinal cord by means of autoradiography. Binding sites for the peptide and its antagonist were observed on a great number of astrocytes in all CNS regions studied. The astrocytes were identified by staining the cultures with a monoclonal antibody against glial fibrillary acidic protein. In addition to astrocytes, a great number of neurones were labelled by the radioligands. Binding of ^{3}H-neurotensin and ^{3}H-SR-48692 (10^{-8}M) to neurones and glial cells was markedly reduced or inhibited by the unlabelled compounds at high concentration (10^{-6}M), suggesting "specific" binding of the radioligands. Electrophysiological studies have shown that neurotensin caused a hyperpolarization of the majority of astrocytes tested. The hyperpolarization was dose-dependent over the concentration range 10^{-7} to 10^{-10}M. To test the specificity of the effect of neurotensin we have used a selective nonpeptide receptor antagonist SR-48692 which reversibly blocked the hyperpolarization by the peptide. Our electrophysiological and autoradiographic findings strongly suggest the existence of specific and functional neurotensin receptors on astrocytes.

15. Poster Session: Disorders of the nervous system I

15.01 ASSOCIATION OF LRP BINDING PROTEINS WITH PLAQUES AND TANGLES IN ALZHEIMER'S DISEASE

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We have studied the expression of Apo-E, lactoferrin (LF) and complement C3 in relation to ß-amyloid and tau-I by immunocytochemistry in early onset AD, late onset AD and Down syndrome patients. in addition the Apo-E genotype of the patients was determined by PCR technology. Our studies show that all LRP binding proteins are colocolized with ß-amyloid in senile plaques. All plaque types, including diffuse, neuritic as well as core plaques contained these antigens. Apo-E was most frequently associated with ß-amyloid, followed by C3 and LF, although there was extensive quantitative variation in the association of LRP binding proteins with ß-amyloid in different cases. This variation did not correlate with the Apo-E genotype. In contrast to the association with ß-amyloid, the association with neurofibrillary tangles was more restricted. Only extracellular "ghost tangles" were dressed with LRP binding proteins and this association was restricted to selected cases.

The study was partly funded by Austrian Science Foundation, Project P.

15.02 **EFFECTS OF MS-8209, A NEW DERIVATIVE OF AMPHOTERICIN B, IN CENTRAL NERVOUS SYSTEM OF SCRAPIE-INFECTED HAMSTERS**

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Scrapie in hamster is a useful model for the naturally occuring transmissible spongiform encephalopathies (TSE) which are seen in many mammalian species like Creutzfeldt-Jakob disease in humans. The agents responsible for TSE are unknown and their nature remains controversial. These fatal neurodegenerative disorders are characterized by accumulation of an abnormal isoform (PrPsc) of host encoded prion protein (PrP) which derives from post-translational modifications and accumulates in the brain. A transcriptional accumulation of Glial Fibrillary Acidic Protein (GFAP) has been also observed. Today, no treatment is available for TSE. Amphotericin B (AmB) is one of the rare drugs which revealed efficacy in experimental models. However, efficacy of treatment is limited by AmB acute toxicity. Here we report data obtained after treatment with a new AmB derivative, MS-8209 (5 fold less toxic) in hamster scrapie. Hamsters were infected intracerebrally with 263K scrapie agent. Treatments were carried out by intraperitoneal route at the doses of 2.5, 10 and 25 mg/kg, 6 days a week. Clinical status was observed and accumulation of PrP and GFAP were determined by Western blot. Our results show that i) Clinically, MS-8209 has strong effect on animal survival in all protocols of treatment. We observed that identical doses of MS-8209 or AmB induced a similar increase in the animal survival time. Treatment efficacy is dose dependent, but high doses of AmB are toxic. However, our new derivative MS-8209, with lower toxicity, administered at high doses (10 mg/kg with continuous treatment) induced for the first time a delay of 84.4 days (prolongation of survival time is of 100%). ii) At the molecular level, this drug delays accumulation of PrPsc and GFAP in the brain. Other experiments are in progress in our laboratory to investigate the effects of MS-8209 and AmB on 263K scrapie agent replication in the brain of infected hamsters. The results of these studies will be discussed at the meeting. In conclusion, we believe MS-8209 could constitute a potent drug to study the pathogenesis and the therapeutical strategies in the TSE.

15.03 PHENOTYPE OF MICE LACKING CALBINDIN-D_{28K}. M.S Airaksinen*, M. Meyer, and H. Thoenen. Max-Planck-Institute for Psychiatry, 82152 Martinsried, FRG.

Calbindin-D_{28K} is an intracellular calcium-binding protein of unknown physiological relevance. This protein is characterized by: (1) its rather high evolutionary conservation (2) its abundant expression in many subpopulations of peripheral and central neurons; (3) its inclusion in a family of calcium-binding proteins, which are mostly expressed in non-overlapping neuronal populations; (4) its potential role as a calcium buffer.

To study the physiological role of calbindin, we generated mice deficient in calbindin by gene targeting. Homozygous calbindin mutant mice are born at the expected Mendelian frequency, thus the mutation is not embryonic lethal. The mice have been observed now for six months and cannot be distinguished from wild-type littermates. They are fertile and have apparently normal littersizes. The null mutation was confirmed by Western blotting and immunostaining. Staining was abolished in homozygous mutants and reduced in heterozygous animals. Anatomy of brain and kidney, as analyzed by Nissl staining, appeared normal. Cerebellar Purkinje cells, which are particularly rich in calbindin in wild-type mice, had an apparently normal dendritic tree. Staining of adjacent sections of brain, kidney, uterus and oviduct for parvalbumin, calretinin, calmodulin, S100 and calbindin-D_{9k} did not reveal differences between wild-type and calbindin mutant animals. This was confirmed by Western blotting. ^{45}Ca overlay assay excluded major compensations by other soluble calcium-binding proteins. We conclude that loss of calbindin does not result in obvious changes in brain structure or animal behavior. Subtle changes cannot be excluded. Calbindin function may be revealed only after challenge, e.g., excitotoxic lesion. These experiments are in progress.

15.04 **THE USE OF THE RESISTIVE MRI SYSTEM IN THE PATIENTS WITH CEREBROSPINAL AND SPINAL TUMOURS.**

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Purpose. The aim of this study was to define true possibilities of MRI in the diagnosis of varios spinal and cerbrospinal tumours and to create optimum tactics of MRI carrying out in such cases.

Materials and Methods. All MRI were obtained on the whole-body resistive MR-tomograph Tomikon BMT 1100 R23 (Bruker, Germany). The techinique of examination was based on two principles - we used: 1). Both T_1-weighted (T_1W) and T_2-weighted (T_2W) MRI; 2). 3 planes: sagittal , axial and coronary. Often for patients with spinal and cerbrospinal tumours and metastasis it is very hard to endure long MRI - so, we prefered fast T_2W SE and GRE methods or anesthtesia. This report based on 2,587 cases.

Results. Tumours were found in 126 cases, metastasis - in 41. Verification of the MRI diagnosis was based on clinical, surgical histology and sectional data. Disjunctions were no more then 0.9% (disjanctions with clinical data - 61%). Anatomical tumours were divided into: intramedullary - 52 plus 3 metastasis, intraduro-extramedullary - 56 plus 24 metastasis, extradural - 18 plus 17 metastasis. 96% of patients were operated on. Histologically meningioma was noted in 73% of patients with intraduro-extramedullary tumours; epindimoma - in 64% of patients with intramedullary tumours and lymphoproliferative process - in 63% of extradural.

Conclusion. Fast MRI (using our MRI tactics) often can take the place of "normal" MRI in spinal and cerebrospinal tumours and MTS diagnosis.

15.05 CHANGES IN THE COMPOSITION OF MUSCLE FIBRES IN PATIENTS WITH PERIPHERAL OCCLUSIVE DISEASE

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To evaluate the extent and the type of muscular changes in chronic ischaemia, muscle biopsies were taken from 10 patients (mean age 65 years old) with peripheral occlusive disease in lower extremities, free of neurological symptoms and no diabetic, and examined histochemically and morphometrically. Samples were taken one-hour before, one-hour and one-day after the repair operation, in order to see possible changes during reperfusion. The samples were frozen and stained for routine histological stainings, for myosin-ATPase to show the fibre types, and SDH and NADH-tetrazolium reductase to demonstrate the oxidative fibres. Morphometric analysis was applied to estimate the type of atrophy and the fibre type predominance. All patients showed type II atrophy, their size being 3856.08±1794 μm^2 compared to control values reported for normal aged subjects (5700±1970 μm^2). Type I fibre size was within normal levels being 3826.8±1830 μm^2 compared to 4050±89 μm^2. Abnormalities typical for denervation, that is, small angular fibres and fibre grouping were seen in every individual, which was possibly due to the susceptibility of the peripheral nerves to ischaemia. The mean proportion of type I fibres was 72.42 % and of type II 27.35 %. The proportion of oxidative fibres was 55.6% and of non-oxidative 44.35%. All these changes observations did not change one day after the reperfusion. Thus, it could be assumed that adaptational changes during chronic ischaemia resulted in a better survival of type I and oxidative fibres, and nerve ending regeneration.

15.06 LOW-MAGNESIUM INDUCED EPILEPTIFORM ACTIVITY IN GUINEA PIG NEOCORTICAL SLICES CAN BE SPATIALLY RESTRICTED.

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The spatio-temporal distribution of low-Mg^{2+} epileptiform activity was monitored in neocortical slices using a voltage-sensitive dye and a fast optical recording method. Coronal slices (350µm) from sensory neocortex were prepared from guinea pigs and stained with the dye RH795. Epileptiform potentials were elicited by removing Mg^{2+} from the bath medium and single pulse stimulation of the white matter or layer I at different mediolateral positions. Fluorescence changes were monitored by a 10x10 photodiode array. The temporal resolution of the system was 0.4ms, the spatial resolution was 94µm.

Epileptiform activity could be elicited by stimulation from all positions of the stimulation electrode tested. In most slices, evoked epileptiform activity was restricted to the lateral part of the slice regardless of the site stimulated. Thus, stimulation in the medial part of the slice evoked activity comparable to control recordings near the stimulation site and epileptiform activity laterally. In some slices with epileptiform activity of particularly large amplitude and long duration, both evoked and spontaneous activity did spread across the entire slice. In conclusion, unlike bicuculline induced epileptiform potentials, low-Mg^{2+} induced epileptiform activity does not always spread across the entire slice, possible due to strong inhibitory activation.

15.07 **SCHISTOSOMA MANSONI INFECTION INDUCES GRANULOMAS AND HIGH LEVELS OF NGF IN THE MOUSE BRAIN.**

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Both in humans and rodents, the key pathogenic event of schistosomiasis is the formation of granulomas in the liver and intestine. However, numerous clinical studies indicate that the infection can reach the brain and spinal cord inducing severe neuropathological and neuropsychiatric disorders. Because nerve growth factor (NGF) is synthetized in the brain and, in addition to its neurotrophic effect, is involved in inflammatory responses, we investigate whether chronic *Schistosoma mansoni* (Sm) infection in animal models influences brain NGF expression. Adult mice were infected with Sm and, after 20-25 weeks, they were sacrificed and brains used for morphological analysis and NGF determination. In addition to liver and intestine, granulomas were found in the brain, localized mainly in the cortex, hippocampus and thalamus. The level of NGF increased in the cortex (23%), hippocampus (34%), and hypothalamus (300%), suggesting an involvement of NGF in such a neuro-inflammatory event. As NGF injection in normal mouse brain does not induce inflammation, the presence of high concentration of NGF in infected brains is most probably associated to reparative processes.

15.08 CULTURED HIPPOCAMPAL NEURONS EXPRESSING THE P21RAS ONCOGENE AS A TRANSGENE PRODUCT ARE PROTECTED AGAINST GLUTAMATE EXCITOTOXICITY

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We have shown previously that intracellular application of the GTP-bound (activated) conformation of p21-Ha-ras protein promotes the survival of cultured peripheral sensory neurons . In order to be able to study p21ras functions in central neurons we established a transgenic mouse model specifically expressing the activated p21ras in neurons. Val12p21ras expression was restricted to neurons by using the promoter of the synapsin I gene. The activated p21ras gene sequence was fused to a virus derived internal ribosomal entry site , followed by the lacZ-reporter gene. The ß-galactosidase was expressed readily from the dicistronic messenger and this allows convenient histochemical detection of transgene expression at a cellular level. In the adult brain the expression of the p21ras transgene is restricted to neurons although the expression level is not uniformly distributed. In the hippocampus there is strong staining of neurons in the pyramidal cell layer of CA1-CA4 and in the dentate gyrus. We next investigated neuronal survival after application of the excitatory neurotransmitter glutamate during a time period of several days in a hippocampal cell-culture system (p1-p5). Transgenic neurons showed a resistance to glutamergic excitotoxic insult: 80% of the neurons survived as compared to 45% survival in neurons of normal animals after 3 days of glutamate (1 mM) treatment. These results suggest that the transgenic activated p21ras gene product mimicks the effects of neurotrophins by enhancing neuronal protection against excitotoxic damage.

15.09 A RAPID AND SIMPLE METHOD TO OBTAIN PURE CULTURES OF HUMAN SCHWANN CELLS.

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Selective expansion and long-term culture of human Schwann cells from nerve biopsy specimens provides a useful tool for studies of diseases of the nervous system. Current approaches have met with limited success because of overgrowth of fibroblasts in the cultures, low yields or relatively tedious experimental procedures.

We developed a method to selectively expand human Schwann cells from sural nerves by simple mechanical disruption of the biopsies followed by culturing cells in the presence of the supernatant of lymphokine activated killer (LAK) cells. Immunofluorescent staining with antibodies to the S-100 protein, the low affinity nerve growth factor receptor and the surface Thy-1 antigen confirmed that these cultures contained >99% Schwann cells and no detectable fibroblasts. The mitotic activity of Schwann cells was measured by bromodeoxyuridine labelling, and was increased when the cells were grown in medium with LAK supernatant compared with medium without LAK supernatant. In the presence of LAK supernatant, Schwann cells could be maintained in continuous culture for a minimum of eight months.

15.10 BEHAVIOURAL EFFECTS OF PRENATAL LOW DOSE IRRADIATION IN MOUSE.

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Pregnant Swiss mice were exposed to 25-50 cGy gamma radiation on days 11.5, 12.5, 14.5 and 17.5 p.c. Learning and memory and locomotory activity of the F1 offspring were assessed at 4, 12 and 18 months of age by standard behavioural tests. The lowest dose, 25 cGy did not produce any significant change in brain function at any of the test periods. Exposure to 35 or 50 cGy on days 11.5 or 12.5 p.c. or to 50 cGy on day 14.5 p.c. resulted in significant impairment of learning and memory at 4 months of age. Recovery was seen at latter ages. Whereas normal behaviour was restored in animals exposed at 12.5 and 14.5 d.p.c. by 1 year, complete recovery was effected only 18 months in mice exposed to 50 cGy on 11.5 d.p.c. A similar effect was observed on locomotory activity also after 50 cGy exposure. Exposure at 17.5 d.p.c. did not significantly change the behaviour pattern at any age. The results indicate that the late organogenesis and early fetal periods are sensitive to low dose gamma irradiation, but only exposure at 11.5 d.p.c. could produce long lasting effects.(supported by Atomic Energy Regulatory Board, Govt. of India).

15.11 EFFECTS OF CABERGOLINE ON STRIATAL DOPAMINE RECEPTOR BINDING AND DOPAMINE SYNTHESIS - IN VIVO STUDY IN MONKEY WITH POSITRON EMISSION TOMOGRAPHY.

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Cabergoline (CBG) is a new potent dopamine agonist, with a prolonged half-life and sustained pharmacodynamic effects. This was demonstrated by long-lasting effects in lowering prolactin levels. In parkinsonian patients CBG was already shown to produce relief of symptoms, with a single daily administration. The present study was undertaken to investigate the time course of CBG interaction with the striatal dopamine-D2 receptors. The experimental set up included positron emission tomography studies in two rhesus monkeys. The amount of free dopamine-D2 receptors was assessed using ^{11}C -raclopride as tracer and the dopamine synthesis with injection of ^{11}C-L-DOPA. After the preliminary studies, the monkeys were given a 1 hour infusion of CBG to a total dose of 1 mg/kg. Repeat PET examinations for the assessment of dopamine-receptor binding and dopamine synthesis were performed 4 hours to 3 days after the administration of CBG.

The results demonstrate at 4 hours after CBG administration a 60 % reduction in the amount of free dopamine receptors and about 20 % reduction in dopamine synthesis. Both receptor binding and dopamine synthesis show a slow tendency towards normalization, but even 68 hours after drug administration a 40 % reduction in receptor binding is observed.

In conclusion the experiments show that Caberguline rapidly after administration excerts a significant effect on the striatal dopamine-D2 receptors. The duration of action on the receptor level is long.

15.12 EPILEPTIC POTENTIALS PROPAGATE ALONG ASSOCIATIVE FIBERS IN THE PIRIFORM CORTEX OF THE *IN VITRO* ISOLATED GUINEA PIG BRAIN.

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The diffusion of epileptic activity from a discrete cortical epileptic focus is due to the propagation of synchronous potentials to regions that are synaptically related to the primary focus. The associative synaptic network in the piriform cortex of the *in vitro* isolated guinea-pig brain have been recently characterized in conditions of normal excitability (Biella and de Curtis, *Eur. J. Neurosci.* 7: 54, 1995) and after the activation of a restricted epileptic focus in the anterior piriform cortex (de Curtis et al., *J. Neurophysiol.* 71: 2463, 1994). In these studies we hypothesized that the associative fiber system might sustain the propagation at distance of epileptic potentials. The present investigation demonstrates by means of selective surgical lesions that epileptic potentials propagate from the disinhibited APC focus to more caudal regions along long-projective associative fibres.

Simultaneous extracellular recordings and current source density (CSD) analysis of field potentials laminar profiles from the anterior and posterior piriform cortices (APC and PPC) have been utilized to characterize the associative synaptic events before and after induction of the epileptic focus in the APC. Surgical lesions of the lateral olfactory tract (LOT), performed by acute knife cuts, allowed to independently activate the APC and the PPC, and therefore to activate separately and in isolation the associative fibers that reciprocally connect these two cortical regions. Once an epileptic focus was activated in the APC by local ejection of bicuculline, synaptic epileptiform potentials were generated in the Ib layer of the PPC, where associative synapses are located. The abolition of the epileptic potentials and the relative current sinks after cutting the long-projecting associative fibers demonstrated that these fibers are responsible for the rostral-to-caudal propagation of epileptic activity in the piriform cortex. Such a modality of propagation may sustain the generation of secondary foci in cortical regions remote from the primary epileptic focus.

15.13 FLUPIRTINE REUDCES FUNCTIONAL AND MORPHOLOGICAL CONSEQUENCES INDUCED BY GLOBAL ISCHEMIA IN RATS.

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Global cerebral ischemia in rats induces selective neuronal damage in the CA1 sector of the hippocampus and in the striatum and deficits in spatial learning. Flupirtine, a non-opiod analgesic, has been shown to protect against NMDA-induced toxicity (Osborne et al, Brain Res. 667:291-294; 1994) and ameliorate retinal ischemic dysfunction (Block et al, Neuroreport 5:2630-2632; 1994). In the present study the effect of flupirtine on spatial learning deficit and neuronal damage following four-vessel occlusion (4VO) for 20 minutes in rats was examined. Flupirtine was administered 20 min before and 70 min after ischemia at a dose of 2.5 or 5 mg/kg. One week after surgery spatial learning was tested in the water maze. Application of the lower dose of flupirtine (2.5 mg/kg x 2) did not affect the behavioural and morphological consequences of 4VO. Treatment with flupirtine (5 mg/kg x 2) reduced the increase in latency and swim distance and increased the reduction in spatial bias induced by 4VO. Neuronal damage in the hippocampus and striatum produced by 4VO was significantly attenuated by flupirtine (5 mg/kg x 2). The present data demonstrate that treatment with flupirtine exerts a protective effect on hippocampal and striatal neuronal damage and deficits in spatial learning induced by 4VO.

15.14 NITRIC OXIDE SYNTHASE INHIBITOR FACILITATES AMINOPYRIDINE INDUCED NEOCORTICAL SEIZURE IN VIVO.

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The effects of L-N^G-nitroarginine (NA), a nitric oxide synthase inhibitor was investigated on the development and propagation of ictal-like seizure activity on the neocortex of anaesthetised rats *in vivo*. Epileptiform events in the primary focus (Pf) were induced by local application of 3-aminopyridine (3Ap) to the somatosensory cortex and later they also developed in the homologous area of the contralateral hemisphere (mirror focus, Mf). Electrocorticograms were recorded by four silver-ball electrodes and analysed in details during one hour time window. One group of animals were treated intraperitoneally (ip) by NA twice a day for four days; an other group was injected by NA into the lateral cerebral ventricle on the side of Pf 30 minutes before the application of 3Ap.

Generalised ictal-like seizures were found more frequent in treated (in 80% of the cases) than in control animals (20 %). In the ip injected group enhanced paroxysmal activity was compressed in a shorter time-window. Ventricular injection of NA had more complex effects on the epileptiform activity: the number of ictal events were increased, while the duration of the individual periods were slightly decreased. As a results the complete duration of ictal episodes was increased. Characteristic changes appeared in the pattern of ictal activity: the ratio of seizure discharges of different frequencies was shifted in favour of higher frequencies (10-15 Hz).

Our findings support the idea that nitric oxide might be involved in the control of the induction and propagation of 3Ap-induced epileptiform activity in the neocortex in vivo.

15.15 ISOLATION OF SERRATIA MARCESCENS FROM CEREBROSPINAL FLUID OF AN INFANT WITH MENINGITIS

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Bacterial meningitis is the most common and notable infection of the central nervous system, can progress rapidly, and can result in death or permanent debilitation. We describe an infant in who Serratia marcescens was cultured in cerebrospinal fluid during nosocomial infection with the same bacterium in the University Children's Hospital, Belgrade. 13 isolates of Serratia marcescens were obtained from 9 patients (medium age of 3.5 years) in the pediatric intensive care unit, and the distribution of infections was: bacteriaemia-sepsis 100% and osteomyelitis 33.3%. Meningitis followed Serratia marcescens sepsis in one infant. Patient was treated with twice-daily Conet (imipenem) during 10 days. Blood culture and cerebrospinal fluid after antibiotic treatment proved negative.

15.16 FUNCTIONAL IMAGING OF THE DOPAMINE TRANSPORTER IN PARKINSONISM: A ^{123}I-ß-CIT SPECT STUDY.

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Parkinson's disease (PD) is a severe progressive neurodegenerative disease which is neuropathologically characterized by a loss of the dopamine (DA) containing cells in the substantia nigra. Moreover, it has been demonstrated that the DAergic cell loss is accompanied by a decrease in the presynaptic DA transporter. A unilateral decrease in the presynaptic DA transporter has also been measured in the unilateral MPTP-lesioned rhesus monkey model of PD. Recently, ß-CIT, a iodinated cocaine analog, was introduced as a suitable ligand for single photon emission computed tomography (SPECT) imaging of the DA transporter in vivo. To visualize the DAergic cell loss we investigated in this study human ^{123}I-ß-CIT binding in 4 healthy controls and 5 late PD (Hoehn and Yahr 3-4). Moreover studies were performed in one control and one unilateral MPTP-lesioned rhesus monkey (both M. mulatta). Following intravenously injection of ^{123}I-ß-CIT, tomographic studies were performed with a specially brain dedicated SPECT camera (Strichman 810X). Selective striatal ^{123}I-ß-CIT binding is calculated as follows: (striatum - occipital cortex/ occipital cortex). In comparison with the controls, the late PD patients demonstrated a marked reduction in the striatal ^{123}I-ß-CIT binding 24 hours following injection (PD 6.43 ± 2.43, controls 1.56 ± 0.47). Both monkeys showed no activity in the occipital cortex 24 hours following injection. However, the control monkey showed no difference in left to right striatal activity 24 hours following injection. In contrast the MPTP-lesioned monkey showed a marked reduction of striatal activity of the lesioned side. In conclusion, by using SPECT degeneration of the DAergic system in late PD and in the unilateral MPTP rhesus monkey model of PD has been clearly demonstrated in vivo with ^{123}I-ß-CIT.

15.17 SELECTIVE N-TYPE VOLTAGE-SENSITIVE CALCIUM CHANNEL (VSCC) BLOCKERS: A NEW CLASS OF THERAPEUTIC AGENT TARGETED FOR THE TREATMENT OF ISCHEMIA-INDUCED BRAIN DAMAGE.

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It has long been held that calcium plays an important role in the pathogenesis of hypoxic neuronal injury. There is a growing body of experimental evidence which indicates that agents that prevent calcium entry through either neurotransmitter receptor-regulated ionophores or voltage-sensitive calcium channels can reduce the vulnerability of brain neurons to hypoxic-ischemic injury. Studies in our laboratory have focused on the neuroprotective properties of neuronal N-type voltage-sensitive calcium channel blockers. One of these, the synthetic form of the naturally-occurring N-type VSCC blocker ω-conopeptide MVIIA (SNX-111; CAS No. 107452-89-1), has shown unusual promise as a pharmacotherapeutic agent for the prevention of brain damage produced by focal or global cerebral ischemia. SNX-111 (5 mg/kg) decreased neocortical infarct volumes by 68% in spontaneously hypertensive rats subjected to temporary focal cerebral ischemia by middle cerebral artery occlusion when it was infused intravenously over 30 minutes immediately after reperfusion. SNX-111 was also neuroprotective in the rat four-vessel occlusion (4-VO) model of transient forebrain ischemia when it was administered intravenously by either bolus injection or slow infusion. A single, intravenous bolus injection of 3.5 mg/kg SNX-111, administered up to 24 hours after 15 minutes of 4-VO, significantly reduced hippocampal damage at 7 days post-treatment; there were no increases in damage at 14, 21, or 28 days, indicating that SNX-111 prevented, and did not simply delay, neuronal cell death. The neuroprotective potency of SNX-111 was increased when the compound was administered over 24 hours by continuous, constant-rate intravenous infusion beginning 1 hour after 4-VO. Under these conditions, doses required to decrease hippocampal CA1 damage by 50% (ED_{50}) were reduced from 2 mg/kg to 0.4 mg/kg (steady-state plasma concentration at ED_{50} dose =14.5 ng/mL). These findings suggest that selective N-type VSCC blockers, exemplified by SNX-111, are effective and potent pharmacological agents for the treatment of ischemia-induced brain injury. SNX-111 is currently in Phase II clinical trials for the prevention of brain damage after closed head trauma.

15.21 CSF IgG anti-GM1 antibodies in patients with active Multiple Sclerosis (MS)

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Aim:To demonstrate anti-GM1 antibodies in patients with active Multiple Sclerosis.

Material and methods:CSF is obtained from 6 patients suffering from definite MS during an active fase of the disease, as shown by MRI and additionale conventional CSF analysis. The results are compared with CSF obtained from patients suffering from other neurological disease (OND) ie. lumbal discopathy.

CSF was analysed using thin layer chromatografy and ELISA techniques and quantified with densitometry. All analyses were performed in duplo.

Results:OD values in OND ranged from 0.226 to 0.576 (mean 0.421 sd 0.13) and in MS from 0.738 to 1.287 (mean 1.013, sd 0.13). Difference was statistically significant ($p<0.05$, MW U-test).

Conclusion:Auto-antibodies to GM1 gangliosides in this demyelating disease are demonstrated in MS patients with active demyelination.

15.22 A FRAGMENT OF PrP ENHANCES SURVIVAL IN CULTURES OF CORTICAL CELLS FROM MICE DEVOID OF CELLULAR PrP.

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The prion protein (PrP) is a cellular glycoprotein normally found in neurones. PrP is involved in transmissible and genetic diseases. In such diseases the normal cellular isoform (PrP^C) is converted to an altered isoform (PrP^{Sc}) which shows greater protease resistance and aggregates to form fibrils. A fragment of the human PrP consisting of amino acids 106-126 has been previously demonstrated to be toxic to rat cortical neurones *in vitro* (1) as has PrP^{Sc}. The aim of the present study was to elucidate whether the neurotoxic effect of the fragment PrP106-126 is in some way mediated by the cellular isoform.

Dissociated cell cultures were established from the cortices of prenatal mice embryos (E16). The mice were either normal mice or mice genetically manipulated to be devoid of PrP^C($PrP^{0/0}$mice)(2). 80µM doses of the peptide were applied at two day intervals for 10days after which time survival of cells was assessed with an MTT assay. Cell culture was carried out in the presence of the mitotic inhibitor AraC and immunostained with antibodies specific for neurones or glia.

After applying PrP106-126 for 10 days in normal mouse cell cultures there was a resultant death of 35% more cells than in controls. However, when the fragment was applied in cultures of $PrP^{0/0}$mice there was no observable toxicity and treated cultures showed at 30% increased survival above controls. There was no observed proliferation of glia in these cultures.

These results support the notion that expression of PrP^C is necessary for the neurotoxic effect of PrP106-126 and that this same neurotoxic fragment enhances survival or neurones in cultures of mice devoid of PrP^C.

(1) Forloni, G. et al (1993) Nature, 362: 543-546.
(2) Büeler, H. et al (1992) Nature, 356, 577-582.

15.23 NMDA RECEPTORS PLAY AN IMPORTANT ROLE IN MEMORY IMPAIRMENT DURING CAVALHEIRO'S MODEL OF EPILEPTOGENESIS.

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The memory-protective effect of the noncompetitive NMDA antagonist ketamine (KET) in the Cavalheiro's pilocarpine model of chronic spontaneous recurrent seizures was studied in adult Long Evans rats. Peripheral cholinergic symptoms were suppressed by methylscopolamine (i.p.1 mg/kg). The status epilepticus (SE) was induced by i.p. injection of pilocarpine (320 - 350 mg/kg) and stopped after 2 hours by Clonazepam (i.p. 1mg/kg). Fifteen minutes after the SE onset in the first experimental group, and immediately after the Clonazepam injection in the second experimental group, KET 100 mg/kg was injected i.p. The cognitive memory was tested in the Morris water maze. Navigation of both KET treated groups was compared with navigation of the standard pilocarpine procedure group, and with a control group of animals without seizures. Less then 3 days in both KET treated groups and more then 6 days in the standard procedure group after status epilepticus, testing was impossible because rats did not stay on the platform. During the following part of silent period until the beginning of spontaneous seizures, deficits of cognitive memory were observed in all experimental groups but were significantly less pronounced in both KET groups. Injection of KET 15 min. after SE onset ameliorates impaired navigation of rats in the Morris water maze more than the same injection at the end of the SE. (Supported by grant UK 215/93/C)

15.24 NULL MUTATIONS OF CONNEXIN32 IN PATIENTS WITH X-LINKED CHARCOT-MARIE-TOOTH DISEASE.

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The X-linked form of Charcot-Marie-Tooth disease (CMTX) is associated with mutations in the gene encoding connexin32 (Cx32), a member of the family of proteins forming intercellular channels. To gain insight into the role played by connexin32 in the pathophysiology of CMTX, we have compared the functional properties of three mutant Cx32 genes with those of the wild-type gene by testing their ability to form intercellular channels in the paired oocyte expression system. While wild-type Cx32 induced the development of large junctional conductance between paired oocytes, no functional channels were detected between pairs expressing CMTX mutants. Despite the lack of functional activity, all mutant Cx32 were expressed by oocytes and correctly targetted to the site of membrane apposition between the two cells of a pair. Furthermore, CMTX mutants acted as dominant inhibitors of intercellular communication by interfering with the channel forming ability of Cx26, a member of the connexin family which is co-expressed with Cx32 in many cell types. The dominant negative effect was selective, as Cx32 mutants did not inhibit the levels of conductance induced by Cx40 in paired oocytes. Together, these results indicate that patients affected by X-linked CMT have null mutations of connexin32 and demonstrate a functional loss in the product of a candidate gene for a demyelinating form of CMT.

15.25 IN VITRO INTERACTION OF CABERGOLINE WITH DOPAMINE RECEPTOR SYSTEMS. C. Caccia *, M.G. Fornaretto, M. Mostardini, G. Marchi, R.G. Fariello and C. De Paolis. B.A. Pharmaceuticals/Preclinical CNS, Pharmacia, Nerviano, Italy.

Parkinson's disease (PD) is characterized by a progressive loss of dopamine (DA) neurons in the nigra leading to a decline of the DA availability to the postsynaptic DA receptors in the striatum. Thus, the striatal deficit of endogenous (presynaptic) DA should be compensated by substitutional agents which directly stimulate postsynaptic DA receptors (i.e. DA agonists). Cabergoline, an ergoline derivative clinically active in PD, is characterized by selective, potent and long lasting DA agonist properties. In the present study, the in vitro interaction of cabergoline with DA receptor subtypes (D_1, D_2 and D_3) was investigated. The DA D_2 affinity of cabergoline was further examined in different brain regions using in vitro autoradiography. It showed a six-fold higher displacing activity in caudate-putamen (IC_{50}=2nM) than in nucleus accumbens (IC_{50}=13nM). This could be beneficial in the therapy of PD. In fact a potent DA stimulation in the accumbens may cause an imbalance in the limbic Daergic transmission and aggravate or elicit ex novo cognitive and psychiatric distrubances. The interaction with DA D_3 was in the same nMolar range found for DA D_2 receptors (IC_{50}=5nM). The DA D_1 receptors were slightly affected (μMolar range).To study the transduction system linked to DA receptors, the cAMP levels were assessed in a cell line transfected with human DA D_1 or DA D_2 receptors. In mouse Ltk$^-$ cells expressing DA D_2, cabergoline was able to inhibit the cAMP formation induced by forskolin (EC_{50}=2nM) as shown by D_2 agonists. The full DA agonism was also found in Ltk$^-$ cells transfected with DA D_1 receptor in which cabergoline stimulated the cAMP production (EC_{50}=1μM). This feature is common to all D_1 agonists, thereby revealing for cabergoline D_1 agonist component, although at very high concentrations and with low efficacy.

15.26 TIME SCALE OF NEURONAL DEGENERATION IN THE HIPPOCAMPAL FORMATION OF ADULT RATS AFTER PROLONGED DIETARY PROTEIN DEPRIVATION. J.P. Andrade, A.J. Castanheira-Vale*, M.M. Paula-Barbosa and M.D. Madeira. Department of Anatomy, Porto Medical School, Porto, Portugal

Previous studies have demonstrated that prolonged low-protein diet induces irreversible neuronal degeneration in the hippocampal formation of the adult rat. The first estimation was carried out after 6 months of treatment and it was found that the total number of dentate granule and CA3 pyramidal cells was markedly reduced. We thought it would be of interest to establish for how long treatment was necessary to induce significant neuronal loss, i.e. to more precisely determine the time scale of neuronal loss. Four groups of 2-month-old rats at the beginning of the experiment were analyzed: a) control-rats fed with a standard diet during 1 and 3 months and b) malnourished rats treated during the same periods with a low-protein diet (8% casein). The numerical density of the granule and CA3 pyramidal cells was estimated with the physical disector method; to obtain the total number of these neurons, the volume of the respective layer, corrected for the respective tissue shrinkage factor was evaluated. No significant differences were found in 1 month treated rats. The total number of granule and CA3 pyramidal cells was reduced in 3 months treated rats when compared to controls. The numerical reductions were accompanied by decreases in the numerical density, but not in the volume of the respective layers.

We can conclude that cell degeneration in the hippocampal formation of the adult malnourished rat is installed during the first 3 months of treatment. Besides, the comparison of the present results with those previously obtained after 6 months of experiment, in which the magnitude of cell loss is higher, allow us to conclude that hippocampal granule and CA3 pyramidal cell loss is progressive.

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15.27 ANTIBODIES TO HUMAN BRAIN SPECTRIN IN ALZHEIMER'S DISEASE

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A growing body of evidence suggests that immunological aberrations may be critical factors in the pathogenesis of Alzheimer's disease (AD), and several reports have correlated the generation of anti-brain antibodies with the symptoms associated with AD. In this report we have investigated the existence of antibodies in sera of AD patients which immunoreact with specific antigens from crude human brain extracts. Sera from 24 out of 49 AD patients immunostained a 240-kDa protein (P240), per only 2 out of 43 control sera ($p < 0.00001$, χ^2 test). Serum antibodies from AD patients were found to immunoreact more strongly with both the α- and β-subunits which formed P240 than those from control sera. The levels of anti-P240 antibodies present in sera increased with age in the subset of P240-immunoreactive AD patients, whereas no variations were found in the control group. The antigen P240 was unambiguously identified by both immunochemical criteria and direct internal aminoacid sequencing as brain spectrin, a cytoskeletal protein which appears to be implicated in synaptic plasticity. Although the immunological trigger for the formation of anti-brain spectrin antibodies is currently unknown, our results raise the possibility that by targeting brain spectrin-associated structures, these antibodies could account for the biochemical alterations of the cytoskeletal network encountered in AD patients, hence playing a direct role in AD pathogenesis.

15.28 BRAIN ISCHEMIA-REPERFUSION INJURY ACTIVATES NEURONAL, CONSTITUTIVE FORM OF NITRIC OXIDE SYNTHASE. MOLECULAR ACTION OF NITRIC OXIDE. Malgorzata Chalimoniuk* and Joanna Strosznajder Depatment of Neurochemistry, Medical Research Centre, Polish Academy of Science,3 Dworkowa Str., 00-784 Warsaw, Poland

Our previous studies indicated, that nitric oxide is involved in ischemia evoked neuronal death in CA_1layer of hippocampus (Ann. New York Acad.Sci. 1994) The purpose of this study was to determinate nitric oxide synthase (NOS) activity and cGMP level in brain at different reperfusion time after 5 min of both common carotid arteries ligation (15, 30 min 1, 2, 4 hours 4, 7 days). Furthemore the localisation and type of NOS activated by ischemia-reperfusion injury and the action of NO on enzymes activity involved in arachidonic acid metabolism was evaluated. NOS activity was measured by [^{3}H]cytrulline formation and cGMP level by radioimmunoassay. The type of NOS and it localisation was determinated by mRNA and Northen blot analysis. It was found that NOS activity increased significantly during ischemia and biphasically during reperfusion time 15 min and 2 h after ischemia. Concomitantly biphasic increase of cGMP was observed. N-nitro L-arginine a specific inhibitor of NOS applied i.p. in a dose of 30 mg/kg 5 min before ischemia, eliminates the effect of ischemia-reperfusion injury on NOS/cGMP. The same effect was observed when animals were treated with specific inhibitor of neuronal form NOS, 7 Nitroinozide (7-NI), in a dose of 25 mg/kg b.w. 5 min before ischemia. Hydrocortisone in a dose of 40 mg/kg b.w. injected i.p. 7 days before ischemia has no effect on NOS/cGMP. There was no activation of gene encoding iNOS during reperfusion period. The inhibitory action of NO on enzymes involved in arachidonic acid metabolism was observed. Our results indicated that ischemia-reperfusion injury activates biphasically neuronal, constitutive form of NOS activity (cNOS). The inhibitor of neuronal form of NOS protects the brain agonist release and action of nitric oxide.

15.29 BRAIN Na,K-ATPase ACTIVITY IN RELATION TO BLOOD AMMONIA CONCENTRATION IN GALACTOSAMINE-INDUCED ACUTE HEPATIC ENCEPHALOPATHY

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Ammonia and other neurotoxins implicated in hepatic encephalopathy (HE) are known to inhibit membrane Na,K-ATPase both *in vivo* and *in vitro*. The inhibition of brain Na,K-ATPase is expected to influence brain function and could be also responsible for mechanisms and manifestations of HE. In the present study we have investigated the relation between blood ammonia levels and brain Na,K-ATPase activity in gerbils with galactosamine-induced acute HE. Experimental animals received 1.5 g/kg b.w. of selective hepatotoxin galactosamine intraperitoneally and were sacrificed by decapitation after 24, 48, 72 and 96 hours. At these times blood samples were drawn for ammonia determination and crude mitochondrial fractions of hippocampus (Hippo), caudate nucleus (NCd), cortex cerebri (Cx) and hypothalamus (Hyth) were used as Na,K-ATPase source. 24 hours after galactosamine application blood ammonia was elevated threefold. During the next three days it gradually decreased to 2.8, 2.5 and 1.6 times. In all the brain regions investigated a significant inhibition of Na,K-ATPase activity was detected; the greatest in Hyth, but without time-dependency. The inhibition of Na,K-ATPase activity in Hippo, Cx and NCd was time-dependent. The increase in blood ammonia 24 hours after the induction of HE was in correlation with the inhibition of the brain Na,K-ATPase activity, while the recovery of the enzyme's activity accompanied the normalization of primary elevated blood ammonia levels at the end of the experiment. These findings confirm the pathogenetic role of ammonia intoxication in HE.

15.30 A WHOLE CELL PATCH CLAMP STUDY OF THE MEMBRANE CURRENTS INDUCED BY HYPOXIA IN DENTATE GRANULE CELLS OF THE RAT HIPPOCAMPUS. G. Czéh* and J. Czopf Institute of Physiology University Medical School of Pécs, H-7643 Pécs, Szigeti ut 12. Hungary

Short periods of oxygen deprivation block neuronal activity in hippocampal slice preparations. CA1 pyramidal cells respond to acute hypoxic insults first with weak than stronger inward current and the membrane input resistance drops. In contrast with the rapid reaction of the CA1 pyramids, most of the dentate granule cells respond much less vigorously to the same insults and rather weak inward current can be recorded in them for a much longer period of time during hypoxia. Input resistance of the granule cells decreases by 40-60% gradually before, - and falls to about 20% of the normoxic value, - during the spreading depression phase of the hypoxia. The direction of hypoxia-induced inward current reverses to outward in cells V-clamped at levels more positive to -5 mV. Cesium or QX-314 solutions in the patch pipette does not block the hypoxia induced current. Cadmium (500 nM in the bath) blocks synaptic transmission but fails to prevent hypoxic spreading depression. The findings are interpreted in terms of selective vulnerability of the principal neurons in the hippocampus but parts of the cascade process remain to be elucidated.

15.31 ACUTE AND CHRONIC LEAD EXPOSURE IMPAIRS OF -SH GROUPS IN HOMEGENATES AND SYNAPTOSOMES FROM RAT BRAINS. B. Dabrowska-Bouta*, L. Strużyńska, U. Rafałowska, Department of Neurochemistry, Medical Research Centre, Polish Academy of Science, 3 Dworkowa st., 00-784 Warsaw, Poland

Lead, nonphysiological metal is know to be toxic by affecting the multiple organ systems in man. The main target for its toxicity is the central nervous system and the major neurologic manifestations are acute lead encephalopathy and lead neuropathy. Our earlier investigations of an isolated synaptosomal fraction have shown the existance of several mechanism of lead toxicity related to neurotransmitter transport. The Pb^{2+}/Ca^{2+} interaction, changes in morphology of synaptosomes and synaptosomal mitochondria, disturbances in oxygen uptake and level of energetic parameters, might play an important role in the toxicity of lead in neurotransmissions. Searching for other mechanism, which can be connected with Pb^{2+}-effects on neurotransmission we considered the changes of -SH groups level in synaptosomes and in homogenates obtained from brain of control and Pb^{2+} chronic and acute poisoned rats. 200mg $Pb(CH_3COO)_2/L$ drinking water was given to 3 weeks-old rats for 3 mounths (chronic model) and 15mg $Pb(CH_3COO)_2/kg$ b. w. was injected introperitoneally by 5 days. We found that lead had no effect on nonprotein -SH groups level in homogenates and in synaptosomes obtained from rat brain. However, the lead decreased statistically significant of total and proteins -SH groups levels in synaptosomes and in homogenates, about 10% in chronic and 15% in acute model of toxicity. This effect can influence activity of same enzymes and conformation of protein receptors what may be one of reasons of disturbances observed in neurotransmitters transport.

15.32 AMINOACID LEVELS FOLLOWING VENTRICULAR INJECTION OF ß-AMYLOID TO RATS. M.L.de Ceballos* and J.Manzanares. Cajal Institute, CSIC, Doctor Arce, 37, 28002 Madrid, Spain.

There are controversial reports about the neurotoxic effects of ß-amyloid (ß-A) in vivo. Alterations in aminoacid levels, receptors and uptake have been reported in Alzheimer's disease (Procter et al.,J.Neurochem.1988, 50:790). In this work the effect of intraventricular administration of ß-A 25-35 on hippocampal aminoacid levels, as measured by HPLC/fluor-imetric detection, has been studied. Single injection of ß-A (5 or 20 µg icv), alone or in combination with a subeffective dose of kainic acid (0.1 µg) did not alter Glu, Asp or GABA levels, 3 weeks later,compared to controls (20 µg scrambled peptide). However, repeated administration (7 days) of ß-A significantly increased hippocampal Glu concentration, without altering GABA or Asp. If increased Glu levels are translated into increased release this may result in neurotoxicity.

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15.33 CEREBROVASCULAR INSUFFICIENCY: ONE OF THE RISK FACTORS FOR COGNITIVE DECLINE IN AGING AND ALZHEIMER'S DISEASE? G.J. De Jong*, C.M. Stienstra, B.T. Stuiver, S. Knollema, J. Korf and P.G.M. Luiten. Univ. Groningen, P.O.Box 14, 9750 AA Haren, The Netherlands.

Although cognitive impairment during aging and in Alzheimer's disease (AD) is usually associated with neuronal alterations, the cerebrovascular systems undergoes prominent alterations as well. Using eletronmicroscopical (EM) techniques we previously showed a progressive deterioration of the microvascular wall in the cerebral cortex of aged rats. In aged rats the basement membrane (BM) of microvessels is thickened, massive bundles of collagen fibrils are deposited within the BM, and pericytes are degenerating. Detailed EM analyses suggest that the observed deviations are associated with a hampered nutrient transport across the blood-brain barrier (BBB).
The importance of the cerebral microvascular system and blood supply for cognitive functioning is studied using two different approaches. 1) The microvascular wall of AD patients and controls is electronmicroscopically analyzed, with the AD diagnosis based on the number of plaques and tangles. 2) The effect of a short period (5 minutes) of hypoxia (10% O_2 and 90% N_2O in respirator) combined with unilateral occlusion of the carotic artery in young adult Wistar rats on spatial learning is determined in the Morris maze (two trials per day) after a survival period of 4 weeks.
In the human entorhinal and prefrontal cortex a high incidence of ultrastructural microvascular anomalies was observed. Besides the deposition of ß-amyloid, thickening of and collagen fibrils in the BM, as well as degenerating pericytes were frequently encountered. With a limited number of cases (1 control and 2 AD's) the first pilot data indicate that the microvascular pathology may be more severe in the AD patients.
Neuronal death (determined after 24 hr-7 days) after the short hypoxic period is almost absent (modified Gallyas silverstaining revealed that <1 % of the total brain area is damaged). The influence of ischemic episode on spatial learning performance in the Morris maze is prominently reflected in the initial learning phase. In trial 1-3 it took the ischemic animals (n=6) significantly longer than the sham-operated controls (n=5) to locate the escape platform. In trial 4-10 animals from both groups reached the escape platform within 10 sec. After training trials on day 3 and 5 a 30 sec. probe trial showded that rats from both groups equally effective searched for the platfrom in the correct quadrant.
In conclusion, microvascular gray matter pathology occurs with high incidence in the aging human brain, and may be more severe in AD patients. Moreover, a short period of cerebral hyponutrition in adult rats yields subtle cognitive alterations.

15.34 SUSCEPTIBILITY OF OCULOMOTOR SYSTEM TO ANTIEPILEPTIC DRUGS.

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The influence of phenytoin (PHT) on spontaneous electrical activity of different pre motor and motor neurons of the oculomotor system was analyzed in rat to explain the oculomotor disturbances frequently observed in epileptic patients treated with some antiepileptic drugs. The spontaneous firing rate of multiunit activity was recorded from neurons localized in the paramedian pontine reticular formation, superior colliculi, III and VI nucleus. Recordings were performed before drug administration and up to 3-4 hours after (500mg/Kg/os). Results show that PHT significantly modifies the spontaneous electrical activity of the premotor and motor neurons of the oculomotor system by inducing excitation, inhibition or biphasic effect. PHT action was observed 10-15 min after drug administration, when plasma and brain concentrations were still low: 0.29 ±0.03 µg/ml in plasma and 0.24±002 µg/g in brain. The oculomotor system neurons appear to show a more precocious susceptibility to this drug, in comparison to other structures, cerebellum and vestibular nuclei, where PHT action has been described 1 hour after drug. It is possible to hypothesize that PHT affects oculomotor neurons directly and only with longer latency indirectly, through cerebellum and vestibular nuclei.

15.35 BRAIN INTERSTITIAL FLUID AMINO ACIDS IN PENTYLENETETRAZOL-INDUCED CONVULSIVE STATUS EPILEPTICUS.

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High doses of I.V. pentylenetetrazol (PTZ) may induce clonic, or tonic-clonic convulsive seizures in animals and man. The proposed mechanism of action of PTZ is a direct effect on excitability and stability of neuronal cell membranes and a selective antagonism of GABA-mediated postsynaptic inhibition. To further elucidate its mechanism of action we evaluated the free aminoacids levels in serum, CSF, and interstitial fluid (IF) of the brain in adult dogs anesthetized with thiopentotal sodium and divided in two groups. Group A rendered epileptic until development of convulsive generalized status by administering PTZ i.v. at 200 mg/kg; group B, anesthetized with thiopentotal sodium only. Blood, CSF and brain IF samples were taken at 5, 10, 15, 30, 60 min. after the appearance of convulsive status. Different dogs (2 to 3) were used at each time. A sufficient volume of brain IF was obtained by a multiperforated polypropylene ball measuring 10 mm in diameter, and implanted for 4 weeks into the parieto-temporal region. Amino acids concentrations were determined by HPLC. A dramatic increase of the extracellular concentrations of aspartate, glutamate and taurine was observed in the first 10 min. (between 8 and 29 times the control levels). A minor, but significant increase in the concentrations of ph-serine, serine, glycine and glutamine was also noticed. The concentration of glycine raised further at 30 min. This neurochemical imbalance may be responsible for the appearance of PTZ-induced convulsive status epilepticus.

15.36 ACTION OF POLYENE ANTIBIOTIC IN MOUSE SCRAPIE.

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Transmissible Subacute Spongiform Encephalopathies are characterized by the presence of a modified, partly proteinase-resistant host protein (PrPsc), which tends to accumulate in the brain of infected individuals. In two experimental models: hamster or mice respectively infected with 263K or C506M3 scrapie strain, treatment with Amphotericin B (AmB) and one of its derivative, MS-8209, prolongs the incubation period of the disease with treatment starting at day of the innoculation. We tested here, the effects of preclinical treatment with AmB and MS-8209 in intracerebrally infected mice. **Methods:** Treatment starting between 80 and 140 dpi, were interrupted after 30 days or continued until death of animals. Treatments were carried out six days a week by intraperitoneal injection, with dose ranging from 1 to 25 mg/kg Incubation period was analysed. The expression of PrP, GFAP genes were determined by Northern-Blot, and accumulation of PrPsc by Western-Blot. **Results:** First, treatment from 90 to 120 dpi induced an increase of 16.2 days in incubation time for MS-8209 treated mice at 2.5mg/kg ($p = 0.02$, t-test). Analysis of PrPres shown that the both drugs inhibit accumulation of PrPres at 120 dpi, whereas 30 days after interuption of the treatment, PrPres level were identical in all groups. Second, when treatment was prolonged until death, survivals in all the groups were significantly different from controls groups. For example we obtained a prolongation of incubation period with treatment at 25 mg/kg of MS-8209 since 80 dpi of 62 days (+40%), versus 13.5 days (+ 8.5 %) since 140 dpi. Molecular analysis revealed a reduce GFAP mRNA expression and PrPsc accumulation after 30 days of treatment initiated at 80 dpi and not at 110 dpi. **Conclusion:** These results suggest that, in experimental scrapie, AmB and MS-8209 seems to interfere either directly on the infectious process or on PrPsc metabolism. In conclusion, this transient effect of preclinical treatment suggests that neuropathological process in scrapie disease could be mediated by factors different from the expression of PrPc and its conversion into PrPres.

15.37 PERSISTENCE OF POLIOVIRUS IN MOUSE MOTONEURONS

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Poliovirus (PV) is the causal agent of paralytic poliomyelitis, an acute disease of the central nervous system in man. Paralyses result from lysis of motoneurons. Some PV strains, including the Lansing strain, have been adapted to mice, in which they cause a paralytic disease after intracerebral inoculation. All animals that become paralyzed following inoculation with the Lansing strain die. We previously isolated a mouse-adapted PV mutant derived from the Mahoney strain. Most animals inoculated with this mutant survived after the onset of paralysis. We took advantage of this model to study morphological alterations of motoneurons during a period of several months following inoculation. Optical and ultrastructural immunohistochemistry studies were performed to detect the presence of PV in the mouse spinal cord and to analyze ultrastructural modifications at 4, 6 and 9 months after inoculation. Virus particles visualized by immunofluorescence and immunoperoxydase assays using a monoclonal antibody directed against the PV capsid, were present in the motoneuron cytoplasm up to 9 months after inoculation. Surprisingly, in addition to chromatolyzed motoneurons, we also observed PV particles in motoneurons which appeared otherwise normal although they did contain a cytoplasm with a disorganized endoplasmic reticulum. Our results show that PV can persist for a long period of time in the spinal cord of symptomatic mice.

15.38 PHYSOSTIGMINE INCREASES ACTIVITY OF CORTICAL PYRAMIDAL NEURONES THROUGH THE M_1 RECEPTOR. Sas.N. Dijk *,Paul T. Francis, Gary C. Stratmann and David M. Bowen Miriam Marks Department of Neurochemistry, Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ.

Both the cognitive symptoms and the development of the histological hallmarks seen in Alzheimer's disease may be related to a reduction in glutamatergic neurotransmission in cortex and hippocampus. This reduction may be compounded by loss of acetylcholine, if acetylcholine positively modulates the activity of cortical neurones. To test this hypothesis we have monitored the activity of the corticostriatal pathway, using glutamate release as a putative marker. Glutamate release was monitored using microdialysis in the terminal field of the corticostriatal pathway, the striatum. Glutamate concentrations in dialysate were determined using HPLC with OPA derivitisation. Data were analysed with an unbalanced repeated measures ANOVA followed by either a LSD or a Students t-test. Significance was taken at $P<0.05$. Administration of physostigmine (0.3 mg/kg i.m but not 10 µM through the dialysis probe) significantly increased striatal concentrations of glutamate (but not aspartate). To gather evidence that this rise was due to an increased activity of the corticostriatal pathway, two experiments were performed. In the first experiment the selective M_1 agonist PD 142505-0028 was topically applied to the frontal cortex in a concentration of 10 µM. This almost immediately increased striatal concentrations of glutamate but not of aspartate. In the second experiment the selective M_1 antagonist telenzepine dihydrochloride was topically applied to the frontal cortex in physostigmine treated rats. Telenzepine nearly completely abolished the physostigmine induced increase in striatal glutamate. In conclusion our data suggest that physostigmine increases the activity of cortical pyramidal neurones through the M_1 receptor. An M_1 agonist may be useful in the treatment of Alzheimer's disease, maybe in combination with a selective 5-HT_{1A} antagonist.

15.39 COGNITIVE DEFICITS IN TWO PATIENTS WITH PROLONGED POSTTRAUMATIC LOSS OF CONSCIOUSNESS-

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We present two patients who sustained severe brain impairment as indicated by immediate and prolonged coma - for a period longer than a month. The aim of our study was to discuss the prognostic value of early indicators of head trauma severity - initial Glasgow Coma Score, Coma length and duration of posttraumatic amnesia - in two survivors of brain injury with similar pathological conditions, types of treatment, age and education, but with different neuropsychological outcomes.

In spite of the equality of their posttraumatic loss of consciousness duration, neither their cognitive status nor psychosocial dependercy were on the same level. While the first patient showed focal cognitive deficits in visual memory, visuoperceptual and visuoconstructive functions and a mild behavioural disturbance (verbosity), the other manifested severe global cognitive deterioration accompanied by a prominent behavioural alternation (inertia and unawareness).

We concluded that analysed indicators are not fully equivalent in prediction of outcome.

15.40 OPERANT PERFORMANCE IS DISTURBED DURING PAROXYSMAL SPIKE-WAVE ACTIVITY IN EPILEPTIC RATS.

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Spike-wave discharges (SWD) in the cortical EEG of epileptics are characteristically accompanied by a diminishment of responsiveness to external stimulation. The extent and the causes of this irresponsiveness are yet largely unknown. Also WAG/Rij rats spontaneously show numerous generalised SWD per hour, and are considered a valuable model for studying epileptogenesis of SWD such as found in human absence epilepsy. It was established in earlier studies that during SWD sensory processing was altered but not completely blocked, and that the meaning of an ictally presented stimulus can still be properly evaluated.

The present study investigated in WAG/Rij rats (n=6) whether during SWD an adequate instrumental response can be generated. Rats were trained in an auditory successive discrimination task, in which a food reward was delivered if the animals pressed the right lever upon presentation of a low frequency tone (7.4 kHz) or the left lever upon presentation of a high frequency tone (11.5 kHz; both 18 dB[A]). After training to criterion (> 75% correct), tones were presented during SWD.

No leverpresses were registered during ongoing SWD. If ictal stimulus presentation did not abort spike-wave activity (43.9% of all presentations), then after the spontaneous end of the SWD in a majority of cases no response (66.5 %) was given. Of the remaining non-aborted presentations 22.6 % was correct and 10.9 % was incorrect. However, ictal stimulus onset mostly (56.1% of all presentations) aborted the ongoing spike-wave activity, in which case animals responding within 1 second with near normal accuracy (60.1% correct; 15.7% incorrect; 24.2% no response).

To conclude, despite earlier reported adequate stimulus evaluation, the organisation and execution of a correct motor response is restricted to non-epileptic EEG activity.

15.41 CHAOS IN EEG SIGNALS FROM PATIENTS WITH "PETIT MAL" ABSENCES

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In recent years, there has been an increasing activity in the application of chaos theory to the understanding of EEG signals. The application of such theory to brain signals may provide a new insight into the dynamics of the physiological processes, and allows a quantitative characterisation of such processes. However, a careful discussion of the applicability of the theory is required.

In our work we analyse 19-channel EEG data from patients with "petit mal" epilepsy, using chaos theory. We analyse the signals before and during the seizures. An analysis of the nature of the signal is made in order to distinguish chaotic behaviour from noise. This is made by comparing the real signal with a signal with the same power spectrum but with random phases. We calculate the correlation dimension D_2 for the different signals. Only when there is a clear difference between the dimensions of the two signals may it be concluded that the real signal is different from noise (white or coloured). Finding a finite value for D_2 does not necessarily imply chaotic behaviour, since a finite D_2 can also be obtained from coloured noise.

We find that before the seizure the real signal and the signal with randomised phases look similar and no convergence was found, up to an embedding dimension of 16, in the calculation of D_2. By contrast, during the seizure we find that the real signal and the randomised signal look different: the former is characterised by a correlation dimension $D_2 \approx 2$, while for the latter no convergence was found for D_2 up to an embedding dimension of 14. Therefore the real signal is clearly distinguishable from noise and seems to exhibit chaotic behaviour. We present maps of D_2 for the 19 channels. We also present an estimation of the Kolmogorov entropy.

Our results will be discussed in relation to other clinical data from the patients, such as localization of neural epileptic sources.

15.42 ENKEPHALINERGIC NEUROMODULATORY SYSTEM IN RAT MYELENCEPHALIC RESPIRATORY REGIONS. EFFECT OF TOLUENE ADMINISTRATION.

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Toluene is a widely used organic solvent. Acute exposure to this toxicant occurs through the practice of deliberate inhalation (glue sniffers) and occasionally among painters and workers in the chemical industry, and can generate neuropathological changes including respiratory depression. Phasic respiratory neurons in rats have been located in the ventrolateral medulla, nucleus ambiguus and lateral reticular nucleus. Althoug little is known concerning the neurotoxic mechanism of toluene induced respiratory depression, enkephalin immunoreactive perycaria and fibers are present in myelencephalon and are abundant in respiration regulatory regions. Due to the regulatory role of enkephalins at this level, we focused on analyzing brain immunostaining for leu-enkephalin in acute and subchronically toluene-treated rats. Morphologic alterations and a reduction in enkephalinergic neuronal density in the nucleus ambiguus after acute toluene exposure in rats were observed. However, subchronic treatment with the toxicant generated an increase in neuronal density of immunostained perycaria for leu-enkephalin, suggesting a stimulatory action on enkephalinergic neuromodulation. Due to the physiological role of enkephalins in the central regulation of respiration, it could be suggested that the myelencephalic enkephalinergic system might play a role in neurotoxic respiratory depression induced by toluene exposure.

15.43 **EARLY MATERNAL DEPRIVATION ENHANCES APOMORPHINE SENSITIVITY AND REDUCES LATENT INHIBITION.**

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In recent years it has become clear that schizophrenic patients suffer from specific information processing and cognitive disturbances such as sensory gating and selective attention deficits. Since these processes can be measured in humans and animals with virtually identical methods, they represent an ideal starting point for studying the neuronal mechanisms underlying the schizophrenic disease process.

Given the increasing evidence that schizophrenia is a neurodevelopmental disorder, we have focussed on the effect of early maternal deprivation on one aspect of information processing known to be disturbed in schizophrenia: latent inhibition.

Rats were deprived from their mothers for 24 h at 10 days of age and tested at an adult age of 60 days. Using the conditioned taste aversion paradigm, we could show that maternal deprivation leads to a disruption of latent inhibition, while not affecting conditioned taste aversion itself. Moreover, maternal deprivation significantly enhanced the sensitivity of rats to apomorphine, thereby confirming the previously observed negative correlation between latent inhibition and apomorphine susceptibility. These data suggest that early maternal deprivation might represent an interesting new animal model for studying developmental aspects of information processing. Experiments in relation to other aspects of information processing known to be disturbed in schizophrenic patients (such as prepulse inhibition and P_{50} gating) are currently underway to test the generalisability of this neurodevelopmental approach.

15.44 NEUROPROTECTIVE EFFECT OF LIPID PEROXIDATION INHIBITORS ON VARIOUS MODELS OF CEREBRAL DISEASES.

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One of the most important inducer of neurodegenerative diseases is the formation of free radicals causing lipid peroxidation (LPO) in the brain. Some LPO inhibitors (U74006F, U78517F, idebenone, vitamin E and allopurinol) were investigated and compared in several ischaemic/hypoxic, edematous and traumatic brain injury models.

Compounds	KCN cytotoxicity (i.p.)	Bilateral carotis occlusion (i.p.)	Traumatic brain injury (i.v.)	Arachidonic acid brain edema (i.v.)	Nitrogen anoxia (p.o.)
U74 06F	+	+	+	+	+
U78517F	+	+	-	-	+
Idebenone	++	+	-	-	-
Vitamin E	-	++	+	++	+
Allopurinol	++	n.t.	-	-	-

n.t. = not tested
- = no statistically significant effect
+ = statistically significant effect
++ = marked statistically significant effect

These results suggest the following effectivity order of the compounds investigated: U74006F > vitamin E > U78517F ~ idebenon > allopurinol.

15.45 **EFFECTS OF SHORT TERM ETHANOL EXPOSURE ON HIPPOCAMPAL CA1 PYRAMIDAL CELLS**

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Chronic alcohol ingestion leads to learning deficits and structural changes in the central nervous system, both in humans and in animal models. The hippocampus is involved in spatial learning, and is also highly sensitive to chronic ethanol exposure. We have examined the effect of high blood alcohol level over a shorter period on the dendritic spine pattern of hippocampal CA1 neurones.

Adult, male Long-Evans rats were given two daily intraperitoneal injections of 12 % ethanol (1.6 ml/kg body weight in isotonic saline, n=6) or the same amounts of saline (control, n=6) for 10 days. This gave two blood alcohol peaks daily (mean value 193 mg/100 ml). The body weight and health status were checked regularly. On the 11th day the animals were anaesthetized, the hippocampi were removed, cut in slices, mounted in a tissue chamber, and CA1 pyramidal cells were filled with the fluorescent dye Lucifer Yellow (4 % in 0.2 M LiCl). After fixation and dehydration we examined a total of 37 cells, 360 dendritic segments and counted about 21.600 spines in a laser-scanning confocal microscope.

In contrast to the expected loss of spines, ten days of ethanol exposure gave a tendency towards increased spine density in the basal (+ 6.5 %, p=0.1) and apical (+ 7.7 %, p=0.06) dendrites, similar to morphological changes induced by spatial training. However, the results were not statistically significant. Coupled to the fact that the alcohol-treated rats lost body weight compared to the control group ($p<0.01$), the results suggest that the observed spine change might be a general, possibly transient, reaction to an altered metabolic situation.

15.46 CORRELATION BETWEEN REACTION TIME MEASUREMENTS AND BEREITSCHAFTSPOTENTIAL IN PATIENTS WITH PARKINSON'S DISEASE

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Prolonged movement initiation time, together with general slowing of movements, are among the cardinal features of clinical presentation of patients with Parkinson's disease (PD). Reaction time (RT) testing give unique opportunity for objective assessment of characteristics of these impairments. On the other side, it is supposed that Bereitschaftspotential (BP) reflects CNS preparatory activity for the execution of voluntary movements. However, there is no clear correlation established yet between the two approaches to the study of movement.

We studied 15 PB patients with idiopathic PD, who have no signs of gross cognitive impairment, and who have never received any antiparkinsonian treatment. BP was recorded from three scalp locations: Cz, C3, and C4. The requested movement was self-initiated pressing of a button with middle finger of right hand. We recorded amplitude of the initial part of BP (at 650ms before movement - NS1) and the maximal amplitude immediately before movement onset (N1) from the Cz, and difference of the amplitudes from C3 and C4 at the same time points (i.e., 'lateralization potentials', C3-C4). From RT testing 3 measures were derived. From simple RT paradigm: a) Central RT (CRT) - time interval from stimulus to movement onset, b) Movement Time (MT) - time interval from depressing resting button (movement onset) to pressing target button. From two-choice RT paradigm: c) Choice Time (ChT) - difference between total Choice RT and Simple RT. Finaly, we calculated the Spearman rank correlation coeficients between the BP and RT parameters.

The only significant correlation was between ChT on one side, and both, NS1 and N1 (r= -0.74, p=0.006; r= -0.59, p=0.026; respectively), from the Cz site, on the other side.

Our data suggest that PD patients with more dificulties in choice decision making (i.e., longer ChT) have smaller BP amplitudes. This association is especially pronounced for the earlier, NS1 amplitude that is supposed to reflect the activity of the supplementary motor area (SMA). The dimminished capacity of SMA activation may be the cause of the actual slowing of the process of decision making.

15.47 **INTRACELLULAR Ca^{2+} LEVELS DURING GLUTAMATE-INDUCED TOXICITY IN CULTURED EMBRIONIC HIPPOCAMPAL NEURONS: INFLUENCE OF OPIOIDS.**

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Glutamate (Glu) is a primary transmitter at many central nervous system synapses. Beyond to his physiological role glutamate can act neurotoxically under certain conditions with intense exposure to Glu of central neurons. This applies to states of acute ischemia, the aftereffects of which result in neuronal death. Hypoxia can led to abnormal neuronal depolarization with spreading depression, resulting in a long-lasting increase of glutamate concentration at the synapses in the focal lesion. The excessive stimulation of glutamate receptors is thought to be the neurotoxic cause. Neurotoxic states after the abuse of glutamate receptors are in particular ascribed to abnormally increased intracellular Ca^{2+} activity.

The aim of this study has been to elucidate the role of calcium in neurotoxicity, and to investigate the interference of activated opioid receptors with glutamatergic, possibly metabotropic actions. The presence of opioids receptors has already been demonstrated in hippocampal mossy fiber system, where glutamate acts as transmitter.

15.48 INCREASED EXPRESSION OF P21-RAS IN ALZHEIMER'S DISEASE.

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The neuropathological hallmarks of Alzheimer's disease are neurofibrillary tangles and senile plaques which are thought to contribute to neuronal dysfunction and massive degeneration of neurons. Paralleling these degenerative changes, dendritic sprouting has been observed in affected brain areas which might either be related to endogenous neuronal alterations or to changes of trophic activity of the neuronal environment. In this context, speculations have aroused whether aberrant activity and localization of components of the intracellular signalling mechanisms might be involved in the formation of the neuropathological changes.

The present study is focused on the plasma membrane associated protein p21*ras*, which is highly abundant in nervous tissue. *Ras* proteins act as molecular switch in signal transduction pathways that regulate cell growth and differentiation. Binding of neurotrophic factors to tyrosine kinase receptors converts *ras* proteins from their inactive, GDP-bound, to active, GTP-bound state and induces the activation of the MAP kinase cascade, which regulates the activity of transcription factors. Furthermore, MAP kinases have been reported in vitro to lead to an aberrant phosphorylated state of the microtubule-associated protein *tau*, the major component of paired helical filaments in AD.

The overall expression of p21*ras* as determined by an ELISA was increased in AD as compared to controls. P21*ras* immunostaining was detectable in neurons and glial cells in a variety of brain areas. In AD brains p21*ras* was localized in tangle bearing as well as in unaffected neurons. P21*ras* immunreactivity was intensely associated with senile plaques. The results suggest a possible involvement of p21*ras* in the formation of neuropathological changes in AD.

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15.49 PICTORIAL PRIMING IN ALZHEIMER'S DISEASE

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It has been reported that dementia of the Alzheimer Type (DAT) is characterized by deficits on lexical and semantic priming. In the present work, we examine whether DAT patients' priming deficits involve pictorial materials. A picture fragment task was used to compare the priming performance of DAT patients and neurologically intact normal control (NC). Subjects were first given a naming test. The fragment identification test was administered after the naming test. Normal controls and DAT patients demonstrated an increase in their ability to identify fragmented versions of previously seen pictures relative to novel pictures. However, the NC subjects demonstrated better performance on the picture fragment test that the DAT patients. This finding provides further support for the proposed pattern of moderately preserved pictorial priming ability in DAT.

15.50 Abstract withdrawn

16. Poster Session: Sensory systems I

16.01 FORMALIN PAIN AND ACETYLCHOLINE RELEASE IN THE RAT HIPPOCAMPUS

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Formalin pain has been found to affect the hippocampal cholinergic system; the activity of choline acetyltransferase (ChAT) decreased in male rats 30 and 60 min after the subcutaneous injection of formalin. The aim of the present experiment was to assess whether the decrease in ChAT is accompanied by a modification of acetylcholine (Ach) release. A microdialysis cannula was implanted in the dorsal hippocampus of male rats. Ach release was measured after the animals had been placed in an open field apparatus, both before and after formalin injection (50 µl, 10%). Introduction to the open field produced a clear increase in Ach release, while formalin-treated animals always had lower levels than controls, although the differences were not statistically significant. The results indicate that novelty stimulates hippocampal Ach release, while pain does not. They also suggest that depression of the cholinergic system can explain the decrease in attention and memory found in humans experiencing pain.

16.02 **THE EFFECT OF A TAURINE MODIFIED DIET ON COCHLEAR ADAPTATION TO HYPOXIA : A FUNCTIONAL AND IMMUNOHISTOLOGICAL STUDY.**

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Taurine, the most abundant free amino acid in mammals, found in all parts of the body, is involved in very numerous physiological processes. Osmoregulation, phylogenetically its most ancient function could underly its many physiological activities. In the inner ear very little data are available. Taurine was found by immunocytochemistry to be localized in supporting cells and disputably in sensory cells; it seems unlikely to be a neurotransmitter, and its depletion was slightly protective against deafness induced by endolymphatic swelling (hydrops). The aim of this study was to investigate again its cochlear localization with a different antibody, and to further assess its implication in another stressful condition involving an hypoosmotic component. Experiments were performed on adult pigmented guinea pigs. The localization of taurine was investigated with a polyclonal antibody, observations of surface preparations and radial slides under light microscopy revealed immunoreactivity in supporting cells of the organ of Corti. Modifications of taurine level was induced by feeding animals with a β-alanine or a taurine supplemented diet. Immunoreactivity was found abolished in β-alanine treated animals. Functional electrophysiological investigations were performed under hypoxic hypoxia known to involve an hypoosmotic stress component. Animals under a taurine-supplemented diet showed reduced adaptation during hypoxic hypoxia. In cochleas observed just at the end of hypoxia no change in immunolabelling was observed compared with controls. These data agree with the localization of taurine in supporting cells of the organ of Corti and further establish the involvement of taurine in pathological conditions. They are compatible with an osmoregulator role of taurine in the organ of Corti.

16.03 CHOLINE ACETYLTRANSFERASE (CHAT) AND ACETYLCHOLINESTERASE (ACHE) IN THE MACAQUE MONKEY OLFACTORY BULB

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The distribution patterns of ChAT and AChE were studied in the olfactory bulb of two species of macaque monkeys, *Macaca fascicularis* and *Macaca nemestrina*. ChAT immunoreactivity was detected by using a monoclonal antibody and the avidin-biotin-peroxidase method and AChE activity by using an histochemical method. The distribution of ChAT and AChE labelings were practically identical in all layers of the olfactory bulb in both species studied. All layers of the macaque monkey olfactory bulb, with the only exception of the olfactory nerve layer, demonstrated a dense innervation of AChE and ChAT positive fibers. The histochemical distribution of AChE was very similar to the immunohistochemical distribution pattern of ChAT, although the density of ChAT-labeled fibers was clearly lower. The deep glomerular layer, the external portion of the external plexiform layer, and the internal plexiform layer showed the highest density of stained fibers. In addition to AChE-positive fibers, a small population of AChE-labeled neuronal bodies was observed. These neurons were presumably identified as periglomerular cells, short-axon cells and/or tufted cells. The distribution patterns of ChAT and AChE activities in the macaque monkey olfactory bulb resembled closely the patterns described in macrosmatic mammals.

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16.04 EFFECTS OF A NON PEPTIDE NK1-RECEPTOR ANTAGONIST (RPR 100893) ON THE TOOTH PULP-EVOKED JAW OPENING REFLEX IN THE GUINEA-PIG

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The selective stimulation of incisor tooth-pulp afferents evokes a long-latency jaw-opening reflex in the awake chonic guinea-pig, similar to the reflex previously described in the same conditions in rat. In contrast to this last species, guinea-pig incisor dental pulp contains a rich peptidergic sensitive innervation, similar to that described in cat and man, mainly composed of Aδ and C nerve fibers.

One of the key areas in which SP is considered to play an important role is in transmission of pain at the spinal cord level and in neurogenic inflammation. Experimental evidence suggests that SP can be released from peripheral nerve terminals of primary nerve afferent C-fibers to produce inflammation of from their central terminals to modulate nociceptive transmission at the level of the dorsal horn.

Recently, a relatively selective non-peptide antagonists of the NK1 receptor, RPR 100983, has been developped.

In the present study, the effects of this NK1 receptor antagonist have been investigated on the tooth pulp-evoked jaw-opening reflex in the guinea pig. RPR 100983 evokes a dose-dependent increase of the long latency jaw-opening reflex threshold, without effects on the short latency jaw-opening reflex, which involves a different group of sensitive afferents. RPR 103253, a stereo-isomer has no effect on these reflex thresholds.

16.05 SINGLE NEURON ACTIVITY IN THE DORSAL NUCLEUS OF THE LATERAL LEMNISCUS OF THE RAT.

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The aim of the present study was to establish the discharge properties of single neurons in the Dorsal Nucleus of the Lateral Lemniscus (DNLL) of the rat, both in absence or presence of acoustic stimulation. Extracellular single unit recordings were conducted in the DNLL of 13 adult albino rats, anaesthetized with a mixture of ketamine and thiazine, using 1 to 3 tungsten microelectrodes driven simultaneously in parallel. On the basis of their spontaneous firing pattern, a sample of 82 units was divided in subpopulations. Type Ia units (n=28) showed regularly spiking, characterized by a spontaneous firing rate below 2 spikes/second (s/s). Type Ib (n= 17) were similar to type Ia, but at a higher rate (mean 7.5 s/s). Type II neurons (n=37) showed a tendency to fire in bursts and discharged on the average at a rate of 3.8 s/s. Independently from the type of discharge, the units with high firing rate tended to be located preferentially in the rostral part of DNLL. The single unit responses to white noise bursts (200 ms, binaurally delivered at 10 dB above threshold) were analyzed by peristimulus time histograms (PSTHs). 104 units could be well-isolated during noise stimulation and 72 units responded to noise bursts. We studied the response pattern to noise subdividing the peristimulus period in 5 time segments. In the early-on period (0-30 ms) 67 neurons responded to noise (53 of them with an excitatory response). In the late-on period (30-80 ms), 59 neurons presented a response while 37 neurons were influenced during the sustained period (80-200 ms). Following offset of stimulation, 28 neurons showed a response in the early-off period (200-250 ms) with inhibitory response in 23 units of them and 20 neurons presented response in the late-off period (250-400 ms). Binaural interactions were studied under noise burst stimulation in 75 DNLL units; 56 units presented an EI response, 10 EE, 8 E0 and 1 I0 response.

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16.06 NADPH POSITIVE CELLS AND PAIN-INDUCED FOS EXPRESSION IN THE LUMBAR SPINAL CORD OF THE RAT.

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Nitric Oxide synthesizing cells have been implicated in pain transduction mechanisms. We examined in the rat L4 lumbar segment a) the distribution and morphology of NADPH positive neurons at light and electron microscopy and b) their colocalization with pain-induced FOS expression following formalin injection in the hindpaw. NADPH positive cells of the marginal type could be found in lamina I and small cells with vertical or radial orientation in clumps or palisades in lamina II. Big bipolar and multipolar cells were found in laminae III and IV. Positive cells were also present along the medial part of the neck of the dorsal horn, around the central canal and at the medialmost border of lamina VIII. FOS and NADPH doubly reacting neurons were rare but constant in location (lamina I, II, X). FOS positive neurons had a broader laminar distribution than NADPH positive neurons especially in the lateral part of the neck of the dorsal horn, where NADPH positive cells were infrequent. Although there is a good correlation between the location of identified pain-responsive neurons and NADPH positive neurons, the contribution of the former to pain transduction following chemical noxious stimuli (as identified through FOS expression) appears limited.

16.07 EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ON CHEMICAL SENSITIVITY OF CORNEAL NOCICEPTORS

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Prostaglandins (PGs) and other eicosanoids formed during tissue injury contribute to activation and/or sensitization of nociceptors. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit cyclo-oxygenase and thus the formation of PGs from arachidonic acid. A direct action of these drugs on nociceptive terminals has also been suggested. In anesthetized cats, activity of single corneal sensory units was recorded from ciliary nerve filaments. Polymodal nociceptive fibers were identified by their firing response to mechanical stimulation with a Cochet-Bonnet esthesiometer and to pH drops elicited by a 30s, 98.5% CO2 jet applied on the cornea at 15 min. intervals. Evoked impulse discharges were compared before and at different times (5-80 min) after a single topical application of sodium diclofenac (0.1%) or flurbiprofen (0.03%). Most corneal afferents (63.6%) were transiently excited by both drugs. Mechanical threshold was not significantly altered by treatment. In contrast, both diclofenac and flurbiprofen reduced significantly the impulse response evoked by CO2 pulses. These results indicate that NSAIDs decrease chemical sensitivity of corneal polymodal nociceptors, without causing anesthesia. They may, thus act as analgesic drugs for topical treatment of corneal pain.

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16.08 ENCODING OF PERIODIC CHANGING FM-SOUNDS IN THE AUDITORY CORTEX OF THE SQUIRREL MONKEY

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The squirrel monkey's vocal repertoire shows a high number of vocalizations with periodically changing up- and downward directed FM-sweeps. We synthesised such FM-sounds with an Apple Macintosh computer. The sounds had a length of 500ms and the frequency sweeps ranged from 2 kHz to 9 kHz with a frequency changing at a rate between 100 kHz/sec and 370 kHz/sec. These sounds were used as stimuli to analyse the way in which neurones in the auditory cortex encode signals with time-varying spectral content. The neural activity of single cells and multi units was recorded extracellulary. The animals were awake during the recording session. It was the aim of this study to find answers to the following questions:

1.) Is there a selectivity of neurones for certain features of periodic FM-stimuli ?

2.) What are the underlying neural mechanisms ?

We found that only < 10% of the neurones investigated responded quite selectively to FM-stimuli but not to pure tones. In contrast, most neurones responded to a certain FM-sweep in exactly the same fashion as they responded to particular static tones. The periodic changing FM-elements in squirrel monkey calls were encoded by temporally precise neural response patterns with preferred periodicity frequencies. These preferred periodicity frequencies were in the same range as the periodically changing FM-sweeps of the natural uttered calls.

16.09 Function of the mystacial vibrissae

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We have investigated transduction operation and function of the mystacial vibrissae. By first documenting qualitative and quantitative invariances of vibrissal architecture in a series of mammals we sought to identify evolutionary conserved features of vibrissal organization. The mystacial pad is invariably comprised of whiskers aligned in regular rows. In each row, whiskers are oriented perpendicular to the animal's rostrocaudal axis and share one dorsoventral orientation. In all species there is a precisely exponential increase of whisker lengths progressing from rostral to caudal. Mechanically the whisker appears to act as a lever-like transducer, providing information as to whether, but not where, it has been touched. We found that the rat's frontal microvibrissae system has a vibrissae tip density that is fifty times higher than that of the mystacial macrovibrissae. Behaviourally we studied spatial and object recognition tasks by a combined investigation of a) search behavior, b) single whisker movement reconstruction, c) psychophysics of object recognition, and d) the effects of selective macro- and microvibrissae removal. We observed a clear functional distinction: Mystacial macrovibrissae were critically involved in spatial tasks, while microvibrissae were critically involved in object recognition tasks. A synopsis of morphological and behavioural data led to the following functional concept: The mystacial macrovibrissae row is constructed as a distance decoder with whiskers acting as binary (touched/untouched) distance detectors. The suggested computational task of the mystacial macrovibrissae is to derive head centered obstacle / opening contours in various dorsoventral angles coded by the rows. This distance-detector model is functionally very different from traditional concepts of whisker function in which the mystacial whiskers are commonly viewed as forming a fine grain touch-like sensory surface.

16.10 PRECISION GRIP IMPAIREMENTS IN CENTRALLY DEAFFERENTED PATIENT

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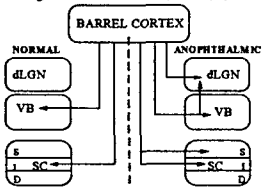
Recent evidence has shown that while a small object is lifted between the index finger and thumb, the control of precision grip relied both on anticipatory programming of isometric forces and on regulatory motor events triggered by reafferent informations. However, the central organisation of somatosensory information processing associated to these various control mecanisms lacks precise description. In order to adress this question, the influence of object weight and object texture on grip force response were tested in 3 deafferented patients showing distinct lesions of the somatosensory information processing systems.

The results reveal dissociated perturbations of precision grip whether the lesion is located at the subcortical level, in postcentral gyrus or in posterior parietal areas. It suggests that several independent anatomo-functional systems of sensory information processing are involved at different stages in the control of precision grip; programming of movement parameters, feed forward control and feed-back control. An interpretation in term of modular organisation of somesthetic information processing is proposed.

16.11 BARREL CORTEX PROJECTS TO SUBCORTICAL STATIONS OF THE "VISUAL" PATHWAY IN BLIND MICE: A TRACING STUDY.

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In congenitally blind mice and, in a lesser extent, in neonatally bilaterally enucleated mice somatic afferents from the dorsal column nuclei enter the dorsal lateral geniculate nucleus (dLGN) *(Asanuma and Stanfield, Neurosci, 39:533, '90)*.



Here, we studied the descending projections from the barrel cortex in 3 groups of mice: (i) anophthalmic mutant mice; (ii) neonatally bilaterally enucleated mice; (iii) eyed normal mice. In these mice, anterograde (dextran-biotin) and retrograde (Fluorogold) tracers were injected in the barrel cortex. In the anophthalmic mutant mice numerous labeled cortical fibers terminated within the dLGN. These fibers entered the dLGN either directly or by passing through the ventrobasal nucleus (VB). Very few retrogradely labeled cells were found in the dLGN after retrograde tracer injections in the barrel cortex. A similar pattern of cortical projections were found in enucleated mice. In the superior colliculus (SC) of the anophthalmic mice, labeled corticotectal fibers formed patches of terminals in the intermediate layers (I) as in normal mice. In addition, in the mutant labeled fibers terminated in the superficial layers (S) of SC. We conclude that in blind mice, the cross-modal rewiring affects also the organisation of descending projections within sensory pathways. Support: Swiss N.S.F. 31-39184.93.

16.12 CALLOSAL AND CORTICO-CORTICAL ZINC-RICH CONNECTIONS TO THE VISUAL CORTEX OF THE RAT

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Zinc-rich boutons are noticeable in the cerebral cortex, particularly in layers 1b, 2/3, upper 5 and 6, where they establish asymmetric contacts with dendritic spines *(J Comp Neurol 329:53)*. In the present study, sodium selenite was used as retrograde tracer to identify callosal and cortico-cortical neurons giving rise to zinc-rich boutons in the visual cortex of the rat. In 24 male adult Wistar rats, sodium selenite was delivered to various sites of the visual cortex. After 24 hours, retrogradely labelled somata were observed in layers 2-3, lower 5 and 6, in the following locations: (1) Ipsilaterally in different portions of the primary and secundary visual cortex. (2) Contralaterally, mainly in homotopic visual areas and sparsely in heterotopic areas. (3) Ipsilaterally, but outside the visual cortex, in cingulate, frontal, orbital, perirhinal and retrospenial cortices.

Injections restricted to superficial layers labelled neurons only in supragranulars layers, while injections encompassing all layers rendered labelled neurons in supra- and infragranular layers. In all cases, zinc-rich neurons were absent in layer 4. Thus, zinc-rich pathways appear to form an ample system of cortico-cortical connections with outstanding self-segregation into supragranular and infragranular layers. These findings suggest that zinc-rich connections may have a specific role in intra- and interhemispheric information processing.

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16.13 RAT PIRIFORM CORTEX HETEROGENEITY: ANATOMICAL AND FUNCTIONAL EVIDENCE.

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Piriform cortex (PC) receives direct massive inputs from the olfactory bulb(OB). This investigation was made for testing our hypothesis that this large paleocortical area could be an assembly of functional subunits rather than an homogeneous functional center. Using combined tracing and neurotransmitters immunohistochemistry we determined the organization of the centrifugal inputs onto the PC. The noradrenergic fibers, arising from the locus coeruleus dorsal part, were homogeneously distributed in the PC. The dopaminergic fibers arised mainly from the ventral tegmental area: parabrachial pigmented and paranigral nuclei. Moreover these fibers were topographically distributed in the PC: a rostral to caudal increase in the number of dopamine immunoreactive fibers was observed and a lateral to medial increase in their density was also noted. Such a PC topographical organization has been already described for the serotonergic projection from the raphe nuclei (Datiche et al., Brain Res., 1995, 671, 27-37). The spatio-temporal distribution of PC activity was studied by using multisite optical recordings with a voltage-sensitive dye. PC activity was recorded in response to rhythmical stimulations delivered in the OB according to the sniffing rhythm (10Hz). Different types of early signals could be distinguished during the successive responses, according to the level of disynaptic activity inhibition. Their spatial distribution allowed us to distinguish two different PC areas: the first, in which the inhibition level remained high, was located close to the lateral olfactory tract. The second, located in the most posterior PC area, exhibited a fast decrease in disynaptic inhibition during the successive responses. Moreover, a late component of PC activity which was sometimes observed was always larger in the posterior PC and was rarely noted in its anterior part. These data agree with the hypothesis of an ensemble of functional subunits in the PC.

16.14 ALTERATIONS OF AVERAGE SPECTRUM OF COCHLEAR SPONTANEOUS ACTIVITY BY ANESTHESIA AND SALICYLATE AS MODELS OF TINNITUS

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The average spectrum of electrophysiological activity recorded in silent conditions has been previously shown to present a peak around 1 kHz which reflects spontaneous sensori-neural activity. This paper demonstrates that the averaged spectrum of spontaneous activity (ASSA) is modified between awake versus sedated or anesthetized conditions. These data further emphasize that caution should be taken when interpreting the physiological significance of spontaneous spike rate measured from single fibers of the auditory nerve under anesthesia. Ipsilateral acoustic stimulation with pure tones at various intensities induced a decrease of the 1 kHz peak of the average spectrum when stimuli were in the frequency range of the best absolute sensitivity of the guinea pig i.e. 4 to 25 kHz. Contralateral stimulation with the broad-band noise produced a decrease of the 1 kHz spectral peak at intensities lower than interaural acoustic cross-talk and an increase at higher intensities. These data confirm the base of the cochlea as the origin of the 1 kHz peak of average spectrum and give some support to involvement of the crossed olivo-cochlear efferent system. ASSA was also found to be very sensitive to even small losses of absolute acoustic sensitivity of the ear as measured with compound auditory nerve response thresholds. ASSA was found to be modified over a wider range of frequencies by administration of salicylate even in the absence of threshold elevation of the compound action potential. At the lower doses of salicylate no threshold elevation was observed whereas clear ASSA alterations occured. At higher doses of salicylate both threshold and ASSA were altered but with different time courses, threshold elevations starting later and recovering sooner. This decoupling presents a remarkable correspondence with tinnitus occuring as a precursor symptom before threshold elevation in humans.

16.15 **Influence of geometric category of the forms in visual processing of hierarchical stimuli : some evidence in normal and brain-damaged subjects**

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The global precedence hypothesis, which asserts that visual processing of hierarchical stimuli proceeds from the global level of structure to the local level, is based on the joint occurrence of a global advantage in response time (RT) and global interference on local-level identification. These effects have been taken as evidence that visual pattern perception is serially organized, but they may be influenced by many factors. The purpose of the present experiment was to examine whether the geometric category (cartesian/polar) of the target form may influence the mode of visual processing of hierachical stimuli. Using Navon's paradigme, a set of stimuli formed from squares and circles was presented to 8 normal subjects with their attention alternatively directed to either local or global identification. A global advantage in RT and global interference were found for both target forms, but local interference was found when the target form was the circle. We subsequently tested two patients respectively presenting bilateral occipito-parietal lesions (OPL) and bilateral occipito-temporal lesions (OTL). The OPL patient showed no global interference and a local precedence effect depending on the identity of the target form. The OTL patient showed an amplification of global precedence effect for both target forms. These results confirm that different modes (parallel/serial) of visual processing are adopted by the two visual subsystems. Furthermore they suggest that these modes are specifically affected by local or global orientation of attention and by the geometric category of the shapes.

16.16 PROSOPAGNOSIA WITH AND WITHOUT ACHROMATOPSIA: RELATIONSHIP WITH EARLY STAGE VISUAL AREAS

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We report on 2 cases with prosopagnosia after bilateral postero-inferior hemispheric lesions. Patient 1, 57 year old man, had infarctions in the inferior occipital lobe on the right and in the inferior occipital & infero-posterior temporal lobes on the left side (& old right frontal infarction). He had superior attitudinal hemianopsia, achromatopsia, lettre-by-lettre alexia, memory deficits, light deficits in executive functions and deficits in visual recognition. The latter included prosopagnosia, topological agnosia and incapacity to recognise plants and fish (for which he had specialised knowledge). Patient 2, 50 year old woman, suffered a closed-head injury. She had bilateral symmetrical lesions of fusiform, and middle & inferior temporal gyri, whereas hippocampal formation, parahippocampal gyrus and occipital cortex were spared. She had severe prosopagnosia and topological agnosia (including for mountains which she knew well before her disease) as well as memory deficit., but no visual field deficit nor achromatopsia. Comparison with anatomically defined visual areas (Clarke and Miklossy '90; Clarke et al. '95) showed that patient 2 had lesions outside early stage visual areas V1, V2, V3, VP, V4, V5 "VOT" and "IT"; whereas patient 1 had some of these areas damaged bilaterally (lower parts of V1 and V2, VP, V4, "VOT", "IT").

Thus, i) prosopagnosia can occur without damage to early stage visual areas and ii) achromatopsia is associated with prosopagnosia when specific early stage visual areas are damaged.

16.17 ASCENDING PROJECTIONS FROM THE INFERIOR COLLICULUS TO THE MEDIAL GENICULATE BODY IN THE RAT.

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The aim of the present study was to demonstrate the distribution, morphology and termination of the colliculo-geniculate projections in the rat. Fifteen albino rats were employed. The animals were iontophoretically injected with BDA in different territories of the inferior colliculus (IC), processed and sections made on the frontal, horizontal and sagittal planes.

In all cases, projections ascending to the brachium, the ipsilateral medial geniculate body (MGB) and -though scanty- to the contralateral MGB were observed. Retrogradely-labelled cortical neurons were also observed in the ipsi- and contralateral auditory cerebral cortex.

The projections to the MGB tended to form fibrilar laminae in the ventral division of the MGB, this was more pronunced in horizontal sections and in the mediolateral direction. Thick bands of fibres and terminals were also seen in different locations, depending on the injection site. In the dorsal division, the number and density of collicular fibres were always lower than in the ventral division.

The collicular axons form perineuronal and peridendritic plexuses and also display large terminals with mossy or oval aspect, these are more common in the dorsal division of the MGB.

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16.18 ETTLINGER REVISITED: SENSORY IMPAIRMENT AND AGNOSIA.

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The concept of agnosia as a higher-order functional impairment, which can occur in the absence of low-level visual perceptual deficits, continues to provoke debate. This controversy is complicated by the fact that, on close examination, agnosic patients do tend have some perceptual difficulties. Thus, the issue centres around the question as to whether these deficits play a causal role in the aetiology of agnosia or whether they are functionally independent, with both impairments resulting from the substantial cerebral lesions involved in agnosia. In 1956, Ettlinger published a study in which he compared the performance of patients with visual recognition deficits and patients with posterior brain lesions whose recognition abilities were intact. He argued that visual perceptual problems could not explain the recognition deficit in agnosia as he observed far worse perceptual impairments in patients who do not experience any problems in visual recognition. Although the logic of Ettlinger's argument is not disputed, a number of criticisms have arisen concerning the study, such as the fact that his experimental group did not include a frank object agnosic patient. In addition, Ettlinger's visual-sensory assessment can no longer be considered comprehensive in the light of present-day knowledge of the cerebral visual apparatus. In this study, we therefore investigated three (prosop)agnosic patients and five patients with unilateral brain lesions without recognition deficits on a extensive battery of visual sensory tests. Our results support Ettlinger's original claim that (in some cases) agnosia cannot be explained as resulting from lower-level visual deficits.

16.19 **DIFFERENTIAL FUNCTIONAL EFFECTS OF UNILATERAL OPTIC NERVE TRANSECTION IN VISUAL PATHWAYS OF CHICK BRAIN.**

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Optic system of avian brain consists of tectofugal and thalamofugal pathways as in mammals. In the present study we investigated the plasticity of the visual system following unilateral visual deprivation using the *in vivo* autoradiographic method of ^{14}C-2-Deoxyglucose. In a day old chicks left optic nerve was cut, under chloroform anesthesia. One and seven days following the operation, local cerebral metabolic activity was determined, by means of glucose utilization. The produced autoradiograms were analyzed, using a computer based image analysis system and the glucose uptake was estimated in 47 brain areas.

One day following optic nerve transection glucose utilization was reduced in most retino-recipient areas (Tectum Opticum, n.Isthmo-opticus, n.Geniculatus lateralis, n.Opticus basalis, n.Dorsolateralis thalami), contralateral to the cut nerve, as compared to those of sham operated animals. Dramatic decreases of metabolic activity were observed in all relay stations of the contralateral tectofugal pathway (SGFSs and SGC layers of optic tectum, n.Isthmi, pars magnocellularis and pars parvocellularis, n.Rotundus, Ectostriatum). In contrast, only primary nuclei of thalamofugal pathway of the contralateral side were affected by the nerve cut, while the visual Hyperstriatum accessorium showed no significant changes. A week after the unilateral visual deprivation the effects on metabolic activity were preserved. In addition bilateral changes were observed in limbic and basal ganglia areas. These results showed that visual deprivation affected more prominently the tectofugal pathway, suggesting that it is the main pathway of processing visual information at day old chick, possibly due to later maturation of the thalamofugal pathway.

16.20 MULTIELECTRODE STUDIES OF NEUROTRANSMITTER FUNCTION IN CHICKEN RETINA WHOLE-MOUNTS.

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For studies of horizontal interaction and neurotransmitter function we developed a whole-mount preparation of P0 chicken retina, using a planar array of 60 microelectrodes. Extracellular single-unit recordings from ganglion cells (cRGC) in retina segments were stable for up to 7h. With electrodes spaced 100µm apart the same cRGC was rarely recorded at neighbouring electrode, unless axons were the source of the signal. Production and design of the microelectrode array (MEA) are reported in Nisch et al. '94 [1]. The retina - cRGC facing towards the MEA - was stimulated with light via the microscopes optic system. cRGC-response to stimuli of diffuse light (500-1000 Lux) varied from ON/OFF responses with fast-onset (60-80ms), brisk, phasic bursts of activity to delayed (ca. 500ms), tonic ON-responses. ON/OFF-responses were found with intact retinal pigment epithelium (RPE) only. Slow responses were prominent when the RPE was removed. In the latter preparation we often observed oscillatory spontaneous activity and frequent occurence of spreading depression. The ON component of the ON/OFF-response was reversibly suppressed by application of the glutamate antagonists AP4 and AP5 to the buffer, but not by AP3.

In contrast to the mammalian retina brisk ON/OFF-responses are the dominating response type in *in vivo* recordings from cRGC axons in the tectum opticum. All other response types constitute appr. 20 % of the cells recorded [2]. Activity in whole-mount preparations with RPE intact is therefore considered to be *in vivo* like. Showing oscillatory activity, frequent spreading depression and delayed ON-responses whole-mounts lacking RPE can, however, not be considered normal. Although ON-responses are attributed to signal transmission via metabotropic glutamate receptors, they were also reduced by the NMDA-antagonist AP5. This suggests a contribution of ionotropic glutamate receptors. AP5 specificity in the chicken retina was, however, not yet confirmed.

[1] Nisch et al. '94, Biosensors & Bioelectronics 9:737-741
[2] Golcich et al. '90, Brain Research 535:288-300

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16.21 ß-ENDORPHIN: POSSIBLE ROLE IN THE REGULATION OF INTRAOCULAR PRESSURE ? C. Erb*, K. Wunderlich, H.-J. Thiel. University Eye Clinic Tübingen, Germany.

Purpose. In ocular tissues, neurotransmitters like ß-Endorphin are becoming more and more of interest in the regulation of physiologic reactions, like control of intraocular pressure. Therefore, the goal of this study was to demonstrate the localisation of ß-Endorphin in the human eye.
Methods. Two enucleated human eyes with a local choroidal malignant melanoma were embedded in paraffin and cut in 5 µm sections for immunohistochemistry. Immunostaining with rabbit anti-ß-Endorphin (Biermann, Germany; 1:600) was performed with the ABC/AP technique.
Results. Immunopositive reaction with anti-ß-Endorphin could be shown at the cornea endothelium, the trabecular meshwork, perivascular of iris and ciliary body vessels, in the ciliary body stroma, in the nonpigmentet ciliary epithelium, in the retinal pigment epithelium, in the retina, perivascular of the choroidea and in the optic nerve. ß-Endorphin was not detectable in cornea epithelium and stroma, lens epithelium and lens fibers, iris pipment epithelium and pigmented ciliary epithelium.
Conclusion. Localisation of ß-Endorphin shows no special association to tight or leaky epithelia. However, positive labeling of trabecular meshwork and ciliary body demonstrates that ß-Endorphin could play a role in the regulation of intraocular pressure: in the variation of the outflow facility as well as in the influence of the active ion transporters in the functional syncytium of the ciliary body.

16.22 NICOTINIC AND MUSCARINIC DISCHARGE PATTERNS IN POLYMODAL C-FIBER UNITS IN VIEW OF NOCICEPTION V.V.Ermishkin*, V.M. Khayutin, R.S.Sonina, S.V.Revenko. Cardiology Research Center, Moscow 121552 , Russia.

Acetylcholine (Ach), carbachol (CCh), nicotine (NIC), methacholine (MCh) or pilocarpine (PIL) in doses 1-100 ng in 1 ml injected in perfused small intenstine in anesthetized cats evoke moderate (less than 20 mm Hg) reflex increase in systemic arterial pressure (Khayutin et al., 1976). In case of M-cholinergic agonists (MCh and PIL), amplitude and steepness of these reflexes gently rise with concentration reaching maximum at 0.1-1 µg. By contrast, the dose-response curves for N-agonists (ACh, NIC, CCh) have one more phase. This steeply rising branch corresponds to the concentrations algogenic for man (Keele, Armstrong, 1964). Thus, these reflexes can be considered as nocifensive. Recently we compared the discharge patterns of the same polymodal C-fiber units isolated from cat's saphenous nerve in response to ACh and MCh (close arterial injections). Only low-frequency (less than 3 imp/sec) discharges were evoked by MCh (1-100 µg) and ACh in non-algesic (1-5 µg) concentrations, while responses to ACh in algesic (10-100 µg) concentrations began with initial high-frequency burst. The dose-response curves for peak rates proved to be similar to those for the reflexes. The difference in 'muscarinic' and 'nicotinic' response patterns may be explained by different location of M- and N-receptive structures: muscarinic - in more sensitive terminals and nicotinic - in less sensitive, but more 'powerful' regenerative part of the sensory unit. Thus the nociceptive quality of stimulus can be encoded by high frequency bursts generated by the sensory units regenerative parts in response to activation of their N-cholinoreceptors.

16.23 POSTNATAL DEVELOPMENT AND REEMERGENCE OF GAP-43 IN AUDITORY BRAINSTEM NUCLEI FOLLOWING COCHLEAR LESIONING. C. Förster*, M. Horvath, R.-B. Illing. Morphological Brain Research, Unit of Oto-Rhino-Laryngology, University of Freiburg, 79106 Freiburg, Germany.

The growth-associated protein GAP-43 is a phosphoprotein of the nerve terminal membrane that has been linked to axonal growth and synaptogenesis in both ontogeny and plasticity.

We examined the temporal and spatial changes in the distribution of this protein from birth to adulthood in the cochlear nuclei, the superior olivary complex and the colliculus inferior of the rat. Perinatally, a dense neuropil staining was found in all auditory brainstem nuclei. GAP-43 is down-regulated between the 4th and 8th postnatal day, i.e. well before the onset of detectable compound action potentials in the VIIIth cranial nerve. A low but distinct level of GAP-43 immunoreactivity persisted in some regions of the dorsal and ventral cochlear nucleus, suggesting a moderate capacity for ongoing synaptic remodeling.

Removal of one spiral ganglion in adult animals caused a substantial reemergence of GAP-43 immunoreactivity in perikarya of the superior olive and in varicose fibers of the ipsilateral ventral cochlear nucleus. Moreover, the level of GAP-43 was increased in neuropil of the central colliculus inferior contralateral to the lesioned cochlea as compared to the ipsilateral central nucleus. The peak of this reaction appeared to occur before the tenth postoperative day, slowly regressing afterwards. We shall discuss the possibility that the reemergence of immunoreactivity in cochlear nucleus and colliculus inferior is due to the reexpression of GAP-43 in axons of olivocochlear and olivocollicular neurons that suffered lesions to their axon collateral innervating the Organ of Corti. Double-labeling immunocytochemistry was used to determine which neurotransmitters and calcium-binding proteins are present in the target neurons of GAP-43 positive axons.

We conclude that the major auditory brainstem nuclei respond to cochlear lesions with a reactive synaptogenesis of limited duration.

16.24 SYNCHRONIZATION OF SINGLE UNIT SPIKE TRAINS IN CAT VISUAL CORTEX REFLECTS GLOBAL STIMULUS PROPERTIES. W.A. Freiwald*, A.K. Kreiter, and W. Singer, Max-Planck-Institut für Hirnforschung, D-60528 Frankfurt, F.R.G.

Theoretical considerations and results from multi-unit recordings suggest that synchronization of neuronal activity could serve as a binding mechanism in the formation of neuronal assemblies. To investigate, whether the synchronization between *single cells* depends on stimulus properties, we recorded simultaneously with several stereotrodes multiple single units in area 17 of the anaesthetized cat. Amplitude and position of the correlation peaks were strongly influenced by the orientation of the moving bar stimuli. The changes of correlation peak position followed in most cases the rule that the more strongly activated cell leads by up to 10 ms over the other. The effect of different global stimulus configurations on the synchronization between pairs of single cells was studied with two different paradigms. If the receptive fields (RFs) of both cells were spatially separated and colinearly oriented, they were simultaneously activated either by a long bar moving over both RFs or by two independent bars moving in opposite directions, each one over only one of the two RFs. Neurons with overlapping RFs but different preferred orientations were both activated either by a single stimulus, or with two bars, their orientations matching approximately the respective preferences of the two cells. We found in both paradigms that for cells which had synchronized their spikes in response to a single coherent stimulus synchronization was reduced or absent when they were activated by two incoherent stimuli. The reverse pattern was never observed. We conclude that correlations between single units depend on the actual stimulus configuration and do not directly reflect the fixed anatomical connectivity. Furthermore, the results indicate that synchronous activity could serve to define the set of neurons whose responses represent features of the same visual stimulus.

16.25 RIVALRY IN SQUINTING CATS: A PSYCHOPHYSICAL STUDY. P. Fries*, P. R. Roelfsema, A. K. Engel, P.König, W.Singer. Max-Planck-Institut für Hirnforschung, D-60528 Frankfurt, FRG

Presenting the two eyes with stimuli that cannot be fused to a coherent percept leads to the phenomenon of binocular rivalry, a regular switching of subjective perception. Rivalry has stimulated detailed investigation in humans but only very few experiments with animals have been carried out so far. Cats with surgically induced squint were dichoptically presented with drifting gratings of varying orientation, velocity and contrast. Optokinetic nystagmus was measured as it has been shown in humans to be an objective indicator for eye dominance. In a first experiment we systematically varied the ratio of contrast between the two stimuli. This reveals a clear asymmetry between the deviating and non-deviating eye: to make the deviating eye control nystagmus, contrast has to be much higher on this side despite the fact that the two eyes had equal grating acuity. In two further experiments we investigated the effect of different grating velocities: Equal contrast on both eyes leads to permanent dominance of the non-deviating eye, if drift velocities are equal, but reducing the velocity on the deviating eye shifts the dominance to this side. To isolate this velocity effect, we repeated measurements at a contrast ratio producing equal dominance at equal velocities. Under this condition a clear negative relation exists between stimulus velocity and eye dominance with stationary stimuli always acquiring dominance. This is in contrast to studies in humans where stimulus velocity and eye dominance are positively correlated. Finally, we tested the role of the orientation of the stationary grating. Orientations orthogonal to the motion vector of the grating presented to the other eye were most and orientations parallel to the motion vector least effective in reducing the gain of the nystagmus. The results show that rivalry is present in cats but some of the major features differ from those characteristic for rivalry in humans.

16.26 PRETECTAL PROJECTIONS TO LATERAL GENICULATE AND PERIGENICULATE NUCLEUS IN THE CAT K. Funke*, U. Neubacher and U.T. Eysel. Ruhr-Universität Bochum, Dept. Neurophysiology, D-44780 Bochum, FRG.

Using the retrograde axonal tracing technique, we can demonstrate that the pretecto-geniculate projection in cat shows a second component which terminates in the perigeniculate nucleus (PGN). Small and separate double-injections of red and green fluorescent latex-nanospheres placed in the PGN and the A-layers of the lateral geniculate nucleus (LGN) labelled almost different populations of cells in the nucleus of the optic tract (NOT) and the posterior pretectal nucleus (NPP). The projection to the PGN is as strong as, or even stronger than that to the LGN. However, the morphology and location of cells labelled from the PGN were not different from those projecting to the LGN. Using immunocytochemical staining methods in addition, we found correlating numbers of cells positive for GABA (or GAD, glutamine-acid-decarboxylase) and PARV (parvalbumine) and which constitute up to 50% of the cells projecting to PGN or LGN. Double-stainings confirmed that most GABAergic projection cells also stain for PARV. Roughly the other half of cells projecting to the geniculate complex was found to be positive for calbindin (CB) and only a small fraction of this group was also positive for GABA. So far, our results demonstrate the existence of a pretecto-PGN projection which seems to have characteristics similar to the pretectal projection to the LGN A-layers. We can further confirm the dual nature of this projection with regard to GABAergic and non-GABAergic projection cells and, in addition, we can suppose that the GABAergic path originates preferentially in PARV+ neurons, whereas CB is associated with the non-GABAergic pathway.

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16.27 SUPPRESSION OF MOTION-ONSET VEP'S BY FLICKER.

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At receptor level motion cannot be distinguished from flicker. So, as long as flicker and motion follow the same pathway they might interact. To study this interaction the effect of whole-field flicker on motion-onset VEP's was considered in 5 subjects.

Methods: A drifting grating with a spatial frequency of 3.5 cyc/deg and a contrast of 5 % was presented with and without a flickering background. VEP recordings were obtained from 5 electrodes positioned in a horizontal array on the back of the head, with the middle electrode 2 cm above the inion, and the other electrodes 2.5 cm apart to the left and the right. The drifting velocities of the grating were 1, 4 and 9°/sec. The flicker frequencies were 5, 10, 15, 20 , 25, 30 and 40 Hz with modulation depths ranging between 7.5 to 50 %.

Results: Motion-onset VEP's with a mean latency of 173.2 ± 16.2 ms were recorded from all recording sites, with the highest amplitude at the most lateral electrode either on the right or left hemisphere. During the presentation of a 9°/sec drifting grating upon a 50 % modulated background, flickering with frequencies of 5, 10, 15, 20, 25 and 30 Hz, the mean amplitudes of the motion-onset VEP's were respectively 38, 34, 29 and 42, 0 and 0.08 % smaller than the amplitudes of VEP's recorded with a steady background. When strong suppression occured, the motion-onset VEP's showed also pronounced latency shifts till 208.2 ± 31 ms. For low velocities or frequencies of flicker higher than 30 Hz, no clear suppression or latency shifts of the motion-onset VEP's were observed.

Conclusion: For high velocities of motion, flicker of frequencies lower than 30 Hz can suppress motion-onset VEP's. The strength of the suppression follows a kind of flicker fusion curve, but with a more shallow high frequency tail.

16.28 ENKEPHALIN IN THE RAT CAUDAL PAG: AN ELECTRON MICROSCOPIC STUDY.

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Enkephalins are opioid peptides which elicit an analgesic effect when injected into the periaqueductal gray matter and in particular into its caudal part. In this study we wanted to investigate the fine structure of the neurons and of the synaptic circuits involved in the enkephalin action in rats using immunocytochemical pre-embedding methods.

The labelled neurons show a small-medium sized soma, with a large nucleus, an absence of an extensive granular endoplasmic reticulum and few synaptic contacts. The synapses on enkephalin dendrites are often multiple, unlabelled and show both symmetrical and asymmetrical junctions. Enkephalin axon terminals make synaptic contacts on dendrites, usually unlabelled; contacts between enkephalin elements were occasionally seen. The enkephalin synapses show the symmetrical type of junction. The results give morphological support to the physiological findings, in particular to those suggesting an inhibitory effect of enkephalin on periaqueductal gray matter cells through a post-synaptic process.

16.29 VISUAL-VESTIBULAR INTERACTIONS IN THE INFERIOR PARIETAL LOBULE OF MACAQUE MONKEYS.

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Orientation in three-dimensional space requires multisensory signal processing resulting in perception and movement. The parietal cortex is known to participate in these functions. In order to generate the reference frames for visually-guided behavior, information about head movements in space is essential. We thus tested the vestibular sensitivity and visual-vestibular interactions of neurons in two different regions within the inferior parietal lobule: (i) in the anterior parietal cortex which is known to receive vestibular input, and (ii) from the ventral intraparietal area (VIP) located in the fundus of the inferior parietal sulcus where bimodal neurons respond selectively to the direction of visual and tactile stimuli.

Single cell responses were recorded extracellularly in two awake monkeys (Macaca fascicularis and Macaca mulatta) trained to perform several oculomotor tasks. Visual stimuli as well as oculomotor targets were back-projected onto a translucent tangential screen. Vestibular stimuli were delivered by vertical axis (horizontal) rotation of a turntable.

In both regions, neurons encoding horizontal visual movement components often responded vigorously to horizontal whole body rotation in light and in darkness, as well as during suppression of the vestibulo-ocular reflex. Vestibular responses seemed to signal head velocity. Neurons also reacted to optokinetic stimuli (large random dot patterns moving in the fronto-parallel plane). In such case, responses could be spatially and directionally congruent or non-congruent. In the former case, preferred directions for vestibular and optokinetic activation were in opposite directions as described for vestibular nuclei neurons. In the latter case, vestibular and optokinetic preferred directions were in the same direction. In area VIP, we found a clear preponderance for neurons responding in the non-congruent manner. The observed visual-vestibular interactions therefore suggest a supramodal representation of movement space in the inferior parietal lobule of macaques.

16.30 VISUAL SPATIO-TEMPORAL PROPERTIES OF THE FIBRES OF THE CORPUS CALLOSUM.

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Behavioral experiments indicate that the corpus callosum (CC) can mediate the interhemispheric transfer of visual pattern discrimination for inputs restricted to one hemisphere. The nature of the visual information transferred across the CC is, however, not well known. To precisely define these properties, we have evaluated the contrast threshold, as well as the spatial and the temporal frequency characteristics of fibres in the CC of cats. Single axonal activity was recorded under paralysis and light anaesthesia: Halotane (0,5%), N_2O-O_2 (70:30). Axonal responses to visual stimulation were displayed an analyzed in conventional manner. Receptive fields (RFs) were tested independently for each eye. Spatial and temporal selectivities were evaluated using sinusoidal gratings, drifting at optimal direction with a contrast of 50%. Contrast threshold was estimated at optimal spatial and temporal frequencies. The stimulus subtented 25°. However, for fibres showing end-inhibition, the size yielding the optimal response was used. Results indicated that most (60/64) of the callosal RFs were binocular and distributed along the vertical meridian. The response of some fibres was modulated to the frequency of the stimulus (4 S- and 5 Sh-types) but most fibres showed an unmodulated increase of their discharge (45 C- and 10 Ch-types) with increasing frequencies. The left and right eyes show similar sensitivities to spatial and temporal frequencies (ranging in different fibres from low to high) and manifest comparable contrast thresholds (≤3% to ≤10%). The effective spatial and temporal frequency bandwidths for each eye are largely superimposed and there is no difference in their respective optimal frequencies. The principal distinguishing factor among fibres with respect to high spatial and temporal frequencies cut-off appears to be ocular dominance.

16.31 GENICULO-CORTICAL SYNAPSES ON VASOACTIVE-INTESTINAL-POLYPEPTIDE (VIP) CELLS: A COMBINED IMMUNOCYTOCHEMICAL AND TRACING STUDY

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VIP-immunoreactive cells of the rat primary visual cortex belong mostly to the population of bipolar cells spanning with their dendrites the full width of the cortex, while their axons arborize mainly in layers II-IV. These cells are thought to influence glucose metabolism within a cortical column. Furthermore, there seems to be a co-localization of VIP and GABA in a subpopulation of bipolar cells which suggests their inhibitory action. This prompted us to investigate if there exists a synaptic connection between VIP-cells and the primary visual afferents.

The dorsal geniculate nucleus of adult rats was injected with Phaseolus vulgaris leucoagglutinin (PHA-L). After sectioning on a vibratome, the tissue was incubated in antisera against PHA-L and VIP. PHA-L was visualized with the nickel-DAB method, while VIP with the conventional DAB staining.

Under the light microscope the brown colour of the VIP-stained elements could clearly be distinguished from the black colour of PHA-L-containing fibres. Under the electron microscope PHA-L appeared as a homogenous, electron-dense deposit, by contrast to VIP showing a light granular precipitate. Both light and electron microscopy revealed that VIP-cells are contacted by several PHLA-stained boutons on their somata and dendritic shafts. Boutons were found to establish axo-somatic and axo-dendritic synapses of the asymmetric type.

These findings suggest that VIP-cells of the visual cortex receive an excitatory input by primary afferents. This argues for a visually driven coordination of local-circuit inhibition and glucose metabolism via VIP-neurons.

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16.32 CNS LESIONS MAY CAUSE PARADOXICAL WARM SENSATIONS

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The term "paradoxical warm-sensation" describes the phenomenon, that a cold stimulus applied to the skin is perceived as warm, hot or painful. This phenomenon has been observed under A-fibre blockade, and is attributed to selective block of cold-fibre afferents.

We now report paradoxical sensations in patients with clinically possible or definite multiple sclerosis. Twenty-two in-patients (23-66y) with disturbances of the somatosensory system and without peripheral nerve lesion, including symptomatic or clinical deficits or electrophysiological signs, were examined with respect to abnormalities in temperature sensibility. Using the method of limits, the cold- and warm-detection threshold and thermal sensory limen (TSL) were measured with a thermal sensory analyzer (TSA 2001, thermode area: 50x25mm, rate of temperature change: 1°C/s, base temperature: 32°C). For the TSL-procedure, alternating cold and warm stimuli were given. The dorsum of the hand and of the foot on both sides were tested in all patients. Eleven patients reported a paradoxical sensation, 4 of them in 2 sites, to cold stimuli during the TSL-procedure (12xwarm, 3xburning). Only 2 patients felt warm instead of cold during cold-threshold testing, i.e. with cold stimuli that were not preceded by any heat.

The paradoxical sensation in these patients must be due to an affection of central temperature-pathways. This is consistent with a recent model of the integration of cold-specific (COLD) and multisensory (HPC) input at supraspinal sites (Craig&Bushnell, 1994, Science 265: 252-255).

16.33 CALCIUM BINDING PROTEIN IMMUNOREACTIVITY AND CONNECTIONAL ORGANIZATION OF MONKEY AUDITORY CORTEX. T. Hashikawa*[1], M. Molinari[1,2], E. Rausell[1,3], M. E. Dell'Anna[1,4], M. G. Leggio[1,2] and E. G. Jones[1,5]. [1] Lab. for Neural Systems, The Institute of Physical and Chemical Research (RIKEN), Wako , Japan, [2]Catholic Univ., Rome, Italy, [3]Autonoma Univ. Madrid, Spain, [4]Univ. of Udine, Udine, Italy, and [5]Dept. of Anat. and Neurobiol., Univ. of California, Irvine, California, U.S.A.

Immunoreactivity for a calcium binding protein, parvalbumin, differentiates functional areas of the auditory cortex in Japanese monkeys, *Macaca fuscata*. On the supratemporal plane a central core zone with intense immunoreactivity coinsides with annectant gyrus typical of this species. This central core zone corresponds cytoarchitectonically to the koniocortex which includes primary auditory cortex (AI) and an anterior extension (R). Surrounding the central core zone are a second and a third zone with moderate to dense and relatively weak immunoreactivity. Outside these zones there is a fourth zone with almost no immunostaining.

The connectivity of these zones has been studied, and it is revealed that central core and its surrounding zones receive thalamic inputs from different subnuclei of the medial geniculate complex, i.e. central core zone from the ventral nucleus and surrounding zones from the anterodorsal and posterodorsal nuclei. AI and R have reciprocal connections posteriorly and anteriorly, respectively, with the second of the outer zones. Commissural connections of these zones are primarily with their corresponding zones on the contralateral side.

16.34 CHANGES IN *c-jun* AND NMDA RECEPTOR mRNA LEVELS IN THE LUMBAR SPINAL CORD FOLLOWING PERIPHERAL NERVE CRUSH IN NEONATAL RATS.

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Neonatal nerve crush results in motor neurone death and has been shown to induce long term changes of gene expression in rat spinal cord. In particular the expression of immediate early genes (IEGs) is increased following nerve crush and has been implicated in potential repair mechanisms. Glutamate receptor expression shows a distinct developmental pattern which may underlie differential sensitivity to excitotoxicity. We have investigated the time course of induction of *c-jun* mRNA in spinal cord after unilateral crush of the common peroneal nerve at second postnatal day (P2). In parallel alterations in glutamate transmission at the N-methyl D-aspartate (NMDA) receptor were studied by analysis of the NR1 subunit of the NMDA receptor which effectively serves as a universal component of this receptor. Lumbar spinal cord ipsilateral and contralateral to the nerve crush was removed at various times after crush, 4h, 8h, 24h, 2d, 5d, 12d and RNA was extracted and analysed using Northern and slot blot techniques and *in situ* hybridisation. Levels of *c-jun* mRNA were significantly elevated by nerve crush, bilateral increases were detected but the maximal increase occurred at 5 days ipsilateral to nerve crush. The induction of *c-jun* mRNA following crush is consistent with other injury models and coincides with dendritic sprouting which may represent abortive attempts at regeneration. The expression of NR1 mRNA showed a marked increase after nerve crush especially at 5-12 days which suggests that upregulation of NMDA receptors is an important component of in the CNS response to nerve injury.

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16.35 THE EFFECTS OF SPATIAL FREQUENCY AND ATTENTION ON THE GENERATORS OF THE VISUAL EVOKED POTENTIAL IN HUMANS.

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The purpose of this study was to localize the generators of the electrical responses of the human brain to stimuli presented in various locations of the visual field, varying in spatial frequency (SF) and subjective relevance. 1000 square wave gratings were randomly presented to each of the 4 quadrants of the visual field. One half of all stimuli had a low SF (0.8 cpd), the other half a high SF (3.2 cpd). On one half of all trials the low SF was relevant, on the other half the high SF. Relevance was achieved by instructing subjects to press a button to combinations of one SF and occasional (5%) horizontal orientations of the grating. EEG was sampled every 2 msec from 60 scalp electrodes. Event-related brain potentials to vertical gratings (95%, all nontargets) were averaged according to the stimulated quadrant, SF, and whether the SF was relevant or not.

From 75 to 95 msec, stimuli in the lower quadrants elicited occipital positivities, whereas stimuli in the upper quadrants elicited occipital negativities. The corresponding generators were localized in the contralateral occipital lobes, 1.5 - 4 cm lateral to the midline. These generators were modulated by SF: their strengths were larger to high SF gratings. Between 100 and 130 msec, all stimuli elicited occipital positivities, with contralateral maxima for stimuli in the lower quadrants, and midline maxima for stimuli in the upper quadrants. The effects of relevance consisted of occipito-temporal negativities, starting at about 200 msec. These potentials had a bilateral distribution with contralateral maxima, and were mainly unaffected by the SF of the grating.

16.36 SPATIO-TEMPORAL DISTRIBUTION OF EVOKED ACTIVITY ACROSS THALAMO-CORTICAL COCULTURES: A STUDY WITH VOLTAGE-SENSITIVE DYES.

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Cocultures of visual cortex with other brain tissues have demonstrated the formation of the specific afferent and efferent connections. Physiological measurements have confirmed the organotypic organisation of the cocultures. We performed fast optical recordings to determine the spatio-temporal distribution of evoked activity in thalamo-cortical cultures.

Cortical slices of 350µm thickness were taken from 4-6 day old rat pups and thalamic explants from E16 rat embryos. One or two thalamic explants were positioned close to the pial and/or white matter side of a visual cortical slice. Cocultures were then maintained for 7 to 42 days on Millipore culture dishes at an air-medium interface. The cultures were stained for 10-30min with 1-50µM RH795 or Di-4-ANEPPS (Molecular Probes Inc.). Recordings were carried out using a 464 element photodiode array read out at 630Hz. Electrical stimuli of 50-200µs duration and 50-700µA intensity were applied via tungsten stimulation electrodes into the thalamic explants.

The optical response typically encountered in the cortex was a depolarizing transient peaking 12-16ms after the stimulus. Across cortical layers highest amplitudes and rates of rise for this component as well as shortest delay times were frequently found in layer 4. Double components with distinct "gaps" between their individual delay times were observed over the apposition zones of the cocultured explants. Applying a paired pulse paradigm, we found depression of the second response, possibly due to the presence of feed-forward inhibitory interactions as described in-vivo. Suppression of the transients was also demonstrated by a similar paired pulse paradigm employing 2 spatially separate stimulation electrodes and was found to depend critically on the duration of the inter-stimulus interval (ISI) used: at ISI 55ms suppression was minute, whereas at ISI 15ms it was almost complete. At ISI 0ms (= coincident stimuli) positive cooperativity was observed.

Our experiments confirm and extend previous findings on the layer-specific spatio-temporal dynamics of synaptic activity in thalamo-cortical cocultures.

16.37 IMMUNOHISTOCHEMICAL LOCALIZATION OF cGMP IN THE RAT OLFACTORY BULB.

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Nitric oxide (NO) is a potent activator of soluble guanylate cyclase. High levels of nitric oxide synthase (NOS) and cGMP in the olfactory bulb (OB) suggest that NO acts as a diffusible intercellular messenger molecule inducing increased synthesis of cGMP and, thereby, plays an important role in olfaction. The cellular localization of cGMP with and without sodium nitroprusside (SNP) stimulation was compared to the distribution of NOS. cGMP was detected immunocytochemically in in vitro OB slices. Under basal conditions, cGMP was present in a few neurons and neuropil of the glomerular layer, axons in the external and internal plexiform layers, and in a few somata and axons of the granule cell layer. This staining could be completely blocked by L-NAME. After SNP stimulation, the olfactory nerve layer was intensely stained as were the glomeruli and many periglomerular cells. In the external and internal plexiform layers axonal staining was increased substantially with multipolar cGMP-positive neurons appearing deep in the external plexiform layer. In the granule cell layer, axonal staining was greatly increased, especially of longitudinally running axons between the cell layers. The distributions of SNP-stimulated cGMP and NOS immunofluorescent neuronal elements overlap in the glomerular and granule cell layers, although there is no co-localization. Microparmacological experiments using the glutamatergic antagonists AP-5 and CNQX showed a distinctive and separate inhibition of cGMP immunofluorescence in different areas of the OB. These findings are compatible with the hypothesis that NO is an intercellular messenger in the OB.

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16.38 THE EFFECT OF ETHYL ACETATE ON THE CHEMORECEPTORS IN Periplaneta americana (L.)

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Electroantennographic studies of the effect of chemical stimulation (ethyl acetate) on the antennae of Periplaneta americana resulted in following observations: 1. Continous stimulation (air stream containing ethyl acetate) at a constant frequency led to a well pronounced adaptation, 2. Preexposure (1 or 7 days) to ethyl acetate markedly changed the pattern of adaptation depending on the time of preexposure.

The obtained results indicate that the fast adaptation of chemoreceptors in the investigated insect is one of the important factors in the influence of the environment.

16.39 CATEGORIZATION OF PHYSIOLOGICALLY DEFINED W CELLS AND THEIR CORRESPONDENCE TO THE ANATOMICALLY DEFINED NON α / NON β CELL S IN THE CAT.

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Both structural and physiological criteria have been used in the past to categorize cat retinal ganglion cells although no concensus on the relations between these two methods has been reached. We have applied fractal analysis (which quantifies the complexity of dendritic branching) to investigate the question of the existance of a distinct morphological class of non α / non β cells corresponding to the (physiologically defined) W cell class. Non α / non β cells could be placed into four groups, the γ, medium γ, δ and ε cells, based on the values of the fractal dimension (Df), 1.24±0.008, 1.35±0.02, 1.44±0.007 and 1.35±0.01 respectively. This could correspond to the subdivision of W cells into W $tonic_1$, W $tonic_2$, and W $phasic_1$, W $phasic_2$. The fractal dimension (Df) obtained for each of the physiological groups was 1.36±0.01, 1.42±0.005,, 1.29±0.01 and 1.43±0.01 respectively. A correspondence between the W $tonic_1$ cells and the δ cells, between W $tonic_2$ cells and ε cells and between W $phasic_1$ and γ cells can be seen. This study demonstrated that there is a correspondence between separately identified structural and physiological groups and that both W tonic and W phasic groups are heterogeneous.

16.40 MICROGLIAL RESPONSE IN THE SUPERIOR COLLICULUS FOLLOWING INTRAOCULAR INJECTION OF DIMETHYL SULFOXIDE. J. Kacza* and J. Seeger, Paul-Flechsig-Institut für Hirnforschung, Jahnallee 59, D-04109 Leipzig, FRG.

Transcellular labelling of retinal microglial cells, following axotomy and retrograde staining of the rat retina with the carbocyanine dye 4Di-10ASP, revealed that the degeneration of ganglion cells is accompanied by microglial phagocytosis of neuronal cell debris (Thanos S., 1991, Europ. J. Neurosci. 3: 1189-1207). In the present study we used combined intraocular injections of Dimethyl Sulfoxide (DMSO) and the also anterogradely transported fluorescent tracer 4Di-10ASP to induce and to monitor a microglial response in the retinotectal target of retinal ganglion cells, the superior colliculus (SC). Young adult rats received 10 µl intravitreal injections of 5% 4Di-10ASP, dissolved in 25% DMSO, in both eyes. After a survival time of 1 and 3 weeks, vibratome sections were obtained from fixed brains. 4Di-10ASP labelled tissue was photoconverted and further prepared for electron microscopy. Following 1 week postinjection time, fluorescence microscopy revealed a pronounced anterograde labelling of optic tract fibers and the superficial layers of the SC. After 3 weeks of survival, numerous microglial cells in corresponding layers of the SC appeared to be transcellularly labelled with 4Di-10ASP. Electron microscopical analysis confirmed that microglial cells contain dye-coupled photoconverted material. The appearance of 4Di-10ASP filled microglial cells suggests that the intraocular injection of DMSO caused a long-term destruction of retinal ganglion cells followed by an anterograde degeneration of retinotectal synaptic terminals. Our observations support previous findings that microglial cells in the SC are essentially involved in the phagocytosis of neuronal debris after anterograde terminal degeneration (Rao K. and R.D. Lund, 1993, J. Comp. Neurol. 336:613-627). This study was supported by the BMFT, grant 0316918A.

16.41 MODIFICATION OF THE ACTION POTENTIAL OF HELIX POMATIA PHOTOSENSITIVE NEURONS BY CGMP G. Kartelija, Institute for Biological Res., 29 November 142, 1160 Belgrade, Yugoslavia

In the recent work we have shown that the onset of light significantly increases the duration of the action potential in a group of photosensitive neurons in the left parietal ganglion of Helix pomatia. The onset of light induced constantly an enhancement of the calcium inward current. The prolongation of the action potential was time and temperature dependent, suggesting involvement of same second messenger in the light-induced modulation of voltage-gated channels. In the present experiments designed to test this possibility we examined the effect of cGMP on the action potential of these extraocular photoreceptors.

The experiments were conducted on isolated subesophageal ganglionic complex. Single photosensitive neurons in the left parietal ganglion were impelled by a single K-citrate microelectrode. A single voltage-clamp apparatus was used for current and voltage clamp measurements. In the present experiments we compared the effects of light and 8-Br-cGMP on the action potential. 8-Br-cGMP as well as light increased significantly (40%) the duration of action potential, but only in the presence of Ca^{2+}, while Cd^{2+} suppressed both the effects of 8-Br-cGMP and light. The effect of 8-Br-cGMP on the inward Ca^{2+} current on the voltage-clamped neuron was tested using barium as the charge carrier. Similarly to light, application of 8-Br-cGMP constantly elicited enhancement of Ca^{2+} current. It can be assumed that cGMp is the intracellular messenger of the light induced modulation of the action potential and the Ca^{2+} current in the Helix pomatia photosensitive neurons.

16.42 **COMPARISON BETWEEN THE ORIENTATIONAL TOPOGRAPHY OF EXCITATORY AND INHIBITORY CONNECTIONS IN CAT CORTEX**

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It was shown that in area 17 tangential connections link columns of neurons sharing *similar* orientation preferences (Gilbert and Wiesel, 1989). Quite opposite to this, in area 18, tangential connections were found to link orientation columns possessing *dissimilar* orientation preferences (Matsubara et al 1985, 1987). In order to unravel whether the two strongly interconnected areas indeed follow different organizational schemes we analyzed the functional topography of tangential connections in these areas. Physiological maps were obtained with electrode recordings of multiple sites spaced 100-300 µm apart followed by iontophoretic injection of biocytin at one location into layer III. An interpolation procedure was applied onto the discontinuous orientation map of the electrode recordings whereby a continuous orientation map could be generated. The anatomical labelling was analysed in the same tissue from which the orientation maps were obtained. On the basis of morphological criteria labelled excitatory and labelled inhibitory boutons were distinguished and reconstructed in the tangential plane with a neuron reconstruction system (Neurolucida). Thereafter the boutonal reconstructions were overlaid with corresponding orientation maps. Using a simple procedure of disecting the orientation maps into iso- (±30°), oblique- (±[30-60]°) and cross- (±[60-90]°) orientational zones the proportion of labelled excitatory and inhibitory boutons was determined, respectively. The results showed that - numbers in parenthesis indicate values relative to all labelled boutons- (i) of the excitatory boutons an average of 56(45)% occupied iso-zones, 30(25)% oblique-zones and 14(12)% cross-zones, (ii) of the inhibitory boutons an average of 47(9)% occupied iso-zones, 34(6)% oblique-zones and 19(3)% cross-zones, (iii) no significant differences in the corresponding proportions between the two areas were found. *We conclude that areas 17 and 18 employ similar functional organizational principles of tangential connections in relation to the topography of orientation columns. Excitatory connections showed a bias in linking similar orientations while inhibitory connections showed a bias in linking dissimilar orientations.*

16.43 PATHWAYS SUBSERVING THE PUPILLARY LIGHT REFLEX. A LIGHT AND ELECTRON MICROSCOPIC TRACING STUDY.

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With increasing brightness the pupil will constrict, thus regulating the amount of light reaching the retina: the pupillary light reflex (PLR). The parasympathetic excitatory component of the PLR originates from the Edinger-Westphal (EW) nucleus and runs via the ciliary ganglion to the iris. During the PLR fibres orginating from the thorical level of the spinal cord, projecting to the sympathetic superior cervical ganglion (SCG), show inhibitory activity subserving a sympathetic input to the iris. Electrophysiologically the EW nucleus, nucleus of Darkschewitsch (ND), interstitial nucleus of Cajal (INC), periaqueductal gray (PAG) and the posterior commissure show pupillary activity. The olivary pretectal nucleus (OPN), receiving primary retinal input, projects to the EW nucleus, ND, INC, PAG and the nucleus of the posterior commissure (NPC). It has been suggested that the OPN-EW nucleus pathway is not the only pathway involved in the PLR, also the NPC should project to the EW nucleus. To detail the pathways involved in the PLR the anterograde tracer *Phaseolus vulgaris* Leucoagglutinin (PHA-L) was injected into the NPC, ND and INC. The labelling was studied using light and electron microscopic techniques.

After injections of PHA-L into NPC, ND and INC labelled varicosities were observed in the EW nucleus. The labelling was observed in terminals containing round, clear vesicles and electron dense mitochondria and the terminals make asymmetric synaptic contacts. The postsynaptic element was dendritic. Injections into the ND resulted in labelled varicosities in the thorical level of the spinal cord.

In conclusion we can say that the EW nucleus not only receives input from the OPN but also from the NPC, ND and INC and that the ND may integrate the parasympathetic and sympathetic component of the PLR.

16.44 EFFECT OF THE HEMICEREBELLECTOMY ON NEURAL NETWORK OF THE CAT SENSORIMOTOR CORTEX ANALYZED BY BEAM TECHNIQUE. Kołodziejak A.*, Tarnecki R., Walerjan P. The Nencki Institute of Experimental Biology, Department of Neurophysiology, 02-093 Warsaw, Poland

The influence of the hemicerebellectomy on the cortico-cortical projection from the somatosensory to the motor cortex in adult cats were studied using Brain Electrical Activity Mapping (BEAM) technique. Animals were immobilized by gallamine under chloralose or nembutal anesthesia. The acute surgery was performed with suction of the right hemicerebellum. Brain potentials, evoked by the electrical stimulation of limb nerves, were recorded bilaterally from sensorimotor cortex before and after the surgery.

The data were acquised, averaged and analyzed by the software designed and tested in our laboratory. Different interpolation procedures for assessing data values between electrodes allowed the mapping of cortical activity across the scalp. We applied analysis in the time domain and drew potential maps. While in many cases it was not satisfactory to observe one map related to the time marker, we also created 16 or 32 small maps on the screen. The animation for such a set of maps let us to make the analysis of evoked potential propagation easier.

The preliminary examination revealed that the location of the activated cortical points and the size of these areas varied before and after the lesion. Changes were strongly depended on the extension of the impairment. Comparing to the preoperative period amplitude of the potentials on the "operated" and "non-operated" sides were altered at some sites and the number of components was changed.

16.45 INJURY-DEPENDENT AND USE-DEPENDENT PLASTICITY IN THE BARREL CORTEX OF NEONATAL MICE

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Early plastic changes in the cortical barrel system can be triggered either by injury to sensory nerve, or by sensory experience. In a neonatal rat the injury-evoked plasticity of a metabolically labeled vibrissal representation develops much faster than deprivation-evoked plasticity. We reexamined this question in a different rodent species. Newborn mice underwent either ablation of vibrissal follicles or plucking out of all whiskers, sparing row C. The cortical representation of the spared row was mapped with 2DG autoradiography at selected times during the first postnatal month. After ablation of follicles the increase of cortical representation of the spared row is visible at p.d.7, with large accompanying changes in the shape of row C barrels but plucking out (sensory deprivation) of vibrissae produced changes at p.d. 15. Plastic changes of cortical representation of vibrissae, evoked by injury of receptors and by sensory deprivation have a clearly different onset, indicating that use-dependent and injury dependent processes may have different mechanisms.

16.46 GENERAL 20 HZ SYNCHRONIZATION WITHIN CORTICO-THALAMIC DIVISION OF THE CAT'S VISUAL SYSTEM SHIFTS TO SPECIFIC PATTERN DURING VISUAL ATTENTION

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We have previously shown (Bekisz and Wróbel, Acta Neurobiol. Exp. (1993), 53: 175-182) that micro-EEG activity recorded from the lateral geniculate nucleus (LGN) and primary visual cortex (VCx) of cats attending to visual stimuli is characterised by increased activity in the 20 Hz band.

We have now analyzed the same data using the Pearson Product-Moment Correlation Coefficient (normalized cross-correlation coefficient with zero lag) between all pairs of band-pass filtered EEG signals (16-24 Hz) from all recording sites.

Such an analysis revealed that during nonvisual situations the recordings from most electrode sites within the visual system show positive synchronization indicating oscillatory rhythm of a general nature. In periods requiring visual attention the synchronization changes toward negative values of Pearson coefficient with an exception of few recording sites from which highly significant positive synchronized activity was observed.

We hypothesize that such a specific pattern of synchronization of 20 Hz beta activity represents the mosaic of functional connections appearing in the visual system during attentive seeing.

16.47 ATROPINE INDUCED CHANGES IN EVOKED POTENTIALS RECORDED FROM THE BARREL CORTEX DEPEND ON THE ACTIVATION LEVEL OF A SPECIFIC COLUMN

E. Kublik*, P. Musiał, and A. Wróbel. *Nencki Institute of Experimental Biology, 02-093 Warsaw, Poland.*

Four hooded male rats were used for the experiments. Under urethan anaesthesia the scull was opened to expose the barrel field and the dura matter was removed. A bipolar electrode was then placed into the cortex at the depth of the granular layer. By stroking each vibrissa with a piezoelectric device we recorded evoked potentials (EPs) and produced a map of the receptive field (map of responses) associated with this particular electrode location. The principal whisker (PW) - corresponding to the biggest EP - was then continousely stimulated with a frequency of 0.2 Hz. In the mean time a drop of Atropine sulphate (20mM) was applied to the surface of the cortex for a period of about 5-7min and subsequently washed out. Evoked potentials were observed on line and recorded on analog tape. Response maps were investigated at approximately 10, 30, 45 min after applying the drug. The amplitudes of EPs were enhanced slightly during the first 3 mins, after the application of atropine and then ceased for the next 3-5 min. There was no response to whisker stimulation for the subsequent 15-20 min period, however, the response recovered after an additional 10-25 min period. During this later period the amplitudes of the main components (N1, P2) where found to be bigger than at the beginning of the experiment. The reponse changes were different for whiskers undergoing continuous stimulation as compared to surrounding ones. The PW responses ceased earlier, were blocked for a longer time and the rebound effect was also more striking. Our results strongly support the notion that ACh is involved with sensory processing in the barrel cortex and that these cholinergic connections are specific.

16.48 CENTRAL CONNECTIONS OF THE AUDITORY SYSTEM IN THE FROG, *RANA ESCULENTA*

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In our earlier experiments we have demonstrated the connections of the cochlear nucleus (CN) with the secondary auditory centers including the superior olive (SO), torus semicircularis (TSC) and nucleus isthmi (NI). The aim of this work was to study the afferent and efferent connections of these secondary auditory centers. After injection of Phaseolus vulgaris leucoagglutinin (PHA-L) into the SO, labelled terminals and cells were found in the CN, reticular formation, principal, magnocellular, and laminar nuclei of TSC, nucleus anterodorsalis tegmenti mesencephali and tectum opticum. The injection of PHA-L into the principal nucleus of TSC revealed anterogradely labelled structures bilaterally in the TSC, SO, reticular formation and ipsilaterally in the tegmentum mesencephali, nuclei of lateral lemniscus and thalamus, NI, tectum opticum and contralaterally in the CN. Retrogradely labelled cells were found in the contralateral CN, SO, nucleus of lateral lemniscus and principal, magnocellular, and laminar nuclei of TSC. After the injection of PHA-L into the NI terminals were labelled bilaterally in tegmentum mesencephali and tectum opticum; ipsilaterally in principal and laminar nuclei of TSC, SO and reticular formation; and contralaterally in NI. Retrogradely labelled cells were present in all structures which received primary auditory afferent fibers.

Our findings suggest that the PHA-L labelling provide a much more extensive network of auditory system of frog that has been achieved with the other methods. Our finding indicate the participation of NI in the processing of auditory information seems to be corroborated by our results.

16.49 NEURONAL RESPONSES TO NATURALISTIC EGOMOTION STIMULI IN THE VISUAL MOTION PATHWAY OF THE MACAQUE. M.Lappe, M.Pekel*, F.Bremmer & K.-P.Hoffmann, Dept. Zoology & Neurobiology, Ruhr-University, D-44780 Bochum, Germany

Several studies of neuronal responses to optic flow in the superior temporal sulcus (STS) of the macaque have suggested an involvement of area MST in the analysis of egomotion. However, all studies so far were done with highly abstracted optic flow stimuli consisting of random dot fields. Visual signals during egomotion in a natural setting differ from these stimuli, since information about the induced motion of extended rigid environmental objects is complemented by other visual sources. On the other hand, the flow field itself has to be determined from the movement of such objects, raising questions such as the aperture problem. Do optic flow responsive neurons in the STS respond differently to naturalistic flow stimuli as compared to random dots? We investigated this in one awake monkey (M. mulatta) by single unit recordings. Recording chamber, scleral coils and a head holder were implanted under deep pentobarbital anesthesia. In the experiments, the monkey was seated in a comfortable chair with his head fixed and fixated a central target on a 90*90° screen during presentation of optic flow stimuli. Back-projected full-field computer generated movies simulated egomotion in different directions in a virtual environment. This environment was either a random 3D-cloud of white dots or a naturalistic scene consisting of a ground plane lined with trees and stones. The stimuli were generated by a ray-tracing rendering program and presented in color. Simulated egomotions were identical for the two conditions. Cell responses to forward motion (expansion) were very similar in the two conditions. This was true for overall response strength, dependence on the position of the focus of expansion, and tuning strength. In contrast, responses to backward motion (contraction) revealed marked but heterogeneous differences for individual cells. The results show that neuronal responses to forward motion are largely invariant to environmental layout (as would be required for neurons involved in egomotion processing) but differences between forward (the natural case) and backward movements exist. Supported by ESPRIT INSIGHT II.

16.50 STRABISMUS ALTERS THE PATTERN OF CORTICOFUGAL PROJECTIONS IN THE CAT LATERAL GENICULATE NUCLEUS

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The lateral geniculate nucleus (LGN) receives massive feedback projections from visual cortical areas which originate from pyramidal cells of layer VI, most of which are binocular. It has been suggested that these projections are involved in the synchronization of activity between geniculate cells [1]. In the present study we examine the hypothesis that cortico-geniculate projections are selected during postnatal development through activity dependent processes in a similar way as the thalamo-cortical and intracortical connections, i.e. according to a correlation rule. To this end we compared the morphology of corticofugal axons in the LGN in normal and strabismic cats. Single axons were stained by biocytin injections into layer VI of area 17 and reconstructed with the help of camera lucida equipment. In strabismic cats most of the corticofugal axons had a pronounced tendency to selectively innervate either lamina A or A1. In these animals most of the boutons, branching points and axon collaterals were confined to only one lamina. In normal cats, by contrast, most corticofugal axons innervated both laminae equally and only a minority of axons exhibited a lamina specific termination pattern. The density of bouton and branching points and the lateral extent of the axonal arbors did not differ significantly between both groups of animals. We conclude that the projection pattern of corticofugal axons is shaped by visual experience. Neurons in layer VI become monocular and because of squint their activity is unlikely to exhibit any correlation with that of LGN cells driven by the respective other eye. The data are, thus, compatible with the hypothesis that corticofugal axons are selected according to a correlation rule. Connections are stabilized selectively between neurons of similar and eliminated between cells of different ocularity.

[1] Silito et al. Nature 369, 479-482

16.51 DOUBLE IMMUNOSTAINING OF CALCIUM-BINDING PROTEIN NEURONS AND FIBERS IN THE HUMAN VISUAL SYSTEM. G. Leuba* and K. Saini, University Psychogeriatrics Hospital, CH-1008 Lausanne, Switzerland

Double immunostaining of calcium-binding proteins was performed with different combinations of parvalbumin (PV), calbindin (CB) and calretinin (CR) in the human visual cortex (VC), lateral geniculate nucleus (LGN), lateral inferior pulvinar (LIP) and superior colliculus (SC). In the VC, there are mostly separate populations of PV, CB and CR interneurons but also scattered double stained PV/CB, PV/CR or CB/CR neurons, both pyramidal and non-pyramidal in shape. In particular, some large pyramidal-like neurons in layer 5 of area 17 and in layer 3 of area 18 are PV immunopositive, sometimes double stained, and could represent projectory neurons rather than interneurons. In addition, single and double stained glial cells are encountered rarely in the grey matter but more often in the white matter. In the LGN and LIP, double stained neurons are scarce, but in the geniculate and pulvinar capsule, as well as in the optic radiation and white matter underlying area 17, both double stained and separate populations of PV, CB and CR neurons and fibers are present. Unlike the thalamic regions, the SC shows double stained neurons and fibers scattered both in the superficial and deep layers. Like in the VC, some of these neurons are large and pyramidal-like in shape. They represent probably projectory neurons.

17. Poster Session: Development and plasticity I

17.01 c-JUN, KROX-24 AND c-FOS EXPRESSION IN HIPPOCAMPAL GRAFTS PLACED IN EXCITOTOXIC HIPPOCAMPAL LESIONS OF THE RAT.

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In order to establish if grafted immature tissue maintains a basic molecular program necessary for gene transcription after grafting to excitotoxic lesions in adult host rat brains, we examined graft and host brain expression of three specific immediate early gene encoded proteins. Hippocampal transplants, derived from newborn donor rats, were analyzed immunocytochemically for the presence of c-JUN, KROX-24 and c-FOS transcription factors 5 months after homotypic grafting to 1 week old ibotenic acid lesions of the adult rat hippocampus. The expression and distribution patterns of these factors in the host hippocampus were identical to those in hippocampal neurons of normal untreated animals. c-JUN, KROX-24 and c-FOS labelled neurons were also present in the transplants, where KROX-24 and c-FOS exhibited a distribution similar to host hippocampus. In contrast, c-JUN was more extensively expressed in the transplants, suggesting for this transcription factor a molecular response to the grafting conditions or environment.

17.02 LOW AFFINITY NGF RECEPTOR RESPONSE IN THE SEPTUM TO THE UNILATERAL LESION OF SEPTO-HIPPOCAMPAL PATHWAYS IN THE RAT BRAIN.

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Our recent studies performed on the model of unilateral partial lesion of septo-hippocampal pathways in the rat revealed bilateral increase in NGF content and immunoreactivity in the septum 7 days after surgery. The present study was aimed to investigate the changes in the low affinity NGF receptor immunoreactivity (NGFR-IR) in the septum in the same lesion model. NGFR-IR was assessed using 192 IgG monoclonal anti-NGF- receptor antibody and biotin-avidin system. The pattern of the receptor changes, assessed 7 days postoperatively, differs from that of NGF. The changes occurred only unilaterally to the lesion side. There was a slight decrease of the immunoreactivity of NGFR located on cholinergic neurons, paralleled to the mild retrograde changes in the latter. Interestingly, we have observed that there was a unilateral, strong accumulation of NGFR-IR in the transected axons in the dorsolateral septum. This "pile-up" pattern matches closely that of AChE staining in the septum after aspirative lesion of fimbria-fornix (Gage et al., 1986, Neurosci.19). The observed differences in the response pattern between NGF protein and NGF receptor obtained in the same lesion model may be interesting in consideration of the regulation of NGF in injured brain and its possible pharmacological manipulation.

17.03 DIFFERENTIAL EXPRESSION OF β-AMYLOID PRECURSOR PROTEIN ISOFORMS 695 AND 751/770 IN CORTICAL AND HIPPOCAMPAL SYNAPSES.

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Most of the studies on the β-amyloid precursor protein (APP) have focused on the role of APP and β-amyloid peptide in Alzheimer's disease. Little is known about the physiological function of this protein in normal brain. We recently showed that some APP isoforms attain maximal levels during brain postnatal synaptogenesis[3]. Moreover, intraventricular infusion of antibodies against APP_{695} isoform impairs cognitive functions in rats, suggesting that APP could be invoved in synaptic plasticity[4].

To determine which of the different APP isoforms are located at synapses, we performed immunoelectronmicroscopy using antibodies specific for $APP_{751/770}$, containing the Kunitz protease inhibitor domain (KPI) and for APP_{695}, in the rat brain. In occipital cortex and hippocampus, APP immunoreactivity for both isoforms was concentrated at the postsynaptic densities of the asymmetrical, axodendritic synapses. Whereas KPI-APPs immunoreactivity labeled various kinds of synapses, APP_{695} labeling was only found on a very small number of distinct synapses. This differential expression of APP isoforms at synapses may reflect specific synaptic functions.

[3]Löffler, J. and Huber,G.J. J. Neurochem., **59**, 1316-1324 (1992).
[4]Huber, G. et al., Brain Research, **603**, 348-352 (1993)
Supported by Roche Research Foundation fellowship for B. Brugg

17.04 MORPHOLOGICAL MATURATION OF ISOLATED LONG-TERM ORGANOTYPIC NEONATAL RAT NEOCORTEX IN VITRO.

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Studies were carried out to assess dendritic growth in long-term organotypic neonatal rat occipital neocortex explants. The current studies were designed to examine the neuronal anatomy within this model system as part of ongoing investigations concerned with network formation following selected blockade of receptor and/or voltage channels. Quantitative light microscopic measurement of dendritic trees within the cortical slice was accomplished using rapid Golgi stained materials traced on an automated microscope developed at this Institute. The overall cellular organization of the slice was maintained over 4 weeks in vitro, with morphologically distinguishable pyramidal and nonpyramidal neurons located within the same layers and with the same orientations observed in situ. The data reveal that cellular maturation is accompanied by significant age-related increases in pyramidal and non-pyramidal somal area and in segment-related growth characteristics. No significant changes in total segment length or number of segments/ neuron, however, were observed. Moreover, there was a significant age-related decrease in the number of basal dendrites for pyramidal neurons coupled with a decrease in apical dendritic length. Preliminary studies show that these latter observations are reversed when the neocortex is in contact with a similar neocortical slice, suggesting that afferent input and/or efferent targets are required for the proper maturation of pyramidal neurons in this model system.

17.05 TRIIODOTHYRONINE AND NERVE GROWTH FACTOR INDUCE DYNEIN EXPRESSION BY PRIMARY SENSORY NEURONS IN RAT DORSAL ROOT GANGLION CULTURES

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Apart from several growth factors which play a crucial role in the development of nervous system, thyroid hormones contribute to the normal development of the nervous system during the fetal and neonatal periods. The effects of nerve growth factor (NGF) and triiodothyroinine (T_3) on cytoplasmic microtubules expression by primary sensory neurons were tested. Dorsal root ganglion explant cultures were prepared from 19-day-old rat embryo. Some cultures were treated either with NGF or with T_3 or with both NGF and T_3 together. Changes in expression of microtubules proteins were studied by SDS-polyacrylamide gels electrophoresis, Western blots and by immunocytostaining. The analysis of gels electrophoresis and Western blots showed that cytoplasmic brain dynein (MAP 1C) is expressed abundantly in cultures treated with both NGF and T_3, while it was never detected in cultures treated with NGF or T_3 separately or in control cultures. In fact only DRG explant grown in the presence of NGF and T_3 together displayed dynein immunoreactivity. In contrast to brain dynein the expression of α-tubulin and β-tubulin was strongly enhanced by NGF alone and at a lesser degree by T_3.

In conclusion interaction between nerve growth factor and thyroid hormone may regulate the expression of cytoplasmic dynein and could be involved in the mechanisms of retrograde axonal transport. (SNF N° 3367-92)

17.06 THAPSIGARGIN BLOCKS LONG-TERM POTENTIATION INDUCED BY WEAK, BUT NOT STRONG TETANISATION IN RAT CA1 NEURONS.

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To elucidate the role of calcium release from internal stores during different paradigms of tetanisation in long-term potentiation (LTP), we have investigated the effects of thapsigargin (4 μM) on the elevation of the excitatory postsynaptic field potential (fEPSP) and the population spike (PS) after tetanisation.

We found no effect on the duration of fEPSP potentiation if thapsigargin was perfused before strong tetanisation. However, the potentiation was reduced significantly from control experiments, if thapsigargin was applied before weak tetanisation. Surprisingly, we did not find any reduction of PS potentiation, which could be due to changes in the recurrent inhibition. Our data indicate that the involvement of inositol 1,4,5-trisphosphate (IP_3) dependent calcium stores critically depends upon the kind of tetanisation employed. A release of calcium from the internal stores seems not be required after strong tetanisation, which could be due to sufficient large external calcium influx through NMDA- and other channels. In contrast the weak tetanisation does not seem to induce such a rise in the Ca_i concentration sufficiently long and high to induce a long-lasting LTP without the involvement of the internal IP_3 dependent calcium release.

Besides this, a high Ca_i concentration could also reduce the affinity of the IP_3 receptors possibly preventing the involvement of internal stores after strong tetanisation. We conclude, that the involvement of internal calcium release in the mechanisms of LTP induction will be reduced if multiple tetanisation is used.

17.07 EMBRYONIC CORTICAL NEURONS DIFFERENTIATE INTO VARIOUS TYPES OF INTERNEURONS WHEN HETEROTOPICALLY GRAFTED INTO THE ADULT RAT BRAIN

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The adult cortex represents a heterogenous mixture of different classes of pyramidal neurons and non-pyramidal interneurons. After grafting embryonic cortical anlagé, obtained on gestation day 14 (E14), into the adult striatum, the present study investigated whether the development of different populations of interneurons in this heterotopic grafts is similar to the normal adult cortex. The presence of specific subpopulations of interneurons in the grafts was assessed by immunocytochemistry using specific antisera against various marker molecules for interneurons such as neuropeptides or calcium-binding proteins. The heterogenous group of cortical interneurons can be divided by their (partially overlapping) expression of different neuropeptides, such as vasoactive intestinal polypeptide (VIP), somatostatin (SS) and neuropeptide Y (NPY), or calcium-binding proteins, such as calbindin-D28k (CB) and parvalbumin (PV). Therefore 8 weeks after the grafting procedure, host rats were perfusion-fixed and immunocytochemistry was performed using antibodies against VIP, SS, NPY, CB and PV. Within the grafts, the number of immunopositive neurons as well as the intensity of the immunostaining for this marker molecules corresponded well with those of the adult cortex but demonstrated clear differences when compared with the striatum. The present study clearly demonstrates, that at E14 at least some cells of the cortical anlage are primed to develop into different classes of interneurons independent of their normal environment and synaptic connections. Thus, different interneuron progenitor cells survive transplantation and develop cell specific morphological and cytochemical characteristics.

17.08 NEUROTROPHINS INDUCE ACUTE TRANSMITTER-MEDIATED CHANGES IN BRAIN ELECTRICAL ACTIVITY

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Neurotrophins have, to date, been considered primarily as mediators of neuronal survival, differentiation and maintenance of specific functions. However, the rapid regulation of BDNF and NGF synthesis and release by neuronal activity, and the enhancement of neuromuscular transmission by BDNF and NT-3, suggested an involvement of neurotrophins in synaptic plasticity. Here we demonstrate that BDNF, NGF and NT-3 injected into the rat hippocampus alter hippocampal and cortical electrical activity reflecting transmitter release from neurons expressing trkB (BDNF), trkA (NGF) and trkC (NT-3) receptors. BDNF elicited epileptiform activity accompanied by corresponding behavioural changes predominantly mediated by NMDA type glutamate receptors, whereas NGF and NT-3 induced epileptiform activity followed by a sustained theta-like activity mediated via muscarinic receptors. K252a, a tyrosine kinase inhibitor, predominantly affecting trk receptors, prevented the effects elicited by neurotrophins. These data show that the acute effects of neurotrophins are mediated by transmitter released from neurons expressing the corresponding trk receptors. These observations also suggest that endogenous neurotrophins released by neuronal activity may act as retrograde messengers to acutely modulate synaptic transmission .

17.09 AGE-RELATED EXPRESSION OF THE α4-1- AND α5- SUBUNIT mRNAs OF THE NICOTINIC RECEPTOR IN THE RAT BRAIN.

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Alteration of the central cholinergic system appears to be associated with memory impairments in humans as well as in animals and is an important feature in normal aging process and age-related disorders (e.g. Alzheimer's disease). In order to improve the knowledge of normal aging process and to devolop new strategies for treatment, it is important to elucidate whether the reduced binding of nicotine may be due to an alteration of the nicotinic acetylcholine receptor (nAChR) subunit composition, to a general decrease in expression of the nAChR or to post-translational modifications.

The expression of the α4-1 and α5 subunits of the nAChR was studied in brain tissue (parietal and frontal cortex) from 3, 24 and 33 months old male Wistar rats. In situ hybridization was performed using digoxigenin-labeled riboprobes specific for the α4-1 and α5 nAChR subunit, respectively. Hybridized probes were visualized by means of an alkaline phosphatase conjugated digoxigenin-antibody and a color substrate reaction.

There were no indications of marked age-related changes in the regional distribution pattern of the α4-1 and α5 subunit. The density of α4-1 and α5 mRNA expressing neurons decreased significantly with aging. Quantitative data showed a concomitant loss of cortical neurons and α5 mRNA expressing neurons for both old age groups (24, 33 months). With regard to the α4-1 subunit, a similar concomitant loss was found for the 24 months old animals, whereas an additional loss of neuronal α4-1 mRNA expression was detected in 33 months old rats. Regional differences could not be observed. These results point to distinct changes in age-dependent gene expression of various subunits of the nAChR.

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17.10 ON THE EFFERENT REQUIREMENTS OF A FUNCTIONAL FETAL GRAFT OF THE SUPRACHIASMATIC NUCLEUS.

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Fetal grafts containing the suprachiasmatic nucleus (SCN) can restore circadian activity rhythms of SCN-lesioned arhythmic rats. The in situ SCN has an extensive efferent network believed to pass on the endogeneous circadian pacemaker activity of the SCN to other brain structures. Indeed SCN grafts placed at the site of the lesion (the bottom of the IIIrd ventricle) and capable restoring the drinking arhythmia, developed afferent outgrowth visible after immunostaining for vasopressin (VP) and vaso-active intestinal polypeptide (VIP). However fiber density is very limited and not reaching far into the host hypothalamus, probably explaining why 60% of the SCN graft-positive rats still failed to recover behaviorally.

SCN grafts taken from VP-deficient Brattleboro donors failed to restore circadian drinking behavior. The presence of the SCN could be confirmed by VIP staining and results seem to indicate the importance of SCN VP for rhythm transfer. However adult Brattleboro rats expose circadian rhythms, so that abnormal development of the fetal VP-deficient SCN had perhaps occurred when grown in a VP-rich adult host environment.

An attempt was made to increase recovery efficiency by grafting the fetal SCN in the host thalamus, a area that receives SCN VPergic input. Graft-to-host afferent outgrowth was still limited, whereas percentage of grafted SCN-lesioned animals showing restored rhythm was even lower. Thus, thalamic reinnervation by the grafted SCN is not likely to be an important prerequisite for recovery.

17.11 DIFFERENTIAL INDUCTION OF THE TWO SNAP-25 ISOFORMS DURING REACTIVE SPROUTING OF MOSSY FIBERS

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SNAP-25 (25kD synaptosomal-associated protein) plays an important role in nerve terminal physiology . Recent studies indicate that SNAP-25 mediates synaptic vesicle fusion with the presynaptic membrane leading to transmitter release as well as the fusion of plasmalemmal precursor vesicles with the axolemma, a prerequisite for new membrane insertion during axonal growth. SNAP-25 mRNA exists in two different splice forms, called a and b, that are differentially expressed during development and in adults (Bark et al., 1995). In adult animals, SNAP-25b is the major isoform expressed in brain, high SNAP-25a m-RNA levels can only be found in the following areas: olfactory bulb, hippocampal hilus region, centromedial thalamic nucleus, medial mammilary nucleus, subiculum, substantia nigra compacta and cortex layer Va. In order to determine if isoform expression heterogeneity in distinct adult terminals may reflect their capacity to undergo plastic changes, we performed expression studies of the two SNAP-25 isoforms after kainic acid (KA 10mg/kg) treatment. Kainic acid induced seizures in adult rats have been reported to cause sprouting of mossy fibres in the inner molecular layer of the dentate gyrus. Only the SNAP-25a isoform mRNA is upregulated in the granule cells of the dentate gyrus 48h after KA treatment. SNAP-25a may therefore play a role in the remodelling of mossy fibre axonal branches after KA seizures.

17.12 INVOLVEMENT OF PHOSPHOLIPASE A2 ACTIVITY IN SURVIVAL AND GROWTH OF ADULT MOUSE SYMPATHETIC AND SENSORY NEURONS IN VITRO.

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We have shown that dorsal root ganglia (DRG) and superior cervical ganglia (SCG) of adult mice survive in organ culture for some days and extend neurites in matrigel, an extract of the extracellular matrix, secreted by the Engelbreth-Holm-Swarm tumour cell line. The effects of various phospholipase A2 (PLA2) inhibitors (BPB, aristolochic acid, OOPC) suggest that neuronal survival and axonal growth is related to PLA2 activity by different mechanisms. Furthermore, immunohistochemical studies reveal a strong upregulation of PLA2 in certain neurons during culturing. This may in part be explained by a PLA2 involvement in apoptosis, since most apoptotic neurons, detected by in-situ nick labelling of DNA-breaks, also show strong PLA2 immunoreactivity.

17.14 TRANSPLANTATION OF SCHWANN CELL COLUMNS INTO THE ADULT RAT THALAMUS INDUCES A HIGHLY ORGANISED AND ORIENTED HOST GLIAL RESPONSE

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Highly purified suspensions of Schwann cells were stereotaxically transplanted, in the form of elongated columns of cells, into the thalamus of syngeneic adult rat hosts. By 2 hours, numerous ramified, OX-42 immunoreactive cells accumulated at the graft-host interface. With increasing survival times, many more, intensely OX-42 and vimentin-positive cells (presumably microglia and macrophages) accumulated within the transplant and subsequently adopted an elongated shape. Reactive host astrocytes responded considerably more slowly to the transplant. However, by 2 weeks, the Schwann cell columns contained intermingled OX-42-positive macrophage/microglia, hypertrophic GFAP-positive astrocytic processes and RT97-positive axons, all of which were orientation in parallel with the donor Schwann cell processes. Electron microscopy revealed Schwann cells and astrocytic processes in association with numerous axonal profiles within a single basal lamina. The properties of this hybrid graft-host tissue, may be use in the design of future therapeutic strategies for inducing directed host axonal growth in the repair of damaged central axon projections.

17.15 INDUCTION OF MAP KINASE PHOSPHATASE BY NEUROTRANSMITTERS IN PC12 CELLS.

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There is accumulating evidence that activation of neuronal receptors by neurotransmitters can lead to changes in neural gene expression. Such changes are mediated by the transcription of immediate early genes. MAP (mitogen-activated protein) kinases are activated in response to growth factors. Activation leads to their translocation to the nucleus, where they phosphorylate and activate several transcription factors. MAP kinases are inactivated by a dual phosphatase, MAP kinase phosphatase (MKP). This phosphatase is itself encoded by an immediate early gene, the *3CH134* gene. Whereas induction of the MKP gene has been reported for growth factors, little information is available concerning its stimulation by neurotransmitters, despite the high MKP distribution in brain. In the present study, we investigated the induction of the MKP gene by neurotransmitters in PC12 cells. This effect was compared to that observed on the expression of the immediate early gene *egr-1*, which is known to be induced by synaptic activity.

The neurotransmitters, agonists and second messenger elevating agents tested (glutamate, 5-HT, cholinergic agonists, depolarization, TPA, forskolin and Ca^{2+} ionophore) were all able to stimulate to some extent the expression of the *MKP* gene, 5-HT being the most effective agent. MKP gene expression was already observed 30 minutes after stimulation. 5-HT was also the most potent agent in inducing *egr-1* transcription. The gene induction was accompanied by increased activity of the corresponding protein. *Egr-1* induction was strongly inhibited by ketanserin and mesulergine, indicating that 5-HT exerted its action via a 5-HT_2 receptor. Our findings suggest that neurotransmitters, by inducing the MKP gene, modulate the growth factor-stimulated MAP kinase pathway.

17.16 MOVEMENT DISCRIMINATION LEARNING IS IMPAIRED IN VISUALLY DEPRIVED CATS.

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Two groups of cats were used: 5 cats deprived binocularly of pattern vision during the first 6 month of life (BD cats) and 4 not deprived controls (C cats). The cats were trained in two-choice discrimination apparatus for food reward. In the movement detection stage the positive stimulus was a light spot moving downward or upward, whereas the negative stimulus was a stationary spot. The spot was 2x2 cm in diameter and the moving spot passed the 37 cm high gate within 0.8 s. The C cats met easily criterion. In contrast, 3 BD cats did not reach criterion within 50 sessions and 2 BD cats only after long-lasting training. In the subsequent, movement discrimination stage, the negative stimulus was a spot moving in opposite direction than the positive one. In this task the BD cats did not reach the criterion, whereas 3 C cats met it easily. In all cats the middle suprasylvian sulcus was removed unilaterally or bilaterally. The lesioned cats got easily the preoperatively criterion. The results are consistent with single-cell recording data showing a severe impairment of analysis of movement in BD cats.

17.17 INTRACEREBRAL XENOGRAFTS OF HUMAN VENTRAL MESENCEPHALIC TISSUE: AN ELECTRON MICROSCOPIC AND IMMUNOHISTOCHEMICAL STUDY.

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The survival of xenogeneic neuronal tissue after transplantation to adult Wistar rats without immunosuppression was studied. Cell suspension was prepared from the ventral mesencephalon of human embryos 7 - 8 weeks of gestation and injected either into the striatum or motor cortex of adult rats. Two weeks and 1,3, 6 ,8 months later the rats were sacrificed and the brains were processed for tyrosine hydroxylase (TH), glial fibrillary acidic protein (GFAP), ferritin immunohistochemistry and electron microscopic study.

Degree of inflammatory reaction of host brain strongly effected the viability of grafted cells and the extent of GFAP and ferritin staining in the tissue around the graft.Grafted humans TH- positive neurons were found for 3 months only in the case of weak immune reaction. Extensive bundles of myelinated fibres transpassing the intracortical grafts were seen 6 - 8 months after implantation.

It is suggested that human fetal mesencephalic cells can survive and provide neurite-promoting influence in rat brain without immunosuppression.

17.18 **DECREASE OF HIPPOCAMPAL ACH RELEASE IN AGING FREELY-MOVING RATS: PREVENTION BY CHRONIC TREATMENT WITH NICERGOLINE (SERMION®)**

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Brain cholinergic disfunction has been implicated in cognitive deficit that occur in Alzheimer's disease and aging. Accordingly drugs which enhance presynaptic cholinergic transmission could be effective against some symptoms of these disorders. Nicergoline is an ergoline derivative with cognitive-enhancing properties in human as well as various animal models of memory impairment. In this study we examine whether aging affects the basal and K^+-evoked release of ACh from rat hippocampus and whether chronic oral administration of nicergoline is able to restore an age-dependent reduction of ACh release. Extracellular ACh in the ventral hippocampus of 3- and 19 month-old Sprague Dawley rats was measured by intracerebral microdialysis coupled with HPLC-ED technique. A significant decline of basal release of ACh (60%) was found in aged rats in comparison to young rats. The out-put of ACh was stable up to the onset of K^+-stimulatory effect (120 min). As expected, upon the addition of high K^+ (100 mM) in the perfusate, the release of ACh markedly increased, reaching 5 fold over the baseline of either young or aged rats, suggesting that aging did not change the magnitude of K^+-evoked ACh release response. Oral administration of nicergoline (5 mg/kg b.i.d.) for 6 weeks to aged rats significally increased basal release of ACh by about 94% leaving unchanged the ACh release evoked by K^+ depolarization. The increase of basal ACh release induced by nicergoline reached almost the value of young controls. Nicergoline treatment did not change either basal or K^+-evoked ACh release in young rats. It is concluded that the effect of nicergoline on hippocampal ACh release could explain at least in part the positive action on memory and other cognitive functions in aged animals and senile dementia.

17.19 DIFFERENTIAL CHANGES IN PKC TRANSLOCATION AFTER INTRAUTERINE EXPOSURE TO METHYLAZOXYMETHANOL, A MOLECULE INDUCING BRAIN DAMAGE AND COGNITIVE DEFICIT.

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The involvement of Protein Kinase C (PKC)-dependent processes in adaptive and plastic changes underlying neuronal plasticity was tested in an in vivo animal model characterized by targeted cellular ablation of cortical and hippocampal neurons, cognitive impairment and lack of induction of long-term potentiation (Ramakers et al., 1993). This animal model has been obtained by in utero exposure to an antiproliferative agent selective for neuroepithelial cells: Methylazoxymethanol acetate (MAM). We have previously demonstrated that the phosphorylation of B-50/GAP 43 is markedly altered in MAM-treated rats (Di Luca et al., 1995). Western Blot analysis of cytosolic and membrane fractions of synaptosomes showed that the alterations in the basal phosphorylation of B-50 are reflected by increased translocation of PKC to the membrane compartment (56±5.5% and 78±6.58% in hippocampus and cortex, respectively) indicating enhanced activation of the kinase at the presynaptical level. All the major PKC isozymes expressed in the presynaps show increased activation; in fact α, β and ε isozymes are more translocated by 22.2±4.2%, 25.4±1.6% and 28.4±1.2% respectively in hippocampus of MAM-treated rats if compared to control animals and similar results have been obtained in cortex. On the contrary the translocation of PKC γ, which is selectively expressed in the neuronal postsynaptic compartment, is markedly reduced in these animals. These data further confirm an involvement of PKC isozymes in mechanisms underlying synaptic plasticity and suggest that different subspecies may play a differential role in pre- and post-synaptic events associated with long term changes of synaptic efficacy.

Ramakers et al., (1993) Neurosci. 54: 49-60.
Di Luca et al., (1995) Eur. J. Neurosci., in press.

17.20 REGENERATION AFTER NERVE INJURY INFLICTED AT DIFFERENT TIME

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From our previous research it follows that changes in conjunctive tissue of the regenerative neuroma influence the nerve fibres regeneration. This study deals with the changes in the sciatic nerve after its injury inflicted at different time. The rats sciatic nerves were cut. A half of the animals was operated at 8 a.m.(the Ist series), the second half - at 8 p.m. (the 2nd series). The nerve trauma area was studied neurohistologically, morphometrically and electrophysiologically in 1-180 days after the operation.

It was shown that the time of injury plays an important role in the time of appearance and peculiarities of the following aseptic inflammation in the regenerative neuroma conjunctive tissue. It influences the neuroma"s nerve fibres (their growth and maturation). The data obtained are of significance for elaboration of new methods in nerve injuries care.

17.21 THE EFFECT OF GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR IN FIBRIN GLUE ON DEVELOPING DOPAMINE NEURONS.

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Glial cell line-derived neurotrophic factor (GDNF), a member of the transforming growth factor-β superfamily, promotes the survival, morphological differentiation, and high-affinity dopamine uptake of cultured nigral dopamine neurons. In order to test potential methodology for peptide delivery in vivo, GDNF-containing fibrin glue balls (8 µg /ball) were incorporated with pieces of fetal ventral mesencephlon (E15) and transplanted into the anterior chambers of sympathetically denervated adult rats. Five weeks after grafting, the number of TH-positive neurons and nerve fibers was significantly increased in the ventral mesencephalic grafts treated with GDNF-containing glue balls compared with those treated with vehicle. In addition, the laminin and GFAP immunoreactivities were similar between the two groups. These data support the concept that GDNF is a potent trophic factor for DA neurons in vivo and also suggest that fibrin glue may provide a unique and safe means to permit prolonged delivery of trophic molecules to CNS tissues.

17.22 DELAYED MATURATION OF THE GLOMERULI WITHIN THE HOMOTOPIC OLFACTORY BULB TRANSPLANT.

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Recent studies on olfactory bulb (OB) homotopic transplantation have shown that regenerated olfactory axons are able to form glomeruli either in the transplant or in the spared OB. To investigate the maturation of olfactory axons and their terminals we employed B-50/GAP-43 immunohistochemistry. Autoradiographically prelabeled presumptive OB (E18) were homotopically transplanted in unilaterally bulbectomized neonatal rats (P6). In 2 months old transplants, outgrowing axons and newly formed glomeruli displayed prominent B-50 immunoreactivity (BIR). Four months postoperatively the regrowing axons were still B-50 positive, while in some glomeruli of the transplant reduced BIR was observed. Intense B-50 immunostained patchy structures were present in some glomeruli of the transplant as well as in the remnants. The persisting BIR in the glomeruli of the transplant and in the remnants of lesioned OB suggests that the maturation of the newly formed glomeruli was delayed in comparison to control OB.

17.23 **ORGANIZATIONAL ACTION OF ESTROGEN ON FEMINIZATION OF THE FEMALE RAT LOCUS COERULEUS**

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Sexual dimorphism was demonstrated in the noradrenergic locus coeruleus (LC) using Nissl stain (Dev. Brain Res., 40, 1988, 306) and using inmunocytochemistry for the noradrenaline biosynthetic enzyme dopamine-beta-hydroxylase (Dev. Brain Res., 67, 1992, 211). Female rats have a larger neuron number than males and this sex difference is affected by gonadal steroids during neonatal period: testosterone treatment of female on the day of birth (D1) or ovariectomy performed on D1 abolished this sexual dimorphism as seen when the subjects were studied in adulthood (90 days old). These data suggest an active role of ovarian hormones on sexual differentiation of the LC. Furthermore it was demonstrated that: a) a single injection of estradiol benzoate (EB) on D1 or D5 fails to promote a female pattern of LC sexual dimorphism in the ovariectomized rats; b) this sex difference already exists in prepubescent period (D20). In order to elucidate a possible mechanism for sexual differentiation in LC, the effect of continuous treatment with estrogen on LC number of neurons was investigated. Three groups were included: 1. ovariectomized females on D1; 2. ovariectomized females injected with EB (0.4 mg/kg) from the D7 to D20; 3. control females. At the age of 20 days the rats were sacrificed. Treatment with estrogen restored LC development in the ovariectomized rat at birth ($F_{(2,12)} = 24.5$, $p < .0001$). D1 ovariectomy decreases neuronal population of the LC and this effect is counteracted by continued administration of EB. This result provides evidence that ovarian hormones play an active role in inducing sexual differentiation in the female brain.

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17.24 EFFECTS OF DENERVATION ON THE EXPRESSION OF NEUROTROPHIN-3 mRNA IN MUSCLE SPINDLES OF THE RAT. J.C.V.M. Copray* and N.Brouwer, Department of Medical Physiology, University of Groningen, Bloemsingel 10, 9712 KZ Groningen, The Netherlands.

In previous studies, we have demonstrated that the intramuscular neurotrophin-3 (NT-3) mRNA expression in the rat is mainly restricted to the muscle spindles (Neuroscience 63:1125,1994). It appeared that the NT-3 mRNA expression in the intrafusal fibers started at embryonal day E19, i.e. after the establishment of sensory innervation, and that it continued throughout life. In contrast to its crucial role during early embryogenesis, the function of NT-3 in mature intrafusal fibers is still unclear. It has been suggested to act as signalling factor controlling the maintenance of proper functional contacts between the intrafusal fibers and their innervating sensory (and presumably motor) neurons.

In order to elucidate the relation between NT-3 expression in the intrafusal fibers and the presence of a functional innervation, we have studied the NT-3 mRNA expression in muscle spindles of rat hindlimb muscles following their denervation. Nerve sectioning was done in neonatal (P1) as well as mature (P30) rats, i.e. before and after normal muscle spindle formation was completed. A non-radioactive in-situ hybridisation procedure was used to demonstrate the intramuscular expression of NT-3 mRNA in muscles, in combination with the immunohistochemical staining for calretinin, used to detect the presence of (sensory) innervation.

Denervation of muscle spindles in neonatal rats resulted in the loss of the developing muscle spindle structures and concomitantly of NT-3 mRNA expression in the intrafusal fibers. Nerve sectioning in mature rats did hardly effect muscle spindle integrity. However, the absence of muscle spindle innervation in mature rats completely abolished NT-3 mRNA expression in the intrafusal fibers.

Our results suggest that the expression of NT-3 mRNA in muscle spindles depends on the presence of an intact (sensory or motor) innervation of the intrafusal fibers.

17.25 TACTILE EXPERIENCE ALTERS THE ORGANIZATIONAL FEATURES OF THE FOREPAW REPRESENTATION OF THE RAT SOMATOSENSORY CORTEX. J.O. Coq*, M. Benelhadj, C. Xerri *Lab. Neurobiology of Functional Restorations, URA CNRS 372, University of Provence, 13397 Marseilles, cedex 20, France.*

Numerous studies support the view that subject-environment interactions have significant effects on brain structure and learning capabilities. Moreover, it is well established that the cutaneous representations of the primary somatosensory (SI) cortex display a remarkable plasticity and can be reshaped through an experience-dependent process. We have designed experiments to evaluate the influence of differential tactile experience on the organization of the cutaneous "maps" of the rat SI cortex. Long-Evans rats were assigned to different tactile environments (standard, enriched, impoverished) for 1 month from the time of weaning. A fourth group of rat experienced a severe restriction of forepaw exploratory movement for 2 weeks after weaning. The "standard" rats were housed in groups of 3, in a conventional environment. The "impoverished" rats were also exposed to a conventional environment, but each animal was housed in a separate cage. The "enriched" animals were housed in larger cages, in groups of 12 and were provided with objects of different shapes, sizes and textures. The animals subjected to deprivation of exploratory movements experienced a forelimb immobilization with a one-sleeved cast. The forepaw representation within SI (contralateral to the immobilization in the deprived rats) was then reconstructed by using microelectrode mapping. The results show that 1) tactile enrichment induces an enlargement of the cutaneous forepaw representation and improves its spatial resolution (smaller cortical receptive fields, RFs); 2) tactile impoverishment and forelimb disuse result in a degradation of the forepaw representation (larger RFs, discontinuities in the representation of contiguous skin territoiries, emergence of non-cutaneous small "islands"). These results indicate that tactile experience plays a critical role in the maintenance of the representational features of the cutaneous cortical maps.

17.26 EFFECTS OF GLUTAMATE RECEPTOR BLOCKADE ON THE FUNCTIONAL DEVELOPMENT OF NEOCORTICAL NEURONAL NETWORKS CULTURED *IN VITRO* R. Nuytinck, M. Corner*, J. van Pelt, P. Wolters and R. Baker, Netherlands Institute for Brain Research, Amsterdam, The Netherlands.

The hypothesis that embryonic (neo)cortical networks 'use' intrinsically generated neuronal discharges to prevent a hyper-excitable state from developing has been confirmed, at least for 'organotypic' cortex cultures, by results obtained from using glutamatic acid antagonists in order to suppress excitatory amino acid transmission during early ontogeny. A mixture of DNQX and APV (to block non-NMDA and NMDA receptors, respectively) led to a considerable increase in (i) the incidence of 'complex burst/slow-wave' discharges within the network, (ii) the intensity of action potential firing during each of the bursts, and (iii) the occurrence of oscillatory after-discharges (field potentials associated with neuronal spiking). These effects were more pronounced at 3 than at 2 weeks in vitro, and were still present 24 hours following transfer to normal growth medium. Although chronic NMDA receptor blockade alone, as monitored after return to normal growth medium, produced less severe functional abnormalities than was the case for total excitatory amino acid blockade, APV-treated cultures were abnormally active in the presence of that agent. This last result reveals a potentiality for compensatory 'up-regulation' of neuronal excitability, presumably involving *non*-NMDA glutamate receptors, under conditions where ongoing network activity is drastically reduced at early stages of development. Despite the return of bioelectric activity, however, cortical network development was still demonstrably abnormal, thereby implicating NMDA receptor activation as a significant maturational factor in its own right, and not just by virtue of its contribution to excitatory synaptic drive. The results as a whole are to be expected on the basis of Kater's hypothesis of the central role of calcium entry in regulating activity-dependent developmental processes in the nervous system.

17.27 **CORTICAL PROJECTIONS TO THE REPRESENTATIONS OF DIGITS I AND II IN MONKEY SOMATOSENSORY CORTEX AFTER PERIPHERAL DENERVATION.** M. Costa*, A. Nuñez, J.A. Gandía and E. Rausell, Depto Morfología, Fac. Medicina, Universidad Autónoma, 28029 Madrid, SPAIN.

It has recently been raised a debate on the anatomical mechanisms that underlie the somatosensory system potential to modify the extent of partial body representations in the somatosensory cortex (SI) under activity dependent conditions. Sprouting of thalamic and cortical axons into cortical territories deprived of afferent activity and/or functional unmasking of previously existing terminals have been suggested as candidates to explain short term changes in the extent of body maps. Evidence supporting significant divergence of thalamic inputs into non-somatotopically related cortical territories in area 3b has been recently provided which points to the "functional unmasking" as a likely candidate for the thalamic contribution to plasticity. However, the role of cortical afferents from somatotopically and non-somatotopically related fields of other somatosensory cortical areas still needs to be explored.

In this study, we have differentially labeled the two sets of cortico-cortical neurons in areas 2, 1, and SII that project to area 3b first and second digit representations (DI and DII) in normal and denervated monkeys. We have then used the degree of cortical overlap between the two sets of neurons as a parameter to explore the presence of pre-existing collaterals or the occurring of sprouting of new cortico-cortical afferents.

The border between the representations of DI and DII in area 3b were identified by means of single unit extracellular recording in adult anesthetized monkeys (Macaca Fascicularis) that had been subjected to peripheral selective cutaneous denervation of the first digit fifteen days earlier. Small injections of Fast Blue (FB) and Diamidino Yellow (DY) were made at each side of this border. Retrogradely single and double labeled cortico-cortical cells were localized, plotted, and counted. The results were then compared with those obtained in a parallel set of experiments performed in normal monkeys. The importance of either of the above mentioned potential mechanisms and the role of the cortico-cortical system in short term cortical plasticity is discussed upon the results obtained from statistical analysis of the quantitative results.

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17.28 CHANGES IN EXPRESSION OF MICROTUBULE ASSOCIATED PROTEIN 2 (MAP2) AND SYNAPTOPHYSIN IN RAT SPINAL CORD FOLLOWING NEONATAL NERVE INJURY. J.Dekkers* & R.Navarrete, Charing Cross & Westminster Medical School, Fulham Palace Road, London W6 8RF, U.K.

We have previously found that neonatal nerve injury arrests motoneurone dendritic maturation and leads to alterations in primary afferent inputs during the first week after injury, at a time when many motoneurones die. To examine the temporal relationship between alterations in pre- and postsynaptic structures we have studied the expression of MAP2, a cytoskeletal protein expressed in soma and dendrites of motoneurones, and synaptophysin, a protein present in synaptic vesicles, using monoclonal antibodies.

Motoneurones were prelabelled by injection of fluorescent dyes into ankle flexor muscles at birth (P0). At P2, the common peroneal nerve was crushed unilaterally. In adults, MAP2 immunoreactivity (MAP2-IR) was localised to the motoneurone soma and dendrites, while synaptophysin immunoreactivity (SY-IR) consisted of punctate profiles apposed to the entire somatodendritic surface. At P3, no apparent difference in MAP2-IR or SY-IR was found between control and operated sides. However, SY-IR in the neuropil of normal and injured motor pool was much higher and showed a wider distribution, particularly in the lateral funiculus, compared to adults. By P7 and progressively to P21, there was a reduction in the number and intensity of MAP2-IR somata in the injured pool, while the MAP2-IR in the dendritic neuropil remained. This may indicate sprouting of dendrites from injured motoneurones that still survive, or invasion of their territory by dendrites by uninjured cells. Concomitantly, SY-IR on the injured side became progressively more irregular along the outline of dendrites. Between P7 and P14 there was a developmental decrease in SY-IR in the neuropil around the motor pool on both operated and control sides. SY-IR became heavily concentrated around thick dendritic bundles extending into the lateral funiculus whereas this distribution was more diffuse on the operated side.

Thus, changes in expression of MAP2 in the motoneurone dendritic cytoskeleton occur during the peak period of cell death and dendritic remodelling following neonatal nerve injury. These changes are accompanied by rearrangement in synaptic inputs.

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17.29 MECHANISMS INVOLVED IN CORTICAL PLASTICITY INDUCED BY INTRACORTICAL MICROSTIMULATION (ICMS) OF ADULT RAT SOMATOSENSORY CORTEX *IN VITRO*. P. Heusler, G. Böhmer and H.R. Dinse*, Inst. Physiol. & Pathophysiol., Gutenberg-University, D-55099 Mainz, * Inst. Neuroinformatics, Ruhr-University, D-44780 Bochum, FRG.

In an *in vivo* preparation of the rat a few hours of ICMS, which utilizes repetitive electrical pulse trains delivered via a microelectrode to the somatosensory cortex, is highly effective in inducing cortical reorganization of skin field representation. Reorganization of representational maps is induced not only in the central zone of the somatosensory cortex, but also in previously non-somatosensory fields beyond the border of the somatosensory cortex. The present study aimed at examining possible underlying mechanisms involved in this type of representational plasticity at the cellular level. Thus, ICMS was performed in an *in vitro* preparation of the rat somatosensory cortex. Cortical slices (350-600 µm) were superfused with carbogen-saturated artificial cerebrospinal fluid (ACSF) at 36 °C. Field-potentials (FP) were evoked by electrical stimulation of cortical layer IV/V using steel-needle electrodes. FP were recorded from cortical layer II/III using glass-microelectrodes filled with ACSF. ICMS was delivered to cortical layer IV/V by means of steel-needle electrodes. Pulse trains of 40 ms duration (13 pulses of 100 µs and 25 µA to 1 mA) were repetitively applied at a rate of 1 Hz. Duration of ICMS was 60 to 90 minutes. FP consisted of an antidromic component (neither blocked by APV, NBQX or low-Ca^{2+} ACSF) and two or more synaptic components. The first synaptic component (S1) was blocked by NBQX, whereas the second (S2) and later synaptic components were blocked by APV. S1 and S2 were thus considered to be mediated by AMPA receptors or NMDA receptors, respectively. ICMS (400 µA and above) induced a reduction of the amplitude of the antidromic component as well as of S1 and S2. The reduction of the amplitude of all components slightly decayed during the first minutes after cessation of ICMS, but reached a constant level of reduction thereafter, outlasting the remaining observation period (90 after cessation of ICMS). Additionally, ICMS induced an increase in latency of S1 and S2. Continuous superfusion of cortical slices with ACSF containing bicuculline resulted in enhancement of depressive effects. The same was true, even to a greater extent, when in addition to bicuculline ACPD, an agonist at metabolic EAA receptors, was added to the bath for a period of 30 min prior to ICMS. These effects of ICMS were interpreted in terms of the induction of long-term depression (LTD). Results imply that LTD may also be involved in ICMS-induced reorganization of representational maps of the somatosensory cortex *in vivo*.

17.30 EXPRESSION OF RECOMBINANT TRKA EXTRACELLULAR DOMAIN AS A SOLUBLE IgG HFc FUSION PROTEIN

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Trk A ($p140^{trk\,A}$) belongs to the family of tyrosine kinase receptors and binds with high affinity to its cognate ligand, nerve growth factor (NGF). The cDNA encoding the extracellular domain of TrkA was amplified by PCR with an enterokinase site added at the 3' end. This construct was subcloned into a metallothionein based expression vector such that it was upstream and in frame with portion of the Fc domain of a mouse IgG. This construct (TS200) was stably transfected into Chinese hamster ovary (CHO) cells and selected for G418 resistance. For control transfections, the extracellular domain of TrkA was inserted into the vector in the opposite orientation (TS800). Clones were checked for TrkA inserts by PCR. Expression of the secreted fusion protein was induced by the addition of 25μM zinc into the culture medium. The conditioned media was collected 36 hours later and the chimeric protein was purified using an anti-mouse Fc affinity column. Fractions were collected and resolved by SDS PAGE. Western blots were probed with a polyclonal antibody to the extracellular domain of TrkA (kindly donated by D Kaplan, Washington) using ECL detection and subsequently stained using Coomassie. Fractions containing positive bands from both Western analysis and Coomassie were pooled and dialyzed for ^{125}I-NGF displacement studies. Results showed that the TrkA-HFc fusion protein binds to recombinant human NGF. This protein will be used for structure / function studies with recombinant human NGF for the design of drugs in the treatment of neurodegenerative diseases, particularly Alzheimer's disease.

17.31 FUNCTIONAL RECOVERY OF THE DAMAGED SEPTO-HIPPOCAMPAL CHOLINERGIC SYSTEM IN THE NEWBORN RAT. EFFECTS OF bFGF AND TGFβ1.

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The basic fibroblast growth factor (bFGF) is known to affect proliferation and maturation of various cultured cell types and in vivo to facilitate the survival of neurons. Previously, we have shown that i.c.v. repeated injections of bFGF (total 80 ng) or even a single injection of bFGF (a high dose of 4 μg/5μl) were efficient to attenuate the fimbria (Fi) transection-induced decrease of choline acetyltransferase (ChAT) activity in the hippocampus of the adult rat. The present study was designed to know whether : i. a high dose of bFGF would be efficient to mitigate the biochemical effects of the Fi transection in the newborn rat, i.i. the bFGF effect could be potentiated by the co-injection of another growth factor such as the TGFβ1 known to enhance the mitogenic effect of bFGF on nerve cells. Newborn Wistar rats sustained an unilateral Fi transection followed or not by an i.c.v. injection of saline buffer containing either a high dose (500 ng/2 μl) of bFGF or TGFβ1 (100 ng/2 μl) or both. The animals were raised until day 26 and were sacrified. The ChAT and the acetylcholine esterase (AChE) activities were measured in the hippocampus and septum. The bFGF alone was efficient to activate the ChAT activity in the septum of the intact newborn rat and to attenuate the ChAT activity decrease in the hippocampus following the Fi transection. The TGFβ1 injected alone or with the bFGF in the intact newborn rat did not activate the cholinergic septo-hippocampal system and when co-injected with the bFGF, the TGFβ1 did not potentiate the bFGF effect in the attenuation of the ChAT activity decrease in the hippocampus of the Fi-transected rat.

17.32 MELANOCORTINS STIMULATE THE NEURITE REGROWTH IN PARTIALLY TRANSECTED SPINAL CORD IN THE ADULT RAT.

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Melanocortins, especially α-Melanocyte Stimulating Hormone (α-MSH), have a neurotrophic effect on Peripheral and Central Nervous System (PNS and CNS) neurons. In vitro, an optimal stimulation of spinal neurite outgrowth is observed at 10^{-8} M α-MSH. In this in vivo study we investigate whether 10^{-8} M α-MSH is able to stimulate regrowth of lesioned axons in adult rat spinal cord. Therefore, we transect the dorsal funiculus completely at lower thoracic levels (T8 to T10). A solid collagen type 1 gel is used as a vehicle to apply α-MSH locally in the lesion area. As a control we use the same collagen graft but without α-MSH. The complete lesion area is studied histologically after intracardial perfusion, 4 weeks postsurgery. Neurite regrowth is studied light-microscopically using antibodies against: 1) the growth associated protein B50/GAP-43, 2) various neural cell adhesion molecule (NCAM) forms and 3) neurofilament. In our in vivo model a major increase of neurite regrowth is observed in the α-MSH treated rats. Ingrowing fibers into the α-MSH containing collagen are both NF- and B50/GAP-43-immunoreactive. The embryonic form of NCAM is re-expressed only on some ingrowing fibers. Our observation demonstrate that α-MSH stimulates the regrowth of injured axons in the adult rat spinal cord.

17.33 INDUCTION OF *c-fos, jun B* AND *egr-1* EXPRESSION BY HALOPERIDOL IN PC12 CELLS: INVOLVEMENT OF CALCIUM.

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Acute injection of haloperidol, a dopamine D2 receptor antagonist used clinically as an antipsychotic drug, increases the expression of the immediate early gene *c-fos* and *jun B*, but not that of *c-jun* nor *junD*, in rodent striatal neurons. We found that this gene induction could be reproduced in the neuronal PC12 pheochromocytoma cell line. An other immediate early gene, *TIS8/egr-1*, was induced in the same cells by haloperidol. Using the cell culture system, we tested whether the enhanced gene transcription was translated into functional proteins and the possible involvement of calcium in this mechanism. Electrophoretic mobility-shift assays show that haloperidol-evoked gene induction was accompanied by a transient and dose-dependent increase in AP1 and EGR-1 binding activities in these cells. Gene expression is tentatively explained by the rapid and transient increase in cytosolic free Ca^{2+} concentration observed upon haloperidol addition. The cytosolic calcium rise and AP1 binding activation elicited by haloperidol were dependent on extracellular Ca^{2+}, suggesting that haloperidol exerted its effects by promoting Ca^{2+} entry into PC12 cells. The haloperidol-induced increase in AP1 binding activity and intracellular Ca^{2+} was not reproduced by two other dopamine D2 receptor antagonists, sulpiride and (+)-butaclamol, or by ligands of σ opiate or α_1 adrenergic receptors. The mechanism whereby gene induction is achieved by a D2 receptor antagonist is discussed.

17.34 **A MATHEMATICAL MODEL FOR THE ESTIMATION OF DONOR AGE IN HUMAN EMBRYONIC AND FETAL TISSUE IN NEURO-TRANSPLANTATION.**

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Determination of donor age in material of induced suction abortions remains a crucial factor in neural transplantation as there is a critical time window in which human fetal neurons can be used for transplantation. In order to provide a mathematical tool for the determination of fetal age between 4 and 10 weeks post conception (p.c.) we have correlated various routinely measured morphometric parameters of human foetuses in induced suction abortions with the anamnestic and ultrasonographically estimated embryonic and fetal age in 81 cases. The experiment was performed with the permission of the ethics committee at the Medical Faculty of the University of Berne. The correlated factors were: the crown-rump length (CRL), crown-heel length (CHL), foot length (FL), and proximal and distal leg length (PLL), (DLL), and proximal and distal arm lengths (PAL), (DAL) respectively. By a multivariate regression model using combinations of several morphometric parameters an accurate determination of fetal age within the range of 4 to 10 weeks p.c. could be achieved. The following formula served to calculate the fetal age. LN = logarithm; measurements in [mm].

$$Age(days[p.c.]) = \frac{\frac{LN(PAL)+0.566}{0.045} + \frac{LN(DAL)+0.668}{0.048} + \frac{LN(PLL)+0.997}{0.049} + \frac{LN(DLL)+0.630}{0.043} + \frac{LN(FL)+0.489}{0.036}}{5}$$

In a prospective study the fetal and embryonic age was calculated as described above in 40 cases . The calculated age highly correlated with the anamnestic age ($R = 0.749$, $p < 0.001$). The present data indicate that this mathematical model allows a reliable determination of embryonic and fetal age which is important in regard to investigating effects of donor age on cell survival and differentiation.

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17.35 THE CORTICAL IDENTITY OF THE CLAUSTRUM IN RODENTS.

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The question of whether the claustrum is a cortical or a subcortical structure has important evolutionary and developmental implications. In rodents, the claustrum is divided into a dorsal part, the claustrum proper and a ventral part, the endopiriform nucleus. Both these nuclei share in common with the subplate and its adult counterpart, the isocortical layer VIb (or VII) a number of characteristics such as molecular markers, neuronal birthdates and hodology. During prenatal development, in coronal sections the claustrum is easily identifiable as a drop-like cellular aggregate which emerges from the dorsally located subplate. Our previous studies have identified some markers shared by the claustrum and the subplate: IgG-like immunoreactivity (Fairén *et al.*, 1992), adhesion molecules, such as G4 or Bravo, and markers of early neuronal differentiation such as MAP2. Additional shared markers have been reported in the literature. Moreover, our results imply (at variance with previous reports) that the times of neurogenesis of the claustrum/endopiriform nucleus and the subplate overlap considerably. In the adult rodent, layer VII is the source of an important system of cortico-cortical fibres (Reep and Goodwin, 1988) and our recent studies revealed that this system is similar to that emanating from the claustrum. Altogether, these data suggest that the claustrum (including the endopiriform nucleus) is a specialized compartment of the subplate and that such a compartmentalization takes place at the onset of the formation of the cortical plate at the ventrolateral region of the cortical primordium.

17.36 CELL PROLIFERATION AND PSA-NCAM EXPRESSION IN THE ACCESSORY OLFACTORY BULB OF THE ADULT RAT. L. Bonfanti[1]*, P. Peretto[1], A. Merighi[2], D.T. Theodosis[2] and A. Fasolo[3]. Depts. of Veterinary Morphophysiology[1] and Animal Biology[3], Turin, Italy; INSERM U. 378[2], Bordeaux, France.

The accessory olfactory bulb (AOB) is a layered structure distinct from the main olfactory bulb (MOB) and innervated by fibers of the vomeronasal organ (Cajal, *Rev. Trim. Micr., t. VI*, 1902). This latter in rodents plays an important role in sexual behaviour. Indeed, female mice form an olfactory memory of male pheromones at mating, and the synaptic changes underlying this memory occur in the AOB (Brennan et al., *Science 250 : 1223*, 1990). In the MOB an important reshaping including a continuous renewal of olfactory interneurons (granule and periglomerular cells) has been recently related to the migration of cells from the subependyma of the lateral ventricle (Lois & Alvarez-Buylla, *Science 264:1145*, 1994) that express the highly sialylated, weakly adhesive isoform of the neural cell adhesion molecule NCAM (PSA-NCAM, Bonfanti & Theodosis, *Neurosci. 62:291*, 1994; Rousselot et al., *J. Comp. Neurol. 351:51*, 1995). In this study, cell proliferation in the AOB was analysed immunocytochemically after intraperitoneal injection of 5-bromo-2'-deoxyuridine (BrdU). In particular, at 15 days post-injection, immunoreactive nuclei were detected in the AOB. Moreover, by using a monoclonal antibody that specifically recognizes polysialic acid (PSA) on NCAM, cells immunoreactive for PSA-NCAM were detected within all of the layers of the AOB: i) bipolar cells with the typical morphology of undifferentiated, migrating neuroblasts, radially-oriented in the granular layer and in the lateral olfactory tract; ii) neuronal-like cells with a triangular cell body (6x8 µm) and longitudinally-oriented dendrites in the plexiform layer; iii) small neuronal-like cells organised around the glomeruli. As observed in the MOB, most of the BrdU- and PSA-NCAM-positive cells were found in the granular layer. The plasticity of the system was further investigated through DNA fragmentation techniques. These results suggest that a renewal of interneuronal populations might occur in the AOB of adult rats, and that PSA-NCAM-positive elements in this region correspond, at least in part, to cells from the migratory stream.

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17.37 **"MINIMAL ABANDONED" NEUROMUSCULAR JUNCTIONS.**

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The existence of retraction at some motor nerve terminal branches is commonly known as a sign of synaptic plasticity. As a consequence of this phenomenon, different kinds of abandon can be identified by transmission electron microscopy depending on the number of postsynaptic folds uncovered by the axon.

In this work, we use the generic term "minimal abandon" to describe neuromuscular junctions (NMJ) showing 1 - 2 uncovered fold/s by the presynaptic membrane. With the aim to describe the particular ultrastructural morphology of these abandoned folds when such a small retraction occurs and in order to look for the existence of differences when compared with both, the subaxonal folds and the completely abandoned folds, we analyzed several pre- and postsynaptic ultrastructural morphometric parameters on 172 NMJ of *Extensor digitorum longus* (EDL) muscles in ten normal adult (3 months-old) Sprague-Dawley rats by using conventional transmission electron microscopy procedure. We previously observed the incidence of "minimal abandoned" synapses in the normal adult EDL muscle (27%).

Results confirm the existence of specific ultrastructural remodelling changes at the abandoned postsynaptic folds of "minimal abandoned" synapses when compared with the subaxonal folds (those covered by the axon). Moreover, these changes show several morphological characteristics of the completely abandoned postsynaptic folds described elsewhere.

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17.38 TRUNCATED AND ELONGATED INSULIN-LIKE GROWTH FACTOR I STIMULATE PROLIFERATION IN THE RAT SCIATIC NERVE.

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We have found that insulin-like growth factors stimulate regeneration of sensory nerve fibers and proliferation of Schwann cells in the rat sciatic nerve *in vivo*. In contrast, IGF-II but not IGF-I enhanced [^{3}H]thymidine incorporation in cultured nerve segments. These findings imply that IGF-I and IGF-II could act via different mechanisms. To further investigate the effects of the IGF's on proliferation we used truncated IGF-I (des 1-3) and elongated IGF-I (R1) which exhibit reduced affinity for IGF-binding proteins. Desheathed sciatic nerve segments from rat were cultured for 48 hours in serum free RPMI 1640 medium, containing 5 ng/ml or 10ng/ml of either native, truncated or elongated IGF-I. [^{3}H]thymidine incorporation was then measured. [^{3}H]thymidin incorporation roughly doubled in the presence of either 10 µg/ml truncated or elongated IGF-I (10 µg/ml) compared to the control while native IGF-I had no significant effect. We suggest that the different effects of the modified IGF's as compared to native IGF-I could be accounted for by the presence of IGF-I binding protein in the nerve segments.

17.39 Calcineurin and calbindin are not involved in Ca^{2+} -induced inactivation of NMDA channels.

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The transient Ca^{2+} - induced inactivation of NMDA channels was observed in hippocampal neurons and HEK-293 cells transfected recombinant NMDA receptors. This phenomenon may be intermediated by Ca^{2+} - binding cytoplasmic proteins. Granular cells from cerebellum lack the two Ca^{2+} - binding proteins, calcineurin and calbindin (Heizmann & Hunziker, TIBS 16, 98-103, 1991). To evaluate whether these proteins are involved in Ca^{2+} - induced inactivation of NMDA channels we studied this process in granular cells from cerebellum using whole-cell patch-clamp techniques.

The Ca^{2+} - dependent inactivation was estimated by analysis of the amplitude of the test NMDA currents (induced by brief 50 ms pulse of NMDA) after long 3-10 s conditioning application of NMDA. The degree of inactivation increased (up to 50%) with prolongation of conditioning NMDA applications or increased extracellular Ca^{2+} concentration $[Ca^{2+}]_o$, it was not observed in 0 mM $[Ca^{2+}]_o$. In presence of ATP - regenerative intracellular solution the NMDA currents (50-400 pA) were stable during 20-30 min of recording (n=18 out of 40), while others showed irreversible rundown. In some of these cells (n=8) Ca^{2+} -dependent inactivation disappeared during 10-15 min of recording without any change of NMDA current amplitude (no rundown).

In cultured hippocampal neurons the calcinurin inhibitor FK-506 (10 µM) prevented rundown of NMDA currents, but did not modulate transient Ca^{2+} - induced inactivation (n=8 out of 8).

Our results indicate that calcineurin and calbindin are not involved in Ca^{2+} -induced inactivation of the NMDA channels.

17.40 REGULATION OF trkB mRNA EXPRESSION IN EMBRYONIC MOUSE TRIGEMINAL NEURONS.

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Mouse trigeminal neurons survive independently of neurotrophins when their axons are growing to their targets and are transiently supported by BDNF during the early stages of target field innervation before becoming NGF dependent. We have used Northern blotting and RT-PCR to study the expression of transcripts coding for the BDNF receptor, trkB, at these different stages of development. During the stage of neurotrophin independence, trkB expression was at a low level. When the neurons responded to BDNF they expressed high levels of a transcript coding for a full-length receptor with a tyrosine kinase domain. Although the level of this transcript fell as the neurons lost responsiveness to BDNF, there were concomitant increases in the expression of transcripts that code for trkB variants that lack a tyrosine kinase domain. The expression of catalytic TrkB receptor was upregulated by both BDNF and NGF early in development and by BDNF but not NGF later on. Our results suggest that coexpressed catalytic and non-catalytic TrkB receptors modulate BDNF responsiveness in developing sensory neurons and that receptor expression may be modulated in turn by neurotrophins.

17.41 INFLUENCE OF GROWTH FACTORS ON THE SPATIAL MEMORY AFTER FIMBRIA-FORNIX LESION IN RATS.

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Neurotrophic factors may play an important role in the adult nervous system by sustaining normal cell function and their administration can prevent neuronal death after the lesion. In an attempt to compare the effects of different neurotrophic factors on impaired memory function, young adult naive rats were trained to find hidden platform in the Morris water maze (3 consecutive days, 8 trials/day). The fimbria-fornix and the cortical area above it were unilaterally removed by aspiration and NGF (11µg/ml and 0.5µg/ml; groups NGF and ngf), bFGF (0.2µg/ml, group FGF) were applied via intra-cerebroventricular infusion (flow rate, 0.5µl/h) and commercially produced nootropic drug Cerebrolysin (EBEWE Arzneimittel, 2.5 ml/kg/day, group CER) via intraperitoneal injection. One group was formed by rats treated with NGF (11µg/ml) and Cerebrolysin (group NGFCer). The treatments were applied during 14 days. Non lesioned and lesioned only rats served as controls (groups INT and LES). After the 14-day-treatment rats were tested for their ability to retrieve the spatial memory task (1 day, 8 trials). On the next day, the rats were trained to find the platform placed in a different part of the water pool (3 days, 8 trials/day). The escape latency and the length of trajectory were recorded. Groups LES, NGF, ngf and FGF were similarly impaired in their ability to retrieve the old position of the platform. Navigation to the changed position of platform was significantly better in the NGF than in LES group; no other groups was improved. Group CER did not significantly differ from groups INT or LES. Group NGFCer was comparable to group INT in retrieval or transfer tests. It is concluded that NGF and Cerebrolysin can support the function of neurons affected by the fimbria-fornix lesion. No short-term influence of bFGF were found. Long-term effect of the above drug are currently evaluated.

17.42 OUTGROWTH AND ELONGATION OF SENSORY FIBERS IN Ca-FREE MEDIUM. FUKUDA. J., KEINO-MASU, K. AND *TORIMITSU,K., Laboratory of Molecular and Cellular Physiology, Department of Physiology, National Defense Medical School, Tokorozawa, and *Material Science Research Laboratory, NTT Basic Research Laboratories, Atsugi, JAPAN.

Growth of nerve fibers has long been understood as mediated by Ca-influx in their growing ends. Here we present an opposite understanding that Ca^{2+} in the somas but not in fibers themselves is essential for growth of new fibers, by representing data that blockage of Ca-influx in the somas inhibited growth of their fibers, while that in the fibers did not. We blocked Ca-influx in the somas of fibers by culturing them in media containing zero-Ca^{2+} using newly designed 2-chamber dish; the dish allowed culture of the somas and fibers of newborn rat DRGs in growth media of different compositions. Blockage of Ca-influx in fibers during culture in Ca-free medium (the somas were in normal Ca^{2+} medium) caused only a small reduction in growth of new fibers by 30%. Intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), which was 150 nM in normal fibers, was reduced to 40 nM in the fibers growing in the Ca-free medium, due to the absence of Ca-influx and to the loss of intra-fibrous Ca^{2+}. When the somas were cultured in either Ca-free or verapamilcontaining media, new fibers failed to grow from the fibers that were bathed in normal Ca^{2+} medium. Fibers already grown in normal medium stopped to grow further when the medium bathing the somas was switched to Ca-free medium. $[Ca^{2+}]_i$ of these fibers remained in normal level even 24 h after the switch of the media. We concluded therefore that Ca-influx in the somas is essential while that in the fibers themselves plays only a small contribution for the growth of new fibers.

17.43 DIFFERENT SEGMENTS OF THE MOTOR NERVE TERMINAL BEHAVE IN A DIFFERENT WAY IN RELATION TO THEIR CAPACITY TO GENERATE SPROUTS. M.A. Lanuza, M. Santafé, M.R. Fenoll-Brunet*, N. Garcia, J. Rigau and J. Tomàs. Unitat d'Histologia i Neurobiologia (uhn). Facultat de Medicina i Ciències de la Salut. Universitat Rovira i Virgili. 43201-Reus. SPAIN.

The neuromuscular junctions are plastic structures that undergo a continous remodelling along the life span. Sprouting and retraction phenomena of the motor nerve terminals are identified as signs of synaptic remodelling. These morphological plastic changes can occur under normal conditions and, to a greater extent, in experimental or pathological situations.

In the present work, the *Levator auris longus* (LAL) muscle of young adult Swiss mice (42 days-old) was used to study, in different situations, the incidence of motor nerve sprouting and to estimate the ability to generate sprouts by the different segments of the arborization. LAL muscle is a convenient neuromuscular model for the study of effects of drugs and toxins applied *in vivo* in young or adult mice. α-Bungarotoxin (α-BTX) (1μg/ml) subcutaneous injections over the external surface of LAL muscles were performed every 48 hours and animals were sacrified 48 hours after the last toxin administration. Animals were killed at 19 days after the first injection. Nerve terminals were observed in whole mount preparations by using different techniques: Gros-Bielschowsky silver impregnation method, methylene blue vital staining and conventional electron microscopy. Several parameters of the motor nerve terminal branching pattern were morphometrically studied.

Main results demonstrate that the segments placed near to the myelin sheath possess higher ability (per micrometer of length) to generate terminal sprouts than do those segments distally placed both, in the control animals and in muscles treated with α-BTX. Supported by FISSS 93/0362.

17.44 TRANSPLANTATION STUDIES INSIDE ONE SINGLE NEOCORTICAL REGION INDICATE THAT THE DISTRIBUTION OF EFFERENTS FROM NEOCORTICAL NEURONS DOES NOT ONLY DEPEND ON THE PLACE WHERE THE CELLS DEVELOP. Cyril Garnier*, Patricia Arnault, Afsaneh Ebrahimi-Gaillard, Jérôme Létang and Michel Roger. CNRS: URA 1869, Département des Neurosciences, Université de Poitiers, 86022 Poitiers, France.

According to O'Leary's hypothesis, the distribution of efferents developed by neocortical neurons depends on where the cells develop in the neocortex, not where they were generated. Heterotopic transplantation paradigms have recently been used in several experiments to test the capacity of various isocortical areas to differentiate connectional characteristics belonging to other isocortical areas. This study aims at determining whether the principle of multipotentiality is still valid within one single isocortical region. Mediolateral bands of embryonic (E16) frontal neocortex were grafted into the frontal cortex of neonate hosts according to either correct or inverted mediolateral orientation. Five to six months after grafting, a retrograde tracer was injected into the dorsomedial or ventrolateral neostriatum of the host. The mediolateral distribution of the cell labeling within the transplant was then compared to that of an equivalent frontal cortical area (ECA) in control cases. In transplants with correct mediolateral orientation, the percentages of cells labeled in the medial or lateral division of the grafts were not significantly different from those found medially or laterally in the ECA in control cases. Following inversion of the mediolateral orientation of the grafts, the percentages of cells labeled in the medial or lateral division of the grafts were nearly equal whatever the site of tracer deposit was within the host neostriatum. The results indicate that: i) strips of embryonic frontal neocortex transplanted according to a correct mediolateral orientation are able to develop a projection towards the host striatum whose mediolateral topographical distribution is similar to that arising from the frontal neocortex of control animals; ii) even within one single neocortical region the principle of areal interchangeability is not entirely validated. It is concluded that the development of neocortical efferents is not only guided by extrinsic factors.

18. Poster Session: Motor systems and sensory motor integration I

18.01 THE SUBCOLLICULAR PRETECTAL NUCLEUS: A NOVEL PRIMARY VISUAL NUCLEUS IN THE PRETECTUM OF THE RAT.
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The anatomy of the subcortical primary visual nuclei is well established. Primary diencephalic visual nuclei in mammals include the superior colliculus, the pretectal nuclei (nucleus of the optic tract and the olivary, posterior, anterior and medial pretectal nucleus) and the nuclei of the accessory optic system (dorsal, lateral, medial and interstitial terminal nucleus). In addition to this scheme we report in the rat a small nucleus, located ventrolateral to the superior colliculus, dorsolateral to the nucleus of the optic tract, dorsomedial to the dorsal terminal nucleus.

Neuroanatomical staining was performed on coronal and horizontal slices of the midbrain. Cells were stained with cresylviolet and toluidine blue and fibers were stained with the Klüver-Barrera method and using Sudan Black B. Anterograde tracing from the eye and retrograde tracing from the medial terminal nucleus and the inferior olive was performed using CTB-HRP.

The additional nucleus is located at the fringe of the brachial fibers to the superior colliculus. It is separated from the nucleus of the optic tract by the brachial fibers. The dorsal terminal nucleus is located more ventrolaterally. A retinal input from the contralateral and ipsilateral eye is demonstrated. The nucleus does not project to the medial terminal nucleus or the inferior olive, whereas the nucleus of the optic tract and the dorsal terminal nucleus do.

In conclusion, we have demonstrated an additional primary visual nucleus in the pretectal area: the subcollicular pretectal nucleus. Classification and putative functions are discussed.

18.02 INNERVATION OF DEEP EXTENSOR ABDOMINAL MUSCLE (DEAM) IN CRAYFISH *ASTACUS ASTACUS*.
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The DEAM in crayfish consists of three distinct muscle bundles L1 (L=lateral), L2, and M (M=medial) responsible for the extension of the tail. The muscle is segmented and fixed to the carapace at each segment. Unlike in some crayfish species (Parnas and Atwood 1966, Comp Biochem Physiol 18:701-723) the nerve innervating the DEAM at each segment in *Astacus astacus* contains five axons, four excitors and a weak 'common inhibitor'. Lucifer yellow was injected iontophoretically or by pressure to identify the five axons and their branching over the muscle. Inhibitory and exitatory axons were distinguished by eliciting contractions stimulating the single axons by means of a suction electrode. The excitatory axons differ in their innervation pattern. One of them branches over all three muscle bundles and the M-bundle of the next distal segment. The L1- and L2-bundles are also innervated by own axons. The one branching on L1 shows additionally a branch to the L1-bundle of the next distal segment. The fourth excitatory axon reaches the M-bundle of the next distal segment, sometimes also innervating the L1-bundle of the segment where the axon originates. There is only one inhibitory axon, and its innervation pattern is similar to the first mentioned excitatory one, innervating all three muscle bundles and the M-bundle of the distal segment. Most of the branches from all axons terminate in the clefts between the muscle bundles and only a minor part of the branches end on the surface of the muscle fibers. With this innervation pattern the animal is able to contract each of the three muscle bundles independently or all together. The transsegmental innervation to the M-bundle of the next distal segment suggests that it is probably necessary to contract muscles at least in two adjacent segments at the same time in order to extend the tail.

18.03 **EFFERENTS OF THE RETRORUBRAL NUCLEUS TO THE SUBSTANTIA NIGRA AND VENTRAL TEGMENTAL AREA IN THE CAT AS SHOWN BY BDA AND PHA-L TRANSPORT**

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Investigations were undertaken to determine whether the retrorubral nucleus projects to the other dopaminergic nuclei in the ventral midbrain of the cat. Injections of *Phaseolus vulgaris* leucoagglutinin (n=2) or biotinylated dextran-amine (n=9) were placed into the retrorubral nucleus (RRN) and after routine histology, the resulting sections were stained with the respective antibodies. In addition, tyrosine hydroxylase immunocytochemistry was used as a marker for the injection site and labeled fibers. Both tracers reveal the same topography of labeled fibers. Fibers with varicosities are found in the ipsilateral substantia pars lateralis, the ipsi- and contralateral substantia nigra pars compacta, ventral tegmental area and RRN. Several axons with varicosities are found to be wrapped around dendrites and perikarya of tyrosine hydroxylase positive neurons.
The data throw new light on the role of the A8 cell-group in the coordination of A9 and A10 systems as well as in the progressive pathology of Parkinson's disease.

18.04 **THE SPATIAL ARRANGEMENT OF THE GRANULE CELLS IN THE GRANULAR LAYER OF THE RAT CEREBELLAR CORTEX.**

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The granular layer of the cerebellum is densely packed with small granule cells whose axons ascend through the granular and Purkinje cell layers and branch in a T manner inside the molecular layer to form the parallel fibers. It is believed that this lay out reflects the developmental migratory path of the granule cells. These neurons originate in the immature external granular layer from which they migrate vertically downwards along the Bergmann glia processes to the internal granular layer. The earliest migrated granule cells are then stacked more and more deeply by later waves of migrating neurons. The initial location is approximately indicated, for each individual cell, by the site of the T branching of its axon. We have tested the logical implications of this theory by calculating, on 50 Golgi impregnated granule cells of the rat cerebellar cortex, the spatial relationship between the location of the T branching of the axon in the molecular layer and the location of the parent granule cell soma in the granular layer. It appears that only about one third of the granule cells have a strong correlation between the relative height of the T and the soma in their respective layers. For all the other neurons their seems to be no rule and one can find granule cells located very deep in the granular layer with an axon branching very superficially in the molecular layer or granule cells located very high in the granular layer with a very short axon branching just above the apical pole of the Purkinje cell layer. Another observation is that only half of the granule cell somatas are located directely beneath the T branching. The other neurons are located quite laterally from what should have been their "theoretical" location, often at an important distance. It therefore appears that our present knowledge about the migration of immature granule cells can not entirely explain the observations presented here.

18.05 IN A RAT MODEL OF PARKINSONISM, LESIONING THE SUBTHALAMIC NUCLEUS DOES NOT SIMPLY ALLEVIATE THE BEHAVIORAL EFFECTS OF STRIATAL DOPAMINE DEPLETION

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There is substantial evidence that lesion or hemorrage of the subthalamic nucleus (STN) alleviate the motor deficits in patients suffering from Parkinson's disease or in animal model of this pathology such as MPTP-treated monkeys. However, only a few studies have investigated the involvement of the STN in the control of movement required in complex sensorimotor tasks. The present study was thus performed in rats trained in a reaction time (RT) task known to be extremely sensitive to variations of dopamine (DA) transmission in the striatum. Animals were trained to release a lever after the onset of a visual stimulus within a time limit to obtain food reward. Discrete DA depletion produced by infusing 6-OHDA bilaterally into the dorsal striatum produced motor initiation deficits revealed by an increased number of delayed responses (lever release after the time limit) and lenghtening RTs. In contrast, bilateral excitotoxic lesion of the STN with ibotenic acid induced severe behavioral deficits opposite to those induced by the dopaminergic lesion, as shown by an increase of 50% in the number of premature responses (lever release before the onset of the visual stimulus) and a decrease of RTs. Lesioning the STN 14 days after the striatal dopaminergic lesion was found to actually reverse the deficits induced by the dopaminergic lesion, but the dramatic increase of premature responses induced by the STN lesion remained unchanged. The animals bearing a double lesion were thus surprisingly still impaired throughout the experiment. The bilateral lesion of the STN was found to only partly alleviate the motor deficits in this model of parkinsonism, but essentially produced over time long lasting deficits that might be related to dyskinesia or cognitive impairment. However, these data strongly support the concept of the predominant influence of the STN on the basal ganglia output structures.

18.06 RELATIONSHIPS OF HIPPOCAMPAL AND AMYGDALOID INPUTS TO CELL GROUPS IN THE NUCLEUS ACCUMBENS WHICH HAVE DIFFERENT MESENCEPHALIC OUTPUTS. AN ANATOMICAL TRACING STUDY IN THE RAT.

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The nucleus accumbens (Acb) is characterised by strong inputs from limbic related structures. The aim of the present study was to reveal the anatomical relationships of limbic afferents with specific populations of accumbal output neurons. Anterograde tracer injections (PHA-L, BDA) were made in the ventral subiculum of the hippocampal formation (VS) and in two nuclei of the basal amygdaloid complex: the parvicellular basal nucleus (Bpc) and the accessory basal nucleus (AB). Retrograde tracer injections (fluorogold) were placed in the peribrachial region (PBR) of the mesencephalon (this area is included in the so-called locomotor region) or in the medial ventral tegmental area (VTAm). Fibers from the amygdala and the VS were found in a largely non-overlapping pattern in the medial Acb. While amygdaloid afferents in the Acb have a limited distribution, mostly in association with cell clusters, the subicular afferents are more widely distributed in the medial Acb with a preference for cell poor areas. Accumbal cells that project to the PBR have a rather strict anatomical relationship with amygdaloid fibers. Retrogradely labelled cells in the dorsolateral border region between shell and core were found among Bpc efferents and labelled cells in the ventromedial border region of the shell were located among AB fibers. In these areas the amount of VS fibers was sparse. In central parts of the shell, a strong coincidence was found for VTAm projecting cells and VS fibers while amygdaloid fibers avoid these cells. These results suggest that neurons in the Acb shell that project to either VTAm or PBR receive different sets of limbic related inputs.

18.07 THE SPECTRUM OF COGNITIVE DEFICITS IN THALAMIC LESIONS.

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This case study aims to extend the knowledge about the spectrum, pathomechanism and course of cognitive deficits in unilateral thalamic lesions. We report neurobehavioural, MRI and SPECT imaging findings of patients JD (with a left) and CR (with a right) hypertensive thalamic, MRI-documented bleeding. JD displayed a severe thalamic aphasia, dyspraxia, and aculculia, whereas CR's deficits included a prominent visuospatial and constructional deficit, neglect, and hypersomnolence. Further behavioural abnormalities included abulia, anosognosia, material specific amnesia, and signs of frontal impairment (set shifting problems, perseverations, confabulations, loss of divergent thinking) in both patients.
SPECT scan of both patients showed decreased perfusion rates in the basal ganglia, and in widespread ipsilateral areas of the cortex and underlying white matter including the parietal and frontal lobe. EEG demonstrated ipsilateral slowing over the whole hemisphere. These findings confirm previous studies indicating that in patients with thalamic lesions a) the spectrum of neuropsychological deficits may be extended, but hemisphere-specific, and b) depression of synaptic activity in the cortex can explain the loss of multiple cognitive functions rather than a local pathomechanism in the thalamus itself. Follow up examinations will elucidate the course of neuropsychological, electrophysiological and metabolic deficits in both patients.

18.08 VESTIBULAR-DEPENDENT HEAD DIRECTION CELL IN THE Oc2MM CORTEX OF THE RAT.

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Head direction cells (HDC) are neurons selectively active as an animal orients its head in a certain direction as it occupies any part of the environment. Such cells have been recorded in striatum, dorsal presubiculum, retrosplenial cortex, anterior and dorsal thalamic nuclei and can be controlled by visual cues. We report here the properties of a HDC of the Oc2MM cortex of a Long-Evans rat. With baseline discharge at 1-2 imp/s, the cell discharged at up to 34 imp/s when the rat was oriented to only 2 of the 8 compass points. The rat was then placed 70 cm higher but in the same position in the room. The preferred direction shifted by 90 deg. Lowering the rat by 130 cm into an arena (a black box with 60 cm sides) returned the preferred direction to the original value. Curtains were closed and the only visual cue was a lit white card in an arena corner. The arena was then rotated as the rat searched for water rewards. If the acceleration was close to or below the vestibular threshold, the preferred angle rotated with the arena and the visual cue. But accelerations greater than this led to shifts in the preferred direction to maintain the same orientation relative to the true north, with no relation to the cue card or arena. Other experiments indicated that this cell could also be influenced by visual cues. Support: French MRE, CEE/ESPRIT/BRA 3149 MUCOM, Human Frontiers.

18.09 SYNAPTIC TERMINAL COVERAGE OF RAT ABDUCENS NUCLEUS MOTONEURONS

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An ultrastructural analysis was carried out to study the somatic synaptic terminal coverage of rat abducens motoneurons. The motoneurons were labelled by retrograde transport of free HRP injected in the lateral rectus muscle. The linear frequence of the synapses (number of synapses per 100 μm of somatic membrane) was about 13. They showed short active zone (approx. 0,5 μm). Two main types of synapses were recognized in about equal proportion. The first type of synapses showed round vesicles and asymmetrical synaptic density. A limited number of these synapses showed or prominent postsynaptic subsurface cisternae or multiple active zones. The second type of terminals, slightly prevailing, showed flattened or pleomorphic vesicles and symmetrical synaptic junctions. In literature the morphological features of the synapses (arrangement of the synaptic density and shape of the vesicles) have been related to the functional activity. An excitatory role has been attributed to the asymmetrical junctions and an inhibitory role to the symmetrical synapses. As regards the vesicles shape, the round vesicles have been related to excitatory activity and the elongated vesicles to inhibitory activity. On the basis of the above considerations we could suggest that the soma of the rat abducens motoneurons receives inhibitory and excitatory projections in about equal proportions.

18.10 CAT PONTOCEREBELLAR SYSTEM: CONVERGENCE AND DIVERGENCE IN THE PATHWAY TO THE PARAFLOCCULUS

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We have studied the numerical capacities and collateral branching of neurons in the pontine nuclei projecting to individual paraflocculus folia. The aim was to obtain an indication of the amount of convergence and divergence in the projection to this part of the cerebellum. Small amounts of three or four fluorescent tracers (Rhodamine-B-isothiocyanate, Fluoro-Gold, Fast Blue, Diamidino Yellow) were injected in individual folia. (The paraflocculus in the cat is altogether made up of 20 or more folia.) Retrogradely labelled cells were recorded in a sample of sections. The estimated total number of labelled neurons on one side of the pontine grey (contralateral to the injection sites) ranged from 5.000 to 46.000. The median value was 18.000 (14 cell populations in 6 animals). In the same animals, using stereological principles, the total number of neurons in the pontine grey was estimated to a mean value of 490.000 (n = 6, range: 420.000 - 640.000). Thus, on the average, labelled neurons contacting an individual folium in the paraflocculus make up approximately 4 % of the total number of neurons in the pontine grey. This figure reflects a high amount of convergence, in the sense that large numbers of cells, distributed across large parts of the pontine nuclei, project to the same very small part of the total available target region. Few double or tripple labelled cells were found, regardless of combination of folia injected. We present a theoretical model to explain that, despite low fractions of multiple labelling, single neurons may contact several adjacent and/or separated folia of the paraflocculus. The pontoparaflocculus pathway is therefore most likely made up of a complicated network of converging and diverging connections. Our findings elucidate quantitative aspects of the network design.

18.11 OVERLAP AND NON-OVERLAP OF PARIETAL REGIONS PROJECTING TO THE PREMOTOR AREAS AND PREFRONTAL CORTEX IN MACAQUES.

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Posterior parietal cortex projects to prefrontal cortex and premotor areas. Whether the various premotor and prefrontal areas share the same information or whether distinct parietal zones project to distinct frontal areas in not known. To investigate this question, we injected multiple retrograde tracers into the dorsolateral prefrontal cortex (DLPF), the dorsal and ventral premotor areas (PMd and PMv), and the supplementary motor area (SMA) in the same monkeys. Retrogradely labeled cells were plotted on coronal sections of the brain, and reported on two-dimentional unfolded maps of the cortex. The maps were then superimposed to examine the overlap and non-overlap of the parietal labeling.

Following injections into PMv and the posterior portion of PMd (PMdp), labeled cells overlap in areas 3, 1, 2, 5, 7b, SII. After injections in PMdp and SMA, labeled cells overlap within areas 1, 2, 5, MDP, MIP, 7b, and SII. Injections into PMv and SMA resulted in partially overlaping labeling in areas 2, 5, anterior intraparietal sulcus (AIP), 7b and SII. By contrast, there was no overlap of labeled cells after injections into the anterior region of PMd (PMda) and SMA, nor after PMda and PMv injections. There are three important points that need to be emphasized. (1) the parietal overlap of cells projecting to PMv, SMA, and PMdp, but not to PMda, was restricted to somatosensory or polysensory areas (2, 7b and SII). (2) The projections terminating in PMda and PMdp (but not in PMv, nor SMA) arise from visual parietal areas including VIP, LIP, 7a, 7m, PP and PO. (3) The latter areas also project to the DLPF and some of them (7a and 7m) contain regions of overlaping labeling following injections in PMda and DLPF. In addition, PMda receives projections from the DLPF. Thus, visuospatial information might reach PMda either directly from parietal areas, or via the prefrontal cortex.

18.12 HOW TARGETS INFLUENCE THE WAY WE APPROACH THEM

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When subjects are instructed to move their finger slowly towards a specified position, the finger follows a path that deviates systematically from a straight line (de Graaf, Sittig and Denier van der Gon, Exp.Brain Res. 84, 1991,434). In the present study we examine whether such deviations depend on what is to be found at that position.

Subjects were asked to move their finger along a straight path from a starting position to each of 5 targets (wooden blocks). There were two experiments. In both experiments, the targets were on a circle around the starting position. The only difference between the experiments was whether the blocks all had the same orientation, or were oriented radially around the starting point. This difference influenced the deviations: the finger's path depended on the target's orientation.

Being able to place one's fingers accurately at desired positions on an object's surface has evident advantages for handling the object. It makes sense, therefore, to approach each position from a direction from which one is least sensitive to the limitations of spatial vision. This will often be the direction perpendicular to the surface. The results of our two experiments are consistent with this suggestion.

18.14 POSTURAL RESPONSES TO PLATFORM PERTURBATION IN SITTING CHILDREN WITH SPASTIC DIPLEGIA

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The study aimed at investigating neural mechanisms underlying impaired postural control during sitting in children with spastic diplegia. Recently it has been postulated that postural responses to external perturbation are produced by central pattern generators organized in two levels. The first level generates a basic direction-specific pattern, triggered by somatosensory input. Moulation of the basic pattern by multisensorial input occurs at the second level.

Postural responses were assessed in seven 7-11 year old children with spastic diplegia and seven age-matched controls, while they were sitting on a movable platform producing horizontal forward translations. Surface EMGs were recorded of ventral and dorsal neck, trunk, and leg muscles.

The perturbation elicited a backward sway of the body and a direction specific postural response in the 'ventral' muscles of all children. Differences existed between the groups in response modulation: 1) the diplegic children showed a reversal in the normal distal-to-proximal recruitment and 2) diplegic children showed in contrast to the controls a high amount of co-activation in neck and leg muscles. The results suggest an appropriate function of the first, but a dysfunction of the second level of the postural CPG:s in children with diplegia.

18.15 HIGH FREQUENCY STIMULATION (HFS) AFFECTS DEITERS NUCLEUS ACTIVITY: AN IN VIVO STUDY.

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In vitro studies demonstrate that HFS of the primary vestibular fibers increases the efficacy of the synaptic transmission in medial vestibular neurons. The present experiments were aimed to verify whether HFS also affects the Deiters nucleus activity. In ten guinea pigs, under barbiturate anaesthesia (thiopental sodium 5mg/kg/h, i.v.), we studied the effects of vestibular nerve HFS (200 Hz, 20 s) on the ipsilateral evoked potentials elicited in the Deiters nucleus by a test stimulus (30 μA, 0.2 msec, 1 Hz) delivered to the same nerve. The following results were observed: **1**-Tetanic stimulation of the primary afferent fibers resulted in a long lasting and steady enhancement (n=7) of N_1 amplitude wave (70 to 80% in comparison with the basal value) which persisted as long as the observation time lasted (60 to 90 min). A further potentiation (up to 120% of the basal value) was induced by a HFS reinforcement delivered after this period (n=4). In no case HFS affected the P and N_2 waves. **2**-Two animals which had intranuclear MK801 (10^{-6} M) microinfusion before tetanic stimulation showed a slight decrease of all evoked potential components as well as the lack of the potentiating effects after HFS. **3**-In one case HFS produced a strong depression of the evoked potential amplitude which regarded both the N_1 and N_2 waves, the latter component showing a partial recovery after 45 min. These results support behavioral observations and suggest that NMDA receptors also participate in synaptic vestibular nerve transmission at the level of the lateral vestibular nucleus.

18.16 DEPTH SPECIFICITY OF SHORT-TERM SACCADIC GAIN ADAPTATION.
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The saccadic system exhibits a considerable degree of short-term plasticity in the frontal plane. Studies have shown that, by shifting a target during a visually guided saccade, the saccadic gain can be reduced or increased. Short-term gain adaptation exhibits direction specificity in the sense that it is limited to a range of neighbouring directions. The direction of saccades in the frontal plane can be similarly modified. Since most natural gaze shifts also have a depth component, we wondered to what extent properties of the saccadic adaptive system, derived from studies in the frontal plane, can be generalized to 3D space.

Binocular eye movements were recorded using the 2D scleral coil technique while subjects made saccades to LED stimuli in a dark room. By alternating two sets of stimuli, we attempted to simultaneously reduce the gain of saccades towards a far target and to increase the gain of saccades towards a near target. Before adaptation began, both targets required equal-amplitude leftward saccades. The target was always shifted at the onset of the primary saccade. In other experiments, we reduced the gain of saccades in the frontal plane and recorded the extent of adaptation of binocular gaze shifts to varying depths.

We observed that gain adaptation of horizontal saccades shows depth specificity. Our results demonstrate that when the saccadic system is pressured, it is capable of simultaneously adopting two different gains for different depths. This suggests that models for saccadic adaptation, which generally imply an important role for the cerebellum, should be extended to include depth information.

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18.17 MEASUREMENT OF SYNCHRONY IN NEURAL POPULATIONS BY COHERENCE ANALYSIS
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The detection and measurement of synchrony in neural populations is often an important step in the study of neural mechanisms. At the same time, it is a difficult task, particularly if the populations comprise many units. A measure of such synchrony has to be in terms of its three characteristics: (a) extent within a population; (b) strength; (c) degree of phase similarity for the correlated units.

Computer simulations (Christakos, Neurosci. 58, 43, 1994), as well as current mathematical analysis, indicate that for a population comprising an uncorrelated and a correlated subset of units, the unit-to-aggregate (UTA) coherence is zero for the former subset, but has a non-zero value at the frequency (band) of synchrony for the latter subset. This value reflects the above three characteristics and the numerical size of the population, and it stays substantial in a very wide range of conditions (e.g., the extent can be 5% of the units). Therefore, UTA coherence computations on a sample of recorded unit/population activities enable the detection of synchrony and the estimation of its extent and strength. Similar analysis indicates that in the presence of some synchrony, the aggregate-to-aggregate (ATA) coherence between two (sub)populations is non-zero, with a value reflecting the same four parameters. Therefore, this coherence can serve as a tool for detection of synchrony. However, the single value per frequency provided by such computations could only be used as a general index of synchrony, since the characteristics of synchrony cannot be determined from it. Moreover, the ATA coherence saturates easily, and may even give the impression of widespread and strong synchrony in cases where the extent and strength of synchrony are limited.

18.18 STRIATAL SLICE CULTURES: EFFECTS OF SERUM-FREE MEDIUM ON GLIAL CELLS AND FIBER OUTGROWTH.
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Organotypic slice cultures of striatal tissue from newborn rats were grown according to the rollerdrum method of Gähwiler. In brief the tissue was cut into 350 µm thick slices on a McIlwain tissue-chopper and mounted on glass coverslips in a drop of coagulated chicken plasma and cultured for 25 days.

The morphology and fiber outgrowth from the cultures depended on the choice of medium. When cultured in serum-containing medium supplemented by Optimem (GIBCO), the striatal tissue slices displayed the usual flattening, while the tissue slices grown in the chemically defined, serum free medium "Neurobasal" with "B27 supplement" (GIBCO) retained a more compact appearance, but with an exceptionally dense outgrowth of GABAergic fibers. The fiber outgrowth correlated with a marked decrease in the number of oligodendroglial cells within and around the cultures in serum-free medium.

The inverse relationship between oligodendroglial cell numbers and fiber outgrowth was further sustained by the observation that an increase of oligodendroglial cells, stimulated by addition of Ciliary NeuroTrophic Factor (CNTF) to the growth medium, was accompanied by a decrease in GABAergic fiber outgrowth.

We conclude that oligodendrocytes within the striatal slice cultures may exert an inhibitory effect on the outgrowth of GABAergic fibers. Such a relationship between oligodendrocytes and neurite extension has previously been described by Schwab et al. (J. Neurosci 8, 2381, 1988).

18.19 THE RUNNING MOVEMENT DIRECTION IS NOT CONTROLLED IN THE SAME WAY AS THE INITIAL MOVEMENT DIRECTION.
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Previously, we have shown that subjects starting a slow arm movement in what they think is exactly the direction of the target in fact start their movements in consistently deviating directions[1,2]. We now use these deviations to investigate whether the process of controlling the direction during a slow movement is similar to that of controlling the movement direction at the start of a movement. One direct way to investigate this, is to compare the running movement direction at a certain point along the movement trajectory with that of the initial direction of a movement towards the same target starting from that particular point. If the processes of controlling running and initial movement direction are essentially the same, the two directions should be similar. Note that the movements are performed at such a low speed that the subjects have ample time to continuously correct the ongoing movement.

Five subjects made slow arm movements from a starting position S1 towards a visual target. A second starting position S2 was located roughly on the mean trajectory we had found in previous studies for slow movements from S1 towards the same target. We analysed the initial direction of the movements starting in S2 and the running movement direction in S2. The results show that the initial movement direction in S2 differs significantly from the running movement direction at the same location. Thus, although the subjects start as well as move continuously in what they think is the direction towards the target, the movement directions are not the same. We conclude that the process of controlling the movement direction at the start of a movement differs from that of controlling the movement direction after the movement has started.

[1]De Graaf et al. (1991) Exp Brain Res 84: 434-438
[2]De Graaf et al. (1994) Exp Brain Res 99: 464-471

18.20 IMMUNOHISTOCHEMICAL LOCALIZATION OF SERUM PROTEASE INHIBITORS IN MOUSE SKELETAL MUSCLE
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The tissue-associated counter part of some plasmatic protease inhibitors has been studied in mouse skeletal muscle by combining immunoperoxidase confocal microscopy and western blot analysis. To remove serum contamination all experiments were performed on C57 BL/10 adult mice perfused extensively with physiological solution under deep anesthesia. The following serum inhibitors were investigated in skeletal muscle by immunoperoxidase staining: α2 macroglobulin (α2M), antithrombin III (ATIII) and interotrypsin inhibitor (ITI). The resulting localization patterns were analyzed by laser transmittance scanning at 488 nm using a confocal microscope. In all muscles examined (soleus and extensor digitorum longus mm.) an extracellular (endomysial) localization was apparent for all inhibitors. By contrast remarkable differences were observed for the intracellular component: In fact α2M was present in about a half of the muscle fibers; ATIII was present inside all fibers; intracellular ITI was completely absent. Western blotting analysis of muscle homogenate was performed to biochemically characterize the above immureactivities. In preliminary experiments α2M-related immunoreactivity could not be found in the soluble fractions of perfused muscle, confirming an absence of serum contamination after in vivo perfusion. By contrast experiments on detergent-solubilized extracts (0.3% Triton X-100) releaved that tissue-bound α2M consisted of two main bands (168-166 KDa) and a minor component (35 KDa); ATIII of a single band (50 KDa); ITI of four bands (180, 50, 45, 40 KDa). These results confirmed that the specific immunoreactivities visualized by morphological techniques corresponded to muscle-associated plasmatic inhibitors. The present data suggest that in mouse skeletal muscle i) numerous tissue-associated plasmatic inhibitors may protect the extracellular matrix from an excess of proteolysis; ii) a more restricted set of inhibitors may be also involved in the down-regulation of intracellular proteolytic processes.

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18.21 REDUCED RESTING DISCHARGE INDUCED GLIAL REACTIONS IN RAT VESTIBULAR NEURONS FOLLOWING UNILATERAL LABYRINTHECTOMY.
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Vestibular compensation is an attractive model for investigations of cellular mechanisms underlying post-lesional plasticity in the adult central nervous system (CNS). Immediately after unilateral labyrinthectomy, the spontaneous activity in the deafferented vestibular nuclear neurons is almost abolished. After about fifty hours, the deafferented vestibular neurons recover a quasi normal resting activity, which is thought to be the key of the compensation of the static vestibular syndromes. In the present study, we have investigated, in rat vestibular nuclei, whether astroglial cells and microglia could be involved in the vestibular compensation process. Adult rats were hemilabyrinthectomized and glial reactions were studied on cryostat sections using several monoclonal antibodies against glial fibrillary acidic protein (GFAP), vimentin and against CR3 complement receptor (OX-42), a selective marker of microglia. Survival times were 1, 2, 4 and 8 days after the labyrinthine lesion. Degenerating axons were also studied using a silver impregnation method. In intact and sham-operated rats, a uniform distribution of GFAP-positive astroglial cells was observed whereas vimentin reactivity consisted only of a slight staining of endothelial cells. OX-42-stained resting ramified microglial cells were also uniformely distributed within the vestibular nuclei. In lesioned animals, numerous vimentin positive cells were observed within the vestibular nuclei ipsilateral to the lesion. This reaction begin one 1 to 2 days after the labyrinthiner lesion, peaked three days after and then slowly declined during the following days. The presence of GFAP positive astroglial cells confirm these results. It is important to notice that very few if any degerating terminals were observed at any times following the lesion. Hence our results strongly suggest that it is the abolition of the neuronal activity which triggers the glial reaction. It remains to be determined the role of the glial cells in the restauration of the spontaneous activity of the deafferented neurons.

18.22 THE INFLUENCE OF BIOMECHANICAL CONSTRAINTS ON THE CONTROL OF GRIP STRATEGY

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Grasping a lengthy object (e.g. a rod) at its smaller ends can be performed either with the forearm everted or inverted. In order to learn more about the selection strategy employed, 7 normal, right-handed subjects were asked to grasp a rod of 8 cm length positionated at different orientation angles. Arm and hand trajectories were recorded using a Selspot II three camera tracking system under three different conditions: (1) no instruction about the grip type to employ, (2) everted grasping , (3) inverted grasping. Eversion grip probabilities for non-instructed grasping (in dependance of orientation angle of the presented object) and time course of limb angles for all trials were calculated off-line.

For all subjects, grip choice probabilities were sigmoid-shaped, with a small orientation angle range where eversion probability changes from 10 to 90 % (about 10 degrees). The orientation angle where eversion probability equals 50 % is highly correlated between the subject's either hands.

Only little variation of forearm pronation / supination angle was observed for either grip type, the two types mainly differing by more proximal angles (i.e. shoulder yaw and elevation). Only extreme angles are established by additional variation of pronation / supination and hand angles.

It seems as if natural choices of grip type were selected in order to minimize biomechanical constraints. A possible explanation could be that selection includes pre-processing of these constraints. Grip types are then executed in order to minimize the number of degrees of freedom, i.e. the number of limb angles varied.

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18.23 PERSISTENCE OF MONOSYNAPTIC GROUP IA PROJECTIONS BETWEEN ANTAGONIST MUSCLES IN SUBJECTS WITH PERINATAL BRAIN DAMAGE

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Co-contraction of antagonist muscles is characteristic of spasticity and a feature of early postnatal motor development. Monosynaptic Group Ia projections from biceps brachii to motoneuronal pools throughout the brachial plexus, shown in the newborn baby become restricted during the first two postnatal years (O'Sullivan et al., 1991;439:529-543). Longitudinal and cross-sectional studies have now been performed to test the hypothesis that these projections persist in children with perinatal brain damage, who develop spasticity. Subjects with spasticity due to brain damage acquired in adulthood were also studied to determine if these projections become unmasked and form part of a general spastic syndrome.

50 healthy newborn babies and 30 at high risk for cerebral palsy, 11 of whom developed spastic quadriparesis, were studied longitudinally for 5 years. 38 subjects (8-30 years) with spasticity of perinatal origin (11 hemiplegics, 11 quadriplegics, 16 with Rett syndrome) and 11 subjects with stroke in adulthood were also studied. The results were compared with those obtained in 372 normal subjects from birth to 55 years. Electromechanical taps were applied to the tendon of biceps brachii when contracting, to elicit the phasic stretch reflex, and when relaxed, to study Group Ia heteronymous projections. Surface EMGs were recorded from biceps and triceps brachii, pectoralis major and deltoid. In the longitudinal group subjects developing spastic quadriparesis showed persistent low threshold of the biceps' stretch reflex and persistent monosynaptic Group IA heteronymous projection to triceps. A normal pattern of restriction of the projections to pectoralis major and deltoid was observed. The same pattern occurred in the older subject groups with spasticity of perinatal origin. In adults with stroke the threshold of biceps' phasic stretch reflex was low, but there was not evidence of abnormal Group Ia heteronymous excitation of triceps. In conclusion, perinatal brain damage leading to spasticity results in abnormal development of heteronymous Group Ia projections between antagonist muscles.

18.24 PALLIDAL MECHANISM OF CONDITIONED TASTE AVERSION IN THE RAT: ELECTROPHYSIOLOGICAL AND NEUROCHEMICAL STUDY

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The globus pallidus (GP), one of the key structures of the extrapyramidal motor system, plays important role in different aspects of feeding and body weight regulation (sensory-motor integration, metabolic control, etc.). Our previous studies proved the existence of exogenously and endogenously chemosensitive pallidal neurons whose major function could be the integration of different feeding-related signals. In addition to neurophysiological evidence for gustatory neurons in the GP, it has also been reported that excitotoxic lesion of GP cells caused deficits in acquisition and retention mechanisms of the CTA. Despite of these and other data in the literature, little is known yet of electrophysiological and neurochemical correlates of CTA learning in the GP. In the present experiments therefore, extracellular single neuron activity of the GP of anesthetized rats was recorded by means of multibarreled carbon fiber glass microelectrodes during 1) gustatory stimulations and 2) microiontophoretic application of neurochemicals. These investigations were performed before, during and after CTA conditioning (LiCl, 0.15 M, 20 ml/kg, i.p.) with saccharine (0.25%). Cardiorespiratory state of the rats was continuously monitored throughout the recording sessions. Evidence has been obtained for electrophysiological correlates of CTA learning in the rat pallidum. The microelectrophoretic studies demonstrated characteristic changes of the pallidal catecholamine (especially dopamine) neurotransmission during CTA learning. Our findings indicate that the GP neurons, especially their catecholaminergic mechanisms, are of great importance in the central processing of feeding-related gustatory signals.

18.25 UNINSTRUCTED SACCADIC MOVEMENTS AS A CORRELATE OF VISUAL EXTINCTION.

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Right brain-damaged patients as well as normal controls were tested on a simple manual reaction time (RT) paradigm. Brief light flashes were presented either to the left or to the right visual hemifield, or bilaterally. The subject was instructed to keep his gaze on the fixation point, to press a key as fast as possible following presentation of uni- or bilateral stimuli and, finally, report on the number and position of the perceived stimuli. Horizontal eye movements were recorded by means of an electro-oculographic technique (EOG) using silver-silver chloride electrodes.

Following double stimulation patients reported having seen only the flash presented to the right hemifield on more than 20% of trials, while with unilateral stimuli, either left or right, detection performance was good.

The main thrust of this experiment is that the proportion of uninstructed saccadic eye movements toward the site of stimulation (mean: 25%) did not differ for the left and the right hemifields. However, following bilateral stimuli there was a markedly higher proportion of rightward vs. leftward saccadic movements and this represented a good correlate of extinction. Interestingly, the latency of rightward movements following bilateral presentation was the same as that for rightward movements following unilateral stimuli while with the latter stimuli there was a marked speed advantage for rightward movements. Taken together these results suggest that the extinguished left stimulus does not interfere with rightward saccades and this is in keeping with an early-processing level of extinction.

18.26 c-FOS EXPRESSION IN THE NUCLEUS OF THE OPTIC TRACT OF THE RAT FOLLOWING OPTOKINETIC STIMULATION

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In mammals the retinal slip signal arising from the self-motion is conveyed along a specific pathway to the nucleus of the optic tract (NOT) and the dorsal terminal nucleus (DTN) of the accessory optic system (AOS). Converging lines of evidence have ascertained that the NOT/DTN complex represents the key structure in organizing the compensatory response of the optokinetic nystagmus (OKN).

In rodents the NOT appears a very fragmented nuclear structure, dispersed in many groups of clustered cells widely extending from the meso to diencephalon. This anatomical arrangement may possibly subserve functional subdivisions within the different parts of the NOT. In fact, its most lateral (caudal) portion has been regarded as another nucleus of the AOS due to its strong reciprocal connections with the other nuclei of this system. On the other hand, the peculiar profiles of GABA immunoreactivity typify only the rostral neurons, specifically projecting to premotor regions. In the present study we have tried to further confirm the double aspect of the NOT organization in the rat. For this purpose we studied the localization of c-FOS protein expression in the NOT of the Long Evans rats submitted to optokinetic stimulation for 1 hour. Significant c-FOS expression was found in the cell population of the rostral (medial) levels, where projecting neurons are located. In contrast, no c-FOS labelled cells were detected in the lateral part of the NOT, near the DTN. Comparing the present results with those previously obtained with our 2-deoxyglucose experiments, in which uptake was substantially confined in the lateral NOT, it appears that a clear segregation exists in this nucleus between the sites of retinal slip elaboration and of committed motor activity.

18.27 REVERSIBLE INACTIVATION OF INFERIOR PREMOTOR AREAS (F4 AND F5) AND PRIMARY MOTOR CORTEX (F1) AFTER MUSCIMOL INJECTION IN THE MACAQUE MONKEY.

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The inferior sector of area 6 is constituted of two distinct anatomical and functional areas: areas F4 and F5. Neurons in F4 discharge during face, neck and proximal arm movements. They have tactile receptive fields (RFs) on the face, arm and the upper part of the body, and, frequently, visual RFs, typically located around the tactile ones. Most visual RFs are coded in body-centered coordinates. In contrast to F4, F5 neurons discharge mostly during distal arm movements. A part of them becomes active also during mouth movements. Some F5 neurons respond to the presentation of visual objects of shape and size congruent to the grip motorically coded by the neurons, others to the observation of hand movements performed by another individual. The aim of this study was to investigate further the dichotomy between F4 and F5 by temporary inactivating them by a GABA agonist (muscimol). The inactivation of F1 was also studied.

Muscimol injections (3µl, 5µg/µl) were performed after electrophysiological mapping of F1 (hand-arm field), F4 and F5. Injection sites were chosen in order to inactivate different somatotopic "modules" inside the investigated areas. Before and after the lesions, the monkey behavior was assessed by using visual and somatosensory stimuli and by testing reaching and grasping movements towards objects of different size and shape, presented at different spatial locations. Kinematics of the wrist and of the thumb and index finger were recorded by using the ELITE system. The results confirmed the somatotopic organization of the region with two distal movement representations (F1, F5) and two proximal representations in between (F1, F4). They showed also complex somatomotor and visuomotor deficits following F4 lesions that are not observed following F1 inactivation. The symptoms following F4 damage changed according to the physiological "module" that was inactivated.

18.28 ROLE OF MONKEY SUPERIOR COLLICULUS IN AUDITORY SACCADES. M.A. Frens* and A.J. van Opstal Neurology Dept., Univ. Hospital, Zürich, CH, and Biophysics Dept., Univ. Nijmegen, NL.

A monkey was trained to make saccadic eye movements towards auditory and visual targets in darkness. Meanwhile, single-unit activity of saccade related burst neurons (SRBNs) in the deep layers of the superior colliculus (SC) was recorded.

The kinematic properties of auditory saccades were only slightly different from visually-evoked eye movements, in the sense that they were on avarage somewhat slower and more variable, and displayed slightly prolonged durations. Latencies were comparable for both saccade types.

Although auditory sensory activity was only occasionally found, all recorded SRBNs displayed clear motor activity in both saccade tasks. We found that the mean firing rate of the SRBN motor burst for auditory saccades was considerably reduced (by ≈60%). However, neither the center position, nor the width of the movement fields differed significantly for the two conditions. Thus, the *same* population of cells was active during a saccade of a given size and direction, irrespective of stimulus modality.

The finding that the activity of 'clipped' SRBNs for matched saccade vectors of comparable kinematics depends strongly on stimulus conditions, does not support the hypothesis that these cells encode dynamic motor error.

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18.29 INVOLVEMENT OF Ca^{2+} CHANNELS IN EFFECTS OF SUBSTANCE P ON SPONTANEOUS FIRING OF DOPAMINE (DA) NEURONS IN THE SUBSTANTIA NIGRA PARS COMPACTA (SNc). T. Futami*[1,2], C.D. Richards[2], and S.T. Kitai[2]. [1] Frontier Research Program, The Institute of Physical and Chemical Research (RIKEN), Saitama, 351-01, Japan, and [2] Dept. of Anatomy and Neurobiology, Univ. of Tennessee, College of Medicine, Memphis, TN 38163.

Striatal neurons projecting to DA neurons in the SNc are GABAergic and contain Substance P (SP). We have investigated involvements of Ca^{2+} channels in the effects of SP on DA neurons by using an intracellular recording technique in *in vitro* rat slice preparations.

Slices (500 µm thick) containing the SN were prepared and intracellular recordings from DA neurons were made using biocytin filled electrodes. SP (10 µl) was applied with a micropipette to the bathing media flowing in the slice chamber. Recorded neurons were double labeled using tyrosine hydroxylase and biocytin histochemistry to identify their morphology and transmitter phenotype.

SP application induced an initial inhibition of spontaneous activities followed by an increase in spontaneous firing. The initial inhibition was partially blocked by either application of sulpiride (1 µM) or bicuculline (20 µM). The effects of SP were suppressed by either nifedipine (10 µM) or w-conotoxin (1 µM). These findings indicate that: 1) SP action on DA neurons may be excitatory. 2) The initial portion of the excitation may have been masked by SP induced inhibition on the activation of GABAergic or dopaminergic elements. 3) The effects of SP may be mediated via L or N-type Ca^{2+} channels.

Supported by NIH NS 20702 and The Human Frontier Science Program.

18.30 **DUAL, EXCITATORY AND INHIBITORY, OUTPUT OF INDIVIDUAL NEURONS OF INTERPOSITUS NUCLEUS IN CATS** **D. GAWROŃSKI,* A. KOŁODZIEJAK, R. TARNECKI,INSTITUTE OF EXPERIMENTAL BIOLOGY, POLISH ACADEMY OF SCIENCES, PASTEURA 3, 02-093 WARSAW, POLAND**

We present analysis of trains of spikes recorded from four structures that are part of premotor network in cats. Under stereotactic control we placed tungsten microelectrodes in nucleus interpositus of cerebellum (IP), red nucleus (RN) of midbrain, ventral nucleus of thalamus and cruciate gyrus of cortex. In different experiments these locations were either stimulated or served as recording sites of mulitunit and intracellular potentials. Neuroanatomical studies revealed that certain axons traveling from IP to ventral nuclei of thalamus branch to give collaterals to RN. The aim of our study was, analysis of functional influences that these bifurcating axons exert.. Our study provided putative functional evidence of specific function of their output. Cross-correlograms produced with software designed at our lab showed following influences. The IP inhibits and stimulates ventral nucleus of thalamus (n=487 neurons). The influence on RN is also stimulatory and inhibitory (n=507). However, what is most important, the influences show an interesting pattern, if a IP neuron stimulates RN it inhibits ventral nucleus of thalamus (n=94) and vice versa (n=36). Judged by the latencies, 0.8-1.6ms between IP and RN, 0.6-1.4 between IP and RN, of these influences we postulate that inhibition was exerted via interneurons while stimulation on those that give origin to tracts descending down the spinal cord. This observation supports notion of different contributions of either structure in movement production. Phase delay between these outputs could serve as a source of information for coordination of motor functions.Regretfully our study did not analyze peripheral effects of stimulations and it requires additional research to verify this hypothesis.

18.31 EXTRAPYRAMIDAL MOTOR PERFORMANCE AND BRAIN ATROPHY IN HIV-1-INFECTION AND HUNTINGTON'S DISEASE

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Introduction: HIV-1 as a neurotropic virus is known to affect predominantly the basal ganglia thus causing both motor abnormalities and cognitive deficits possibly due to disturbances of frontal-basal ganglia networks.

Methods: We therefore correlated standard morphometric parameters (CC = distance between the heads of the caudate nuclei, IT = distance between the inner tables of the skull; FH = distance of the frontal horns) quantifying frontal ((FH/IT) and caudate (CC/IT) atrophy in computed tomography and electrophysiological parameters (tremor peak frequency, most rapid alternating movements, reaction (RT) and contraction time (MRC)) evaluating extrapyramidal motor function both in 41 HIV-1 seropositive patients, 43 patients with manifest Huntington's disease (HD) and 58 patients at risk for HD.

Results: MRC was the most affected electrophysiological parameter in both diseases. MRC alterations highly significantly correlated with caudate atrophy in HD ($r = 0.3352$; $p < 0.01$) and HIV-1 infection ($r = 0.391$; $p < 0.05$). In contrast to HD, in HIV-1 seropositive patients correlation with frontal atrophy was even more significant ($r = 0.484$; $p < 0.01$).

Conclusions: These results suggest that disturbances of frontal - basal ganglia circuits contribute to HIV-1 encephalopathy.

18.33 EYE-HEAD COORDINATION IN AUDITORY & VISUAL SACCADES. H.H.L.M. Goossens*, N. Cappaert and A.J. Van Opstal.
Univ. Nijmegen, Biophysics, P.o. Box 9101, 6500 HB NIJMEGEN, NL.

Common sense suggests that eye-head coupling in human orienting behaviour can not be too rigid because one can easily redirect the eyes without a head movement. Task-dependent eye-head coupling may therefore be expected. We studied 2D combined eye-head movements in four human subjects during auditory and visual localization tasks using search coils. The eyes and head were initially aligned or unaligned (in which case the direction of motor error was different for eyes and head). We found that when eyes and head were initially aligned temporal eye-head coupling was quite loose for visual saccades, whereas it was more tight for auditory saccades. Furthermore, the contribution of eye and head saccades to the total gaze movement depended on their relative onset timing (ΔT). Differences in ΔT could explain the larger contribution of the head in auditory evoked gaze movements. If eyes and head were initially aligned the directions of eye and head movements were very similar, but in the unaligned condition there were clear differences. This spatial decoupling was associated with a high degree of temporal decoupling. We argue that our data are adequately described by a modified Common Gaze model which explicitly deals with temporal aspects and modality dependence of two-dimensional eye-head coordination.

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18.34 INFLUENCE OF THE ETHANOL ON THE DISCHARGE PATTERN OF CEREBELLAR PURKINJE CELLS IN THE CAT R.Grigorian* and T.Ismailov. Institute of Evolutionary Physiology and Biochemistry, 194223, St.Petersburg, Russia

In this study some peculiarities of the ethanol action on the resting activity of cerebellar Purkinje cells (PC) have been investigated. The effect of intravenous injection of moderate doses (2-4 ml/kg ,30% solution) of ethanol was studied in experiments on anesthetized adult cats. The ethanol level in the blood was determined by using of gas chromatography method. The following statistical parameters were studied: interspike intervals (ISI) of PC discharge; time frequency histogram of PC discharge; standard deviation of cerebellar PC discharges. The range interspike intervals of the spontaneously active PC was in order of 45-77 ms giving a discharge frequency respectively within 12 ±1.7 and 21±1.2 imp/s. Four to six minutes after ethanol injection the Purkinje cells discharge frequency began increasing up to 33-35 imp/s at the 30th in, which followed by gradually decreasing of PC discharge frequency to the initial level at the 75th min. after ethanol injection. The most interesting phenomena in the ethanol action on the resting activity of cerebellar PC was a considerable decreasing of the Purkinje cells discharge standard deviation and duration of postclimbing inhibitory pause .

18.35 IMMUNOHISTOCHEMICAL DISTRIBUTION OF GLUTAMATE-RECEPTOR-SUBUNITS IN THE NUCLEUS OF THE OPTIC TRACT IN THE RABBIT

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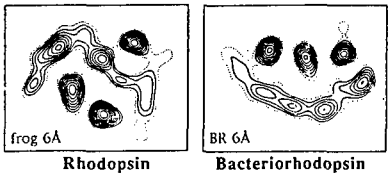
Immunohistochemical studies suggest that glutamate is most likely the excitatory neurotransmitter in retinofugal projections. Moreover, pharmacological studies have shown that AMPA- and kainate-, as well as NMDA-receptors play a role in the transfer of visual input in the nucleus of the optic tract (NOT) and the adjacent dorsal terminal nucleus (DTN) of the accessory optic system: two nuclei involved in generating the slow-phase of the horizontal optokinetic nystagmus (hOKN). Recently, antibodies became commercially available against the different glutamate-receptorsubunits recognizing (i) specific epitopes in the AMPA-receptorsubunits GluR1, GluR2 and GluR4, (ii) a common epitope in the kainate receptorsubunit GluR5/6/7 and (iii) a specific epitope in the NMDA-receptorsubunit NMDAR1. The antibodies against GluR2 recognized also GluR3 or GluR4 in testsystems with transfected cells.

In the present study we analyzed the distribution of these antibodies in the NOT and DTN of the rabbit. Antibodies specific for receptorsubunits GluR1, GluR4, GluR5/6/7 and the NMDAR1 showed immunostaining in the NOT and DTN. Strong immunoreactivity was found for GluR5/6/7 staining somata and dendrites in the NOT and DTN, while antibodies against NMDAR1 and GluR1 showed only moderate immunostaining of neurons throughout the NOT. The GluR4 specific antibody showed staining of some neurons in the NOT and DTN. However, the antibodies against GluR2 did not show significant immunostaining of neurons in the NOT or DTN. These results show that visual input regulating the hOKN is mainly mediated by kainate and NMDA-receptors and to a lesser extent by AMPA-receptors. The specificity regarding the presence of the different receptorsubunits will be investigated further.

19.01 THREE DIMENSIONAL STRUCTURE OF RHODOPSIN OBTAINED BY ELECTRON CRYO-MICROSCOPY.

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All members of the family of G-protein-coupled receptors are expected to have a similar basic structure in the membrane-embedded part of the protein. Rhodopsin is the only seven helix receptor available from natural sources in milligram quantities for crystallisation. Two dimensional crystals with p2 symmetry of frog rhodopsin were obtained by extracting photoreceptor membranes with Tween detergents. Electron cryo-microscopy was used to determine the three dimensional structure of frog rhodopsin. The resolution limit in a map calculated from 60 crystals with nominal tilt angles up to 45° were 7.5Å horizontally and 16.5Å normal to the plane. In the three dimensional map, seven regions of density are visible from which the approximate tilt angles of all seven helices can be deduced. In particular, the overall tilt of the more tilted helices is unambiguously defined in the frog rhodopsin map. There is clearly additional density visible on one side of the membrane that cannot be explained by transmembrane helices; this additional density may represent a compactly folded extracellular (i.e. intradiskal) domain. The structure is more open on the intracellular side of the membrane and only little density, mainly extending from one straight helix is visible. This could indicate that a looser arrangement of loops is involved in the binding and activation of the G-protein transducin.



Rhodopsin Bacteriorhodopsin

20. Symposium: Calcium signalling in neurons

20.01 CA^{2+} AND THE RATE OF EXOCYTOSIS IN SINGLE GLUTAMATERGIC TERMINALS.

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Transmitter release from nerve terminals is rapidly triggered by an increase in the presynaptic calcium concentration, $[Ca]_i$. Quantitative study of this fundamental process has been hindered by the small size and inaccessibility of most CNS nerve terminals and an inability to measure the critical calcium concentration. We used flash photolysis of caged calcium, to rapidly and uniformly elevate $[Ca]_i$, in combination with high-time resolution measurements of membrane capacitance, as an index of exocytosis, and fluorescence measurements of $[Ca]_i$, to address this issue in single synaptic terminals of retinal bipolar neurons. When $[Ca]_i$ was abruptly raised to $> 10\ \mu M$, capacitance rose at rate that increased steeply with $[Ca]_i$. The steepness suggested that at least four calcium ions must bind inorder to activate synaptic vesicle fusion. Half-saturation was at $\approx 194\ \mu M$, and the maximal rate constant of secretion was $\approx 3000\ s^{-1}$. In contrast to neuroendocrine cells, transmitter release from synaptic terminals exhibited a cooperative interaction between the calcium binding sites, a lower affinity trigger for exocytosis, and higher maximal rates of vesicle fusion. These data reveal specializations of the synaptic secretory process that allow temporal fidelity of fast neuronal signaling to be maintained.

20.02 MODULATION OF HIPPOCAMPAL CALCIUM SIGNALS BY STEROID HORMONES.

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Steroid hormones are secreted from peripheral tissue into the circulation. Due to their lipophylic character they pass the blood-brain barrier and bind to discretely localized receptors in the brain. The hippocampal formation of the rat is enriched in receptors for steroids. Activated steroid receptors bind to the DNA and act as transcription factors. We used combined electrophysiological, molecular and imaging techniques to investigate the effect of corticosterone, estradiol and progesterone on Ca signals in hippocampal CA1 neurons, in vitro. It appeared that activation of high-affinity receptors for corticosterone, a situation occuring during rest, resulted 1-4 hrs later in a low amplitude of voltage gated Ca-currents. Additional occupation of high affinity corticosterone receptors, as happens after stress, evoked a delayed enhancement of the Ca-current amplitude. In the absence of corticosterone Ca-currents were even larger. Imaging studies with Fura-2 indicate that corticosteroid treatment may not only affect Ca-influx but also Ca-buffering in the cell. Presently, in situ hybridisation and single cell RNA amplification techniques are used to investigate if the steroid-dependent changes in Ca signals are associated with altered mRNA expression of Ca-channel subunits. Gonadal hormones also affect Ca-influx: In estrogen primed female rats receiving progesterone 4 hrs before the test Ca-currents display large amplitudes when compared to rats without gonadal hormones. These data support the idea that steroid hormones of peripheral origin can regulate Ca-signals in hippocampal neurons over a prolonged period of time.

20.03 Ca^{2+} REGULATION AND VESICLE RECYCLING IN INDIVIDUAL PRESYNAPTIC VARICOSITIES

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Cultured cerebellar granule cells extend neurites, possess a variety of voltage-activated Ca^{2+} channels both on somata and neurites and exocytose endogenous glutamate, or exogenously accumulated ^{3}H-D-aspartate in response to high KCl. The sites of exocytosis and subsequent membrane recovery can be visualized by FM1-43; most intense labelling is seen in varicosities along neurites, frequently where two neurites appear to make a pseudo-synaptic contact. Ca^{2+} entry and exocytosis can also be induced by uniform field stimulation; while neurites show reproducible Ca^{2+} transients in response to trains of stimuli, the activation kinetics of somatic Ca^{2+} channels appear to be too low to respond unless the evoked action potentials are lengthened by 4-aminopyridine. Field stimulation induces exocytosis of the same pool of vesicles as does high KCl. Subsequent endocytosis does not require exogenous Ca^{2+} or plasma membrane depolarization. Both the neurite and somatic Ca^{2+} responses to KCl depolarization are enhanced when mitochondria are uncoupled by protonophores; however this is not due to abolished mitochondrial Ca^{2+} sequestration, but is rather due to a lowered ATP level in the neurones inhibiting non-mitochondrial pathways removing Ca^{2+} from the cytoplasm. When ATP depletion granule cells show no enhanced cytoplasmic Ca^{2+} response to an imposed Ca^{2+} load, even though the mitochondria do accumulate Ca^{2+}. A negative feed-back inhibition of voltage-activated Ca^{2+} channels appears to be primarily responsible for limiting the elevation in cytoplasmic free Ca^{2+}.

20.04 SYNAPTIC CALCIUM SIGNALS IN DENDRITIC SPINES

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By combining fluorometric fast confocal laser scanning microscopy, patch clamp recordings in brain slices and stimulation of afferent excitatory fibers, localized changes in intracellular calcium concentration were detected in fine dendrites and their adjacent spines of cerebellar Purkinje and hippocampal pyramidal neurons. The calcium signals were short-lived (lasting around 1-2 seconds) and were detected even during single subthreshold excitatory synaptic potentials. In cerebellar Purkinje neurons, these synaptic calcium signals seemed to have a time-course that was similar in spines and in the adjacent dendrites. Several lines of evidence indicated that these signals were caused by the local activation of voltage-gated calcium channels. There was neither a contribution of metabotropic glutamate receptors nor evidence for calcium entry through AMPA-gated receptor channels (Eilers, Augustine & Konnerth, *Nature* 373, 1995). By contrast, in hippocampal CA1 pyramidal neurons single stimulation of the afferent Schaffer collateral fibers produced a transient calcium signal that was initiated in spines and had a much smaller amplitude in the adjacent dendritic shaft (Eilers, Lisman & Konnerth, in preparation).

21.01 LANGUAGE-SPECIFIC INFLUENCES ON INFANTS' SPEECH PERCEPTION. L. Bosch. Departament de Psicologia Bàsica. Universitat de Barcelona. Passeig de la Vall d'Hebron, 171, 08035 Barcelona (Spain).

In trying to explain how innate factors and early experience with a specific language interact in the development of speech perception, research in the last ten years has established that different types of perceptual modifications seem to take place before the child starts learning a lexicon. Exposure to a specific language is considered to alter infants' perception in that the abilities to discriminate certain phonemic contrasts that do not belong to the native language seem to decrease at around ten months of age. For vowels, the effect of native language experience seems evident at a younger age: by six months, infants show a within-category vowel generalization, being unable to discriminate different exemplars of vowels from a prototype which represents the center of a phonetic category. More recent work with even younger infants has shown that by two months of age they not only are no longer able to discriminate two foreign languages from each other, but they also orient faster to their native language for as long as prosody is not disrupted.

For the bilingual child, the process of identifying one's maternal language and the effects of native language experience on speech perception will probably present with special characteristics. One of the issues to be analysed refers to the early discrimination of the two languages in the bilingual environment, an ability which could be delayed depending on the proximity between the languages in terms of their general phonological features. Preliminary results from an ongoing project on the ability to distinguish short utterances from Catalan and Spanish by 2 to 3-months-old monolingual and bilingual infants will be discussed. Analyses of the orientation times observed will give us valuable information concerning the capacity to represent languages separately by bilingual infants.

21.02 THE ROLE OF PROSODY IN LANGUAGE ACQUISITION. A. Christophe*, M. Nespor and T. Guasti. MRC-CDU, 4 Taviton Street, London WC1H 0BT, UK; Universität of Amsterdam, Amsterdam, The Netherlands; San Raffaele Institute for Cognitive Science, Milano, Italy.

Where does language acquisition start? Researchers working on the acquisition of syntax have generally assumed that the input to the syntactic analyzer was a string of words. But getting at the string of words is not so easily done. As a matter of fact, most if not all models of lexical access in adults (with full knowledge of the lexicon) use syntactic and semantic information to solve the many segmentation ambiguities that arise when one considers speech as an uninterrupted string of phonemes. The process of language acquisition has to start somewhere: it has to be *bootstrapped*.

"Prosodic bootstrapping" is the hypothesis that the prosody of speech, its melody and rhythm, may provide information allowing one to start acquiring language. There is experimental evidence that prosody is processed by very young infants (e.g. newborns can discriminate languages on the basis of their prosody only).

Two specific prosodic bootstrapping hypotheses will be offered, suggesting how prosody may help in acquiring a lexicon, and in setting one of the major syntactic parameters, namely right vs left branching. Acquiring a lexicon implies segmenting the continuous speech stream into word-sized units; we suggest that the speech stream may be spontaneously perceived as a string of prosodic units, each containing one or two content words at most. The process of finding the actual word boundaries would be quantitatively and qualitatively simplified if carried out on such a prosodically segmented representation instead of whole utterances (further segmentation may involve using distributional regularities and phonotactics). Furthermore, prominence within these same prosodic units falls on the right for right-branching languages (e.g. English, Italian), and on the left for left-branching languages (e.g. Japanese, Turkish). Thus, perceiving prominence within these prosodic units would allow the infant to set the right vs left-branching parameter at a very early age.

These proposals are assessed through experimental work on both infants and adults.

21.03 WORD SEGMENTATION STRATEGIES IN THE INFANT R.Coolen*, Max-Planck-Institut für Psycholinguistik, Wundtlaan1, 6525 XD Nijmegen, The Netherlands

The understanding of spoken language requires the identification of the individual words in the utterance. The adult language user's speech segmentation is supported by acquired lexical knowledge. The prelingual child, however, cannot rely on lexical knowledge and, must therefore, base segmentation of continuous speech on other cues in the speech signal.

There are basically two types of cues the infant might use for initial segmentation of speech: segmental (e.g., phonotactic features) and suprasegmental cues (e.g., metrical features). Experiments will be reported on both types of cues. In a first series of experiments, the role of syllable frequency (high-frequent versus low-frequent syllables) in speech segmentation was examined. In a second series of experiments, the role of stress pattern (stressed versus unstressed syllables) in recognizing words in sentences was investigated.

Infants of 7 1/2 and 9 months old were presented with different speech samples through one of the loudspeakers on the right or left side panel of a test booth. The amount of time that the infant kept its head turned towards the loudspeaker presenting a speech trial was measured (Head Turning procedure). Syllable frequency and word stress were both shown to affect the mean looking times. The implications of these results for the early phases of language acquisition will be discussed.

21.04 SPEED OF SPEECH PROCESSING IN INFANTS. G. Dehaene-Lambertz. Laboratoire de Sciences Cognitives et Psycholinguistique, 54 bd Raspail, 75270 Paris cedex 06, France.

The experimental paradigms classically used in linguistic research in infants assess discrimination capacities. However, they give no indication about the speed of stimulus processing. We will present experiments where a behavioral method (eye orienting procedure) and an electrophysiological method (high-density event-related potentials) were used to provide temporal information in linguistic tasks.

Young infants discriminate maternal and foreign language. Our first study examined how much time, and thus how much linguistic information, they need in order to decide whether a sentence belongs to their maternal language or not. The latency of the first ocular saccade toward a speaker playing short sentences in maternal language or in a foreign language was measured in two-month-old infants. The infants oriented 300 ms faster toward maternal language. This behavior persisted when sentences were low-pass filtered or reduced to clauses as short as one second. When the prosody of the sentences was destroyed, no difference in orienting latency toward the two languages was found. Thus, language recognition is fast and can be based on short segments, as long as prosodic information is present.

Infants are also able to discriminate almost all the phonemic contrasts used in human languages. By using high-density event-related potentials in two-month-old infants, this capacity was decomposed in three successive stages of processing, the cerebral bases of which were specified. The data indicated that the infant brain recognizes a phonetic change in less than 400 ms .

Behavioral and electrophysiological methods thus converge in showing that, shortly after birth, language processing is already fast, highly efficient, and organized as series of functional stages with identifiable characteristics.

22. Symposium: Structural biology of neuronal proteins: a novel approach for rational drug design

22.01 THE USE OF PHAGE DISPLAY TECHNOLOGY FOR STUDIES OF CNTF-RECEPTOR INTERACTION. I. Saggio, I. Gloaguen, A. Di Marco and R. Laufer* Istituto di Ricerche di Biologia Molecolare P. Angeletti (IRBM), Via Pontina km 30.600, 00040 Pomezia, Rome, Italy.

Ciliary neurotrophic factor (CNTF) is a neuro-cytokine that stimulates the survival and/or differentiation of a variety of neuronal and glial cells in the peripheral and central nervous system. We describe the use of phage display technology (1,2) to study the molecular basis of CNTF-receptor interactions, and to guide the development of cytokine analogs with improved therapeutic potential. A library of human CNTF mutants was constructed, displayed on the surface of filamentous bacteriophage, and submitted to affinity selection using immobilized CNTF α-receptor (3). We isolated CNTF variants that displayed significant increases, with respect to the wild-type protein, in α-receptor binding affinity, biological activity, and receptor selectivity. We will describe the properties of these molecules and discuss the structural and functional significance of their specific amino acid substitutions.

1. Smith, G.P. & Scott, J.K. (1993) *Meth. Enzymol.* **217,** 228.
2. Clackson, T. & Wells, J.A. (1994) *Trends Biotechnol.* **12,** 173.
3. Saggio, I. *et al.* (1995) *Gene,* **152,** 35.

22.02 RECOMBINANT ACETYLCHOLINESTERASE AS DRUG SCAVENGER. A. Shafferman*, A. Ordentlich, D. Barak, C. Kronman, H. Grosfeld, D. Stein, N. Ariel, S. Reuveny, A. Lazar, D. Marcus, Y. Segall , A. Bromberg and B. Velan. Israel Institute for Biological Research Ness-Ziona, Israel

Combination of recombinant DNA technology, kinetic studies and molecular modelling, are being employed in the design of novel biocatalysts with potential pharmacological use against organophosphate (OP) poisoning, based on the human acetylcholinesterase (HuAChE) template. Besides identification of the catalytic triad (Ser203, Glu334, His447), these studies[1] revealed the anionic subsite (Trp86) which operates via π-cation rather than electrostatic interactions, the components of the acyl pocket (Phe295, Phe297), the putative hydrogen bond network (Glu202, Glu450) in the active center and the peripheral anionic subsite (PAS) located 20Å away from the catalytic serine (Tyr72, Asp74, Tyr124, Trp286, Tyr341). All these functional substructures were found to alter the basic OP-scavenging properties of the native enzyme. Some of the engineered enzymes were more efficient scavengers due either to increased affinity towards OP's or resistance to "aging" of their OP-adducts. In addition these studies unraveled the nature of the enigmatic allosteric modulation of AChE activity which apparently operates via a specific "cross talk" between the PAS and the anionic subsite of the active center, involving aromatic-aromatic interactions.

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[1]Shafferman *et al.* (1992) *EMBO J.* 11,3561; Shafferman *et al.* (1992) *J.Biol.Chem* 267,17640; Ordentlich *et al.* (1993) *ibid.* 268,17083; Barak *et al.* (1994) *ibid.* 269,6296. Ordentlich *et al.* (1995) *ibid.* 270,2082; Ordentlich *et al.* (1993) *FEBS Lett.* 334,215.

22.03 EXPRESSION OF A7 NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR

Jim Patrick, Danong Chen, Lorna Colquhoun, Hong Dang, Kelly Dineley, Finn Göldner, and Santosh A. Helekar

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Genes encoding neuronal nicotinic acetylcholine receptors (nAChRs) are expressed throughout the brain. α–bungarotoxin (α-BTX) binding sites are found on one class of nAChRs known to be widely distributed in the brain and the nAChR subunit α7 is an important component of the receptor that binds α-BTX. The α7 subunit forms a homo-oligomeric ligand-gated ion channel when expressed in *Xenopus* oocytes. This ligand-gated channel is activated by nicotinic agonists. The agonist-induced current through this channel desensitizes rapidly, is inwardly rectifying at positive membrane potentials, and is carried by monovalent cations although there is a significant divalent cation permeability that suggests a role for this channel in neural plasticity.

We have studied the expression of this receptor in the *Xenopus* oocyte. An initial result of these studies was the observation that expression of the alpha7 homo-oligomer was sensitive to CyclosporinA suggesting that the peptidy-prolyl isomerase cyclophilin was required for expression of functional receptors on the surface of the oocyte. Cyclophilin is required for expression of functional receptors, α-BTX binding sites, and alpha7 antigenic determinants. Cyclophilin is not required for expression of the hetero-oligomeric muscle nicotinic receptor. Studies with mutant forms of cyclophilinA and CyclosporinA derivatives demonstrate that the requirement for cyclophilin is independent of the known immunosuppression pathway and involves either the chaperone or isomerase activity of this molecule. Co-expression of the alpha7 subunit with the muscle nicotinic receptor subunits removes the requirement for cyclophilin and the delta subunit alone can supply this function. We have made chimeras between alpha7 and the muscle delta subunit to explore the basis for the rescue by the delta subunit. The requirement for cyclophilin is not unique to the alpha7 homo-oligomeric receptor; expression of the 5HT3 receptor is also sensitive to CyclosporinA.

22.04 TACHYKININ RECEPTOR - SELECTIVE ANALOGS

Z. Selinger[1], R. Goldsmit[1], D. Halle[1] and M. Chorev[2] Dept. of Biological Chemistry[1] and Pharmaceutical Chemistry[2], Hebrew University of Jerusalem 91904, Israel.

To date more than 20 naturally occurring substance P-related tachykinin peptides have been characterized, yet all of them show only modest receptor selectivity for the three tachykinin receptors that have been identified. We have reasoned that development of receptor selective peptide analogs should be carried out by structural modifications that neither evolution nor recombinant DNA technology can achieve. We have therefore concentrated our efforts on modification of the peptide backbone. Of the many modifications that we have tested N-alkylation proved to be remarkably successful. Systematic N-methylation of each of the peptide bonds in the C-terminal hexapeptide of substance P resulted in some cases in remarkable selectivity toward a particular receptor subtype. These experiments culminated in the development of two peptide analogs with extreme receptor selectivity (by five orders of magnitude): Senktide: Succinyl-[Asp^6, N-methyl Phe^8] SP6-11 with selectivity for the NK-3 receptor and Septide: Acetyl-[Arg^5, Pro^9] SP6-11 with selectivity for the NK-1 receptor. The application of these receptor-selective analogs for dissection of complex physiological responses and further modification which confer on the peptide metabolic stability will be described.

23. Symposium: Computer vision and robotics meet the neurosciences

23.01 Abstract not received

23.02 Abstract not received

23.03 Abstract not received

23.04 Abstract not received

24.01 THE ROLE OF OXIDATIVE STRESS IN THE ETIOLOGY OF PARKINSON'S DISEASE.
B. Drukarch*, J.C. Stoof, C.H. Langeveld, Dept. Neurology, Research Instit. Neurosciences Vrije Universiteit, Amsterdam, The Netherlands

The preferential loss of nigral dopamine (DA) containing neurons in Parkinson's disease (PD) is assumed to be related to the high exposure of these cells to reactive oxygen species, released during normal metabolism of DA (e.g. hydrogen peroxide). This hypothesis is supported by autopsy data showing a consistent increase in the indices of oxidative damage in the substantia nigra of PD patients. The earliest of these parameters and most specific for the disease process seems to be a lowering of the level of glutathione (GSH). Earlier studies showed that brain GSH is mainly contained in astrocytes, thereby suggesting a defect in glial function as a causative factor in PD. In contrast, using a combination of biochemical and immunocytochemical techniques in primary culture, we found that both neurons (including DAergic) and astrocytes synthesize large amounts of GSH. Moreover, our data indicate that GSH metabolism plays an important role not only in the astrocyte mediated protection of DAergic neurons against oxidative damage, but also in astrocyte mediated stimulation of DAergic neuronal survival and outgrowth. Thus GSH, through as yet unknown mechanism(s), seems to be an important mediator of astrocyte induced changes in the function of DAergic neurons.

24.02 NEW PHARMACOTHERAPEUTIC STRATEGIES IN PARKINSON'S DISEASE
P. Jenner*. Neurodegenerative Diseases Research Centre, Pharmacology Group, King's College London, Manresa Road, London SW3 6LX, UK.

The treatment of Parkinson's disease centres on the use of L-DOPA and D-2 dopamine agonist drugs. However, long-term complications of therapy, including psychosis and the loss of drug efficacy, result in poor disease control. However, a number of therapeutic advances are being developed and these include:-

1) COMT inhibitors
2) D-1 dopamine agonists
3) Adenosine A2a antagonists
4) Glutamatergic antagonists
5) Transdermal drug administration

The advantages and disadvantages of these novel approaches to the treatment of Parkinson's disease will be discussed. It may become possible to provide better control of motor symptoms, to prolong drug action, to avoid or reverse the onset of dyskinesias and to use non-dopaminergic approaches to the illness.

24.03 SPECT IMAGING OF THE DOPAMINE TRANSPORTER: POTENTIAL DIAGNOSTIC TEST FOR PARKINSON'S DISEASE.
R. Innis*, J. Seibyl and K. Marek. Yale University and VA Med. Ctr./116A2, 950 Campbell Ave., West Haven, CT 06516 USA

We have evaluated a new radiotracer, [^{123}I]ß-CIT (2ß-carboxymethoxy-3ß-(4-iodophenyl)tropane), which labels dopamine transporters and can be imaged with single photon emission computed tomography (SPECT).

PD patients show markedly abnormal striatal uptake, more pronounced in putamen than caudate, with larger decreases on the side contralateral to the side of greatest motor impairment. In a sample of eight PD patients with exclusively unilateral symptoms, all eight patients showed decreased striatal uptake on both the contralateral *and* ipsilateral sides compared with age and gender-matched controls suggesting [^{123}I] ß-CIT SPECT may be sensitive to changes in dopamine binding sites occurring prior to the onset of motor symptoms. A further study of 28 l-DOPA-responsive idiopathic PD patients and 27 healthy controls underwent SPECT brain scans at 18, 21 and 24 hr after injection of [^{123}I]ß-CIT. In the healthy controls,the striatal uptake demonstrated age-related decreases in striatal uptake of 7% per decade. In the PD patients age-corrected striatal activity were correlated with disease severity. PD patients demonstrated greater reductions of uptake in putamen than caudate and greater contralateral/ipsilateral striatal asymmetry.

These data suggest [^{123}I]ß-CIT SPECT has utility as a clinical tool for the early diagnosis and serial monitoring of idiopathic PD.

24.04 CELL TRANSPLANTATION AND GENE THERAPY IN PARKINSON'S DISEASE.
O. Lindvall*, Restorative Neurology Unit, Department of Neurology, University Hospital, S-221 85 Lund, SWEDEN

More than 150 patients with Parkinson's disease (PD) have been grafted with human fetal mesencephalic tissue in the caudate nucleus and/or putamen. Minor to moderate alleviation of motor symptoms has been reported in almost all patients, but the mechanisms of improvement are unknown in most cases. Using positron emission tomography (PET), significant increase of [^{18}F] fluorodopa uptake in the grafted striatum has been demonstrated in about 20 patients. This is most likely due to survival and growth of the grafted dopamine (DA) neurons. Repeated PET scans and clinical assessment in two PD patients with unilateral putaminal implants have indicated that grafts can survive and have functional effects at least for 5 years, but that the graft-induced improvement is counteracted by degeneration of the patient's own DA neurons. Further improvements of the symptomatic relief are necessary before neural grafting should be performed in a large number of patients. Increased DA neuron survival and reinnervation volume, more complete engraftment bilaterally in both the caudate and putamen, and development of alternative sources of donor tissue, e.g., genetically engineered cells, represent some of the current research strategies for the further development of a transplantation therapy in PD. Before any clinical trials with dopamine-producing, genetically engineered cells can be carried out, it remains to be demonstrated in animals, that the long-term capacity of these cells to reverse functional deficits relevant for the human disorder is comparable to that of fetal neurons.

25. Symposium: Intracellular traffic and targeting

25.01 POLARIZED TRANSPORT OF PROTEINS TO THE CELL SURFACE IN NEURONS AND EPITHELIAL CELLS
Frank Lafont, Klaus Fiedler, Elina Ikonen, Carlos Dotti and Kai Simons
European Molecular Biology Laboratory. Cell Biology Programme. Postfach 102209. 69012 Heidelberg. Germany

A hallmark of epithelial cells and neurons is their highly polarized cell surface. To maintain the functionally specialized plasma membrane domains, membrane constituents are segregated into different carrier vesicles which are specifically delivered to the cell surface domains. Increasing evidences suggest that there are common features in the molecular mechanisms involved in vesicular transport processes in the different compartments of epithelial cells and neurons. For instance, the vectoriality of transport of membrane proteins in epithelial cells and neurons has shown similar characteristics: several proteins targetted apically in epithelial cells are targetted towards the axon in neurons, whereas those with a basolateral fate in epithelial cells are targetted to the dendrites.

However, our recent results show that the molecular machineries involved in vesicular transport in epithelial cells and neurons also show some significant differences. We have recently identified a new annexin isoform, annexin 13b, as the most enriched protein in the apical exocytic vesicles in MDCK cells. Moreover, this annexin was shown to be involved in the transport of membrane proteins towards the apical surface. So far, no annexin 13b has been identified in neurons. On the other hand, recent data provides ecvidences that the MDCK cognates of the NSF-SNAP/SNARE machinery found in synaptic vesicles are not invoved in apical trafficking. Therefore, integration of the two molecular mechanisms by studying the role of annexins in the axonal pathway should bring new clues about the general paradigm proposed for vesicular docking and fusion.

25.02 TRAFFICKING AND METABOLISM OF AMYLOID PRECURSOR PROTEIN IN MDCK CELLS AND HIPPOCAMPAL NEURONS.
B. De Strooper*, M. Simons, F. Van Leuven, K. Beyreuther and C. Dotti
CME,univ.Leuven, Belg; ZMBH univ.Heidelberg;EMBL Heidelberg, Ger.

Amyloid precursor protein (APP) is the precursor of bA4 peptide, the major component of the amyloid plaques typical of Alzheimer's Disease (AD) patients. One of the predilection sites for these plaques is the hippocampus. We have thus investigated human APP processing in rat hippocampal neurons using recombinant Semliki Forest Virus coding for human APP and for APP containing the clinical mutations associated with AD.

APP trafficking and metabolism were studied by immunofluorescence microscopy and biochemical methods. In addition, the polarised sorting of APP in neurons was compared to its sorting in MDCK cells. It is demonstrated that APP in neurons is transported axonally and in MDCK cells basolaterally, which suggest that APP is sorted by a distinct sorting mechanism , different from other axonally transported proteins such as HA. The metabolism of APP in neurons is complex and occurs along different metabolic pathways, in accordance with the observed complex trafficking of APP in neurons. Several new aspects of the aberrant metabolism of APP mutants associated with AD will be represented as well.

25.03 SPHINGOLIPID TRAFFICKING IN NEURONS

Anthony H. Futerman, Dalia R. Abrams, Swetlana Boldin, Koret Hirschberg, Andreas Schwarz, Anat Sofer and Rivi Zisling.
Department of Membrane Research and Biophysics, Weizmann Institute of Science, Rehovot 76100, Israel.

Sphingolipids (SLs), particularly the sialic-acid containing glycosphingolipids (gangliosides), are major components of neuronal membranes where they have been postulated to play a variety of important functions. We are studying SL metabolism and intracellular transport with a view to understanding how these processes are regulated during neuronal development. Inhibition of SL (ceramide and glucosylceramide) synthesis causes a reduction in the length of the axon plexus in cultured hippocampal neurons by inducing the retraction of collateral axonal branches, and blocks the ability of laminin to stimulate axonal growth. However, there is no apparent effect on dendrite development. In contrast, inhibition of SL (glucosylceramide) degradation stabilizes the formation of new collateral axonal branches. We have also observed that the acquisition of new memories in adult rats, analyzed by a conditioned taste aversion behavioral paradigm, is blocked upon injection of an inhibitor of ceramide synthesis directly into the gustatory cortex. Possible mechanisms to explain how SLs mediate these effects on neuronal development and plasticity will be discussed.

We have also analyzed the internalization of SLs from the neuronal cell surface. Cholera toxin (CT), which binds to endogenous ganglioside GM1, is internalized by vesicular transport to the Golgi apparatus in hippocampal neurons. Transport can be blocked by cationic amphiphilic drugs, which had previously been shown to inhibit receptor recycling by disrupting the assembly/disassembly of clathrin at the plasma membrane and on endosomes. The rate of internalization of CT to the Golgi apparatus decreases as neurons mature. In addition, the internalization of a short-acyl chain fluorescent derivative of GM1 to endosomes decreases in axons during development, but is unchanged in dendrites. These data suggest that flux through the endocytic pathway is regulated during neuronal development.

25.04 MOLECULAR INSIGHTS INTO THE FORMATION OF NEUROSECRETORY VESICLES

Wieland B. Huttner
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Three types of neurosecretory vesicles exist, (i) secretory granules which store neuropeptides, (ii) synaptic vesicles which contain classic neurotransmitters, and (iii) small dense core vesicles which contain biogenic amines.

Secretory granules originate from the trans-Golgi network (TGN). Sorting of secretory proteins to these vesicles involves their selective aggregation induced by the lumenal milieu of the TGN, and the recognition of signals by specific membrane components. The cytoplasmic machinery mediating secretory granule formation includes cytosolic phospho-proteins, classical heterotrimeric G proteins and a novel "extralarge" G protein, XLαs.

Synaptic-like microvesicles of neuroendocrine cells originate from early endosomes. The biogenesis of these vesicles is independent of that of secretory granules.

Small dense core vesicles are a hybrid of the synaptic vesicle and the secretory granule membranes.

Recent progress in the identification of the components and mechanisms involved in the biogenesis of these vesicles will be presented.

TUESDAY

26. Symposium: Brain mechanisms involved in face processing

26.01 FACIAL ELECTROMYOGRAPHIC RESPONSES TO FACIAL EMOTIONAL EXPRESSIONS. J.K. Hietanen 1* and V. Surakka 2. 1. Inst. Biomedicine, Dept. Physiology, P.O. Box 9, FIN-00014 Univ. Helsinki, Finland. 2. Dept. Psychology, Univ. Tampere, P.O. Box 607, FIN-33101, Tampere, Finland.

A human face contains information not only about one's identity, but also about one's emotions. There is a number of facial expressions which are considered to be elicited by certain experienced emotions universally. In this study we were first interested to study whether seeing a static facial expression can induce a compatible emotion in the observing subject as indexed by his or her own facial expressions. The second issue related to the existence of two different types of smiles. Genuine pleasure is associated, not only with muscle activity in the cheek region, but also in the periocular region, whereas pretended pleasure (social smile) leads to the activation of the former muscle group only. Thus, we investigated whether seeing an expression of genuine pleasure induces a different facial expression in the subject than a social smile.

In order to detect subtle changes in the subjects' facial expressions we recorded facial electromyography from the periocular and cheeck muscle regions while the subjects were viewing pictures of faces with a neutral expression, social smile and genuine pleasure expression. Subjective experiences of emotions were also requested. The results showed that both types of smiling faces elicited enhanced muscle activity in the periocular region as compared with the activity elicited by the face with a neutral expression. Moreover, the expression of genuine pleasure elicited stronger activity than a social smile in both recorded muscle regions. The periocular muscle activity differentiated between subjects ranking high and low in the subjective feeling of pleasure. It is concluded that other peoples' emotional states as expressed and transmitted by their facial expressions are contagious and that seeing an expression of genuine smile induces stronger feelings of pleasure than seeing a face with a social smile.

26.02 NEUROPSYCHOLOGICAL STUDIES OF FACE PROCESSING IN MAN AND MONKEY. A. Cowey*. University of Oxford, Department of Experimental Psychology, Oxford, UK.

In terms of its anatomical connexions, its position in a topological representation of cortical visual areas, and the receptive field properties of many of its cells the rostral inferior temporal cortex of macaque monkeys is a higher order visual area. Many of its cells respond selectively to faces or parts of faces and perhaps even to the identity of faces. Such observations suggest that this region could be the "face-cell area" and that it is the destruction of a functionally similar region in the human brain that leads to selective disorders of facial recognition. This hypothesis was tested by measuring facial discrimination and recognition in monkeys in which the region had been removed bilaterally (Heywood and Cowey, Phil. Trans. Roy. Soc. B, 335, 31-38). Any impairments were slight, in contrast to the severe impairments on the same and similar tasks shown by prosopagnosic patients. Nor were they specific for faces. When present they were just as prominent for non-facial shapes (Eacott et al., Neuropsychologia, 31, 609-619). On the other hand the monkeys were impaired at discriminating the angle of gaze in pictures of faces or in only those parts of the face that included the eyes. The "face-cell area" could be important in perceiving visual social signals, including facial expression and clues to intentions as well as direction of gaze, rather than the identity or familiarity of particular faces. The latter may be disturbed by more ventral and medial brain damage, as suggested by many studies of the locus of the brain damage in patients with prosopagnosia and by functional neuroimaging studies in normal subjects while they are carrying out tasks of facial recognition.

26.03 VISUAL PROCESSING OF HUMAN FACES

H. Spekreijse*, B. Blum, A. van den Enden and D. Reits. The Netherlands Ophthalmic Research Institute, P.O. Box 12141, 1100 AC Amsterdam-ZO, The Netherlands

There is MEG evidence for a presumably posterior parietal component in the human face response (Hämäläinen et al., 1991). We used face stimuli that varied in attributes like rotation and item displacement and recorded the VEPs from up to 12 striatal, peristriatal and parietal scalp locations. Similar VEP changes were observed in angular and supramarginal leads to both rotation and face item displacement but not in striatal leads. Since these changes were around 60-80 ms and significantly shorter ($p<0.01$) than the striate response, a fast pathway seems to be involved in early judgments of relative spatial position and object orientations, probably related to inferior parietal lobal response.

26.04 ACTIVATION OF HUMAN HIPPOCAMPAL FORMATION DURING MEMORY FOR FACES: A PET STUDY

Dr N Kapur
Wessex Neurological Centre, Southampton, England

Functional brain imaging studies of memory for faces are reviewed. Allowing for activation of posterior brain areas as a result of the perception of faces, there is evidence for specific right and left temporal lobe activation in faces memory tasks, both in episodic memory and in semantic memory tasks. Other brain regions appear to be involved to a relatively minor degree. Some findings suggest more specific involvement of lateral or medial temporal lobe structures, and also more specific involvement of anterior temporal lobe structures, though these activations appear to depend on the particular demands of the memory task. It would seem that both temporal lobes may play a part in memory for faces, with specific contributions made by anterior and posterior, and by left and right, temporal lobe structures, according to the task demands of the particular experimental paradigm that is used.

27.01 Abstract not received

27.02 HIPPOCAMPAL CELLULAR CORRELATES TO RATS' SPATIAL LEARNING.

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The hippocampus is important for the learning of spatial relations. The associative properties of hippocampal synapses and the duration of hippocampal short- and long-term potentiation (STP, LTP) have made the latter popular cellular models for mechanisms involved in hippocampus-dependent learning and memory. Nevertheless, it has been difficult to find electrophysiological correlates to behaviourally induced learning. Like STP and LTP, learning through exploration gives increased synaptic field potentials in the perforant path/dentate synapses. However, a large part of this effect is due to a brain temperature increase coupled to the enhanced muscle activity during the exploration. Motor and arousal effects also contribute. On the other hand, if the temperature, motor and arousal effects are subtracted, spatial learning elicits a moderately strong STP-like change in the field potential

We have used two approaches to look for structural changes associated with spatial learning or LTP: *a)* three-dimensional reconstruction of dendritic spines in dentate granule cells based upon serial electron microscopical sections after LTP has been allowed to last for 30 minutes and *b)* a confocal microscopical study of the effect of a period of intense spatial training on the dendritic length, branching and spine density of CA1 pyramidal cells filled with a fluorescent dye. The last method combines sufficient sensitivity with the possible collection of a large sample. In the EM study, we found an increased number of spines, a subset of thicker spine necks and an increased number of bifurcating spines. In the confocal study, adult rats which were trained spatially to show faster spatial learning than two control groups showed about 10 per cent higher overall spine density compared to the two other groups. These purely behaviourally induced changes were mainly expressed in a subset of CA1 pyramids.

27.03 COMPUTATIONAL MODELLING OF NEUROPSYCHOLOGICAL SYNDROMES

Tim Shallice SISSA, Trieste, Italy and University College London, Gower Street, London, WC1E 6BT. UK.

Cognitive neuropsychological methods have been very successful at characterising the broad modular structure of the cognitive system. However many aspects of many syndromes are not transparently explained by an account in terms of a pattern of differential degrees of impairment across subsystems. It will be argued that connectionist modelling provides a promising complementary theoretical approach. It will be applied to three syndromes - deep dyslexia, optic aphasia and graphemic buffer disorder.

28. Oral Session: Neural disorders

28.01 MOLECULAR EFFECTS OF ABNORMAL PRION PROTEIN ON PRIMARY CULTURES OF MOUSE ASTROCYTES

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The pathological processes occurring in the central nervous system during Transmissible Subacute Spongiform Encephalopathies (TSE) affect both neuronal and glial cells: the first encounter degeneration, whereas the latter proliferate and hyperexpress a number of specific markers (GFAP, F4/80) and cytokines. The agents responsible for TSE copurify with PrPsc, an abnormal isoform of the host encoded PrP protein (Prion Protein). Direct neurotoxicity of PrPsc has been demonstrated in primary cultures of neuronal cells but its effects on glial cells are poorly known. Therefore, we studied the effect of PrPsc on astrocyte activation. PrPsc was extracted from brains of mice terminally affected with experimental scrapie, strain C506M3, using a SAF technique, and incorporated into liposomes. Astrocytes were obtained from four days old C57BL/6 mice. We investigated by Northern Blot gene expression of GFAP (Glial Fibrillary Acidic Protein), GS (Glutamine Synthetase), PrP and also GAPDH as a standard control. We observed a 5 fold increase in GFAP expression 24 hours after exposure to PrPsc, and a return to initial level at 48 h. A doubling of GS gene expression and a slight increase of PrP gene expression were observed at the same time. No modification was observed with denatured PrPsc. No effect on cell viability or proliferation was observed after two days of exposure to PrPsc.

The evaluation (by Western Blot) of the level of inoculated PrPsc in culture medium and in cells during 4 days following exposure permitted to show that the peak of PrPres associated to the cell fraction was concomitant with the GFAP gene hyperexpression.

These results are consistent with a direct and early action of PrPsc on astrocyte activation, which in turn could contribute to neuronal dysfunction. Wether of not astrocytes are infectable remains to be determined.

28.02 INSULIN PARTIALLY REVERSES DEFICITS IN NERVE BLOOD FLOW AND CONDUCTION VELOCITY IN EXPERIMENTAL DIABETES

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Diabetic neuropathy is a frequent complication of diabetes mellitus. So far no effective treatment is available. Studying the pathogenesis may lead to the development of adequate therapy. Decreased nerve blood flow appears to be a major pathogenetic factor. Previously it was shown that insulin prevents the development of a nerve blood flow deficit in the streptozotocin-diabetic rat. The present study sought to determine the effect of chronic (one month) and acute (one hour) insulin treatment on an existing nerve blood flow deficit in the streptozotocin-diabetic rat. Sciatic nerve blood flow was assessed with laser Doppler flowmetry. Nerve conduction velocity, resistance to hypoxic conduction block and nerve sugars and polyols were measured in addition to blood flow. Treatment with insulin was initiated after one month of diabetes.

One month of insulin treatment significantly ameliorated nerve Doppler flux (NDF) in diabetic rats ($p<0.01$); in untreated diabetic rats NDF was 51% of NDF in control animals, in insulin-treated diabetic rats NDF was 85% of control values. In association with blood flow we found a significant amelioration of both motor ($P<0.05$) and sensory ($p<0.01$) conduction velocity but not of the resistance to hypoxic conduction failure in the sciatic nerve. Moreover, insulin restored both systemic (blood) and local (sciatic nerve) metabolic parameters. In a second group of diabetic rats, acute infusion of insulin led to a significant ($p<0.001$) reduction of plasma glucose values of 47%. The fall in plasma glucose was related to an increase in NDF ($p<0.05$). Sensory, but not motor, nerve conduction velocity was increased after the insulin infusion.

The data indicate that insulin is able to reverse existing deficits in nerve blood flow and nerve conduction velocity in diabetic rats.

28.03 **Contrasting effect of 1,25-Dihydroxyvitamin D3 on astrocytes and glioma cells : induction of glioma cell death**

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1,25-Dihydroxyvitamin D3 (1,25-D3) is a hormone known to control calcemia, and to exert regulatory effects on the production of some lymphokines by blood peripheral mononucleated cells. Our recent work has shown that 1,25-D3 is also active in the brain. It can be synthesized, at least in vitro, by activated microglial cells, and stimulates the production of NGF or neurotrophin 3 by cultured primary astrocytes. Furthermore, the hormone induces in these cells the gene coding for its own receptor, VDR, and a gene coding for a 24-hydroxylase, an enzyme which degrades 1,25-D3. Interestingly, 1,25-D3 exerts a marked cytotoxic effect on glioma cells, which takes place 6 days after a one day treatment with 10^{-9} to 10^{-7} M 1,25-D3. Besides its action on the VDR, NGF or NT3 genes, the hormone causes a DNA fragmentation and induces genes like c-*myc*, gadd 45 or p53, known to be involved in apoptosis. However ultrastructural observations suggest that cell death occurs by a different mechanism. A cytotoxic effect was also observed with analogues of 1,25-D3 which are less active on calcemia. These compounds, therefore, offer interesting promises in the treatment of glioma.

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28.04 CENTRAL ACTIONS OF BOTULINUM NEUROTOXIN.

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Botulinum neurotoxin (BoNT) acts as a blocker of acetylcholine release from presynaptic terminals in the peripheral nervous system. Its has been described that the effects of BoNT on the discharge rate of motoneurons innervating the affected muscle are a consequence of neural disconnection from its natural muscle-fiber target, in a way similar to the effects produced on motoneuronal cells by their axotomy. Present experiments were carried out to ascertain whether a single injection of BoNT in a muscle was able to modify the firing activity of motoneurons innervating this muscle and the characteristics of such a modification. In accordance with the 86/609/EEC directive, cats were injected with a single dose (0.003 - 3 ng/kg; lethal dose: 4ng/kg) of BoNT in the lateral rectus muscle and the activity of abducens (ABD) motoneurons (Mns) innervating the muscle recorded extracellularly up to six months after the injection. The activity of ABD Mns was highly modified by BotN (>0.3 ng/kg), but with a pattern different to that produced by their axotomy. In short, 2-5 days after BoNT injection, ABD Mns did not longer modulated their firing in relation to on- or off-directed eye movements. Electron microscopy analyses showed that ABD Mns survived even to the highest BoNT doses, but that doses >1 ng/kg produced the retraction of most terminal boutons from the membrane of the Mn. Even in this situation, ABD Mns showed a low rate (10-20 spikes/s), tonic firing that was not modulated by sensory stimuli of any modality. This tonic firing seemed to depend exclusively on the animal's level of alertness. It is proposed that BoNT may be used as a model to study plastic properties of adult mammal Mns and the basic mechanisms underlying attentive motor responses.

28.05 SPECIFIC INDUCTION OF PKCδ ISOZYME IN FOCAL BRAIN ISCHEMIA

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Protein kinase C (PKC) is a family of enzymes that can be divided into three groups: conventional (cPKC; α β1, β2 and γ); novel (nPKC; δ, ε, η, and θ); and atypical (aPKC; ζ and λ). cPKC activity increases in the rat brain following an ischemic insult, and may be involved in Ca^{2+}-mediated neuronal degeneration. On the other hand, feed-back inhibition of NMDA receptors by PKC may be neuroprotective, and PKC is also involved in trophic factor signalling and regenerative responses of neurons, indicating that PKC activity may also be beneficial to the injured brain. Therefore, we screened changes in the expression of multiple PKC isozymes following temporal focal brain ischemia.

MCA occlusion in halothane-anesthetized rats was produced using an intraluminal suture without craniotomy. The rats were decapitated 0, 1, 4, 12 or 24h, or 3 or 7 days following 30 or 90 min of ischemia. In *in situ* hybridization experiments with oligonucleotide probes mRNA levels of PKCα, β, γ, δ, ε and ζwere found to be decreased in the infarct core 4h, and completely lost 12h following the ischemia. In areas adjacent to the core, PKCδ mRNA was specifically induced 4h following the ischemia, and still 7 days following the insult the infarct core was surrounded by a rim of strong mRNA expression of PKCδ. No other isozymes showed induction. Northern blotting confirmed the spcificity of the induction, and preliminary immunoblotting and immunohictochemical results also indicate that the mRNA induction is followed by an increase in PKCδ protein.

The study demonstrates that isozyme specific PKC gene induction can occur in the injured brain. The selective localization of the PKCδ induction to the penumbra indicates that it is more likely to be involved in neuroprotective responses than neuronal degeneration after ischemic brain injury.

28.06 FOCAL ISCHAEMIA CAUSES A RAPID REVERSIBLE AND REGIONAL SPECIFIC INDUCTION OF COX-2 mRNA.

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Recently maximal electroshock seizures have been shown to cause a marked induction of a mitogen-inducible form of cyclooxygenase, COX-2 (Yamagata *et al.*, 1993, *Neuron* 11:371-386) which is sensitive to MK-801 indicating a potential role for COX-2 as an immediate early gene (IEG). This prompted us to investigate whether COX-2 was also induced in ischaemia where a number of IEGs have been shown to be induced with a distinct time course and similar sensitivity to treatment with MK-801 (Collaço-Moraes *et al.*, 1994, *Stroke* 25:1855-1861). In this study we have investigated whether COX-2 is induced following permanent middle cerebral artery occlusion (MCAO). MCAO was performed by occluding the middle cerebral artery supplying the cerebral cortex with an intraluminal suture introduced through the carotid artery (Nagasawa and Kogure 1989 *Stroke* 20:1037-1043). The brains were then removed, anatomically dissected and frozen in liquid nitrogen. RNA was extracted and quantitated by Northern and slot blot analysis. The effect of MCAO was studied in five brain regions both ipsilateral and contralateral to the occlusion; the 'core' ischaemic area of the cortex in the central region of the middle cerebral artery territory, the immediate surrounding area, frontal cortex, caudate and hippocampus. MCAO caused a large induction of COX-2 mRNA in core ischaemic area of cortex, caudate and frontal cortex. This was rapid in onset and unilateral to the occluded artery. These findings indicate that MCAO causes a profound modulation of COX-2 and other IEGs whose products may be useful in targeting drug treatment.

We are grateful to Bayer for their financial support.

28.07 GLUTAMATE LEVELS AND UPTAKE IN PLATELETS: POSSIBLE PERIPHERAL MARKERS OF EXCITOTOXIC PHENOMENA IN NEURODEGENERATIVE DISORDERS.

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Platelets contain and release glutamate, and present an energy-dependent uptake similar to that described in neurons. Since modifications of glutamate release and uptake have been described in brain samples in degenerative disorders, we aimed to investigate these processes in platelets, as possible peripheral markers of these phenomena.

We first used polyclonal anti-peptide antibodies that specifically recognize EAAC1, GLT-1 and GLAST glutamate transporters (provided by Prof. JD Rothstein, Baltimore, MD) to assess, by Western-blot and electron microscopy coupled with the immunogold method, the type of transporter present in platelets. Uptake experiments were then performed using [^{3}H]glutamate; glutamate content was investigated by reverse-phase HPLC with pre-column derivatization with o-phtaldialdehyde and fluorimetric detection.

Data from platelets of normal volunteers were then compared to those of 34 Parkinson's Disease (PD) patients and 10 age related controls.

Both western blot and the immunogold studies revealed that the neuronal type EAAC1 transporter is present in human platelets.

A significant 80 % increase of glutamate levels was observed in PD patients, compared to controls. The increase was more consistent in patients with normal CT scan, while was variable and not significant in atrophic or ischemic patients. Uptake studies are now in progress to investigate possible mechanisms of increased glutamate levels in these patients.

29.01 THREE-DIMENSIONAL TOMOGRAPHY OF THE BRAIN ELECTRIC ACTIVITY

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Functional imaging of the human brain has developed exponentially during the past years. PET, SPECT and fMRI are supposed to image human brain functions. Besides being costly and invasive they have the limitation of a poor temporal resolution in the order of seconds or minutes. They are therefore unable to resolve the millisecond interactions of neural functions. There is only one method that has this time resolution necessary to follow in real time brain functions: the multisensor measurement of the electro-magnetic field on the scalp by means of the electro- or magnetoencephalogram (EEG, MEG). Mapping these fields over time illustrates the fast changes of the neuronal activities in the brain. Up to now, real 3-dimensional tomographies based on these measurements have not been possible due to the non-uniqueness of the inverse problem. Single or multiple source localization's using dipole models of the neuronal activity are commonly used, but they do not result in real 3-dimensional images of the electric activity. We present a new method (Pascual-Marqui et al., Int. J. Psychophysiol. 18: 49-64, 1994), called Low Resolution Electromagnetic Tomography (LORETA). The method is based on the model of synchronized activity of neighboring neurons in the brain. Using this basic neurophysiological constraint, authentic images of the electrically active areas (not point sources) in the whole brain space at each moment in time can be made. We will illustrate this new method with visual and auditory evoked potential data and with cognitive event-related potentials including CNV and P300. The results illustrate the potential capabilities of the new method as a tool for real-time imaging of human brain functions.

29.02 EARLY DETECTION OF ISCHAEMIC LESIONS AND OF THE PENUMBRA ZONE BY MRI IN THE RAT BRAIN.

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The early detection of the ischaemic focus and of the surrounding cerebral parenchyma, the penumbra, is of utmost interest for the diagnostic and the future therapeutic treatment. We show here that the injection of a superparamagnetic contrast agent, AMI-227 (200 µmol Fe/kg, i.v.; Guerbet, Aulnay Sous Bois), having a long blood half life, may be : 1. useful for an early detection of the lesion using a T2 weighted sequence, and 2. when used with a DW sequence it may lead to the detection of the penumbra. Ischaemia was induced by middle cerebral artery occlusion (MCA-o). MRI was performed with a 2.35 T horizontal magnet (MSL, Bruker) and a spin echo T_2 weighted (TE=80 ms, TR=2,000 ms, e=1 mm, matrix=128*128, FOV=3 cm) and DW (b=1,200 s.mm^{-2}) sequence. Two ml/kg of AMI-227 were injected in the saphena 50 min after MCA-o. The T2 weighted images were hypointense because of the presence of the contrast agent in the vasculature giving a relatively more intense signal (35.1±7% higher) in the hypoperfused zone. DW images, obtained after the injection of the contrast agent, showed a much higher contrast between the hyperintense lesioned tissue and the hypointense unaffected tissue. The surface of the lesion after the injection was, however, smaller than that before the injection. This suggests that the difference between DW images after and before the injection may give the extension of an oedematous zone where blood circulation, although reduced, is still possible, i.e. the "penumbra" zone.

29.03 THE INTERACTION BETWEEN MOOD AND COGNITION STUDIED WITH PET

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Although depressed mood is characteristic of depressive disorders, its relationship to cognitive and motivational dysfunction in this condition is not clear. We used a mood induction technique to investigate the functional anatomy of emotion in normal subjects and the interaction between mood and cognitive function.

Methods: Elated or depressed mood was induced in 9 male volunteers by a combination of music and a modified Velten technique. Significant mood change occurred in all subjects, measured by the PANAS rating scale. 12 scans were performed using a bolus infusion of $H_2{}^{15}O$. Subjects performed verbal fluency or repetition tasks during scanning in an AB design. Mood induction material was presented in the interval before each scan in 3 counterbalanced blocks of 4 scans in depressed, neutral and elated mood.

Results: Compared to the neutral condition highly significant rCBF increases were observed bilaterally in orbitofrontal cortex in both depressed and elated mood compared to the neutral mood condition, activation was also found in the region of the ventral tegmental area and hypothalamus. Cognitive activation in the verbal fluency task compared to repetition was attenuated by depressed mood in left DLPFC, inferior frontal and cingulate cortex .

Conclusions: Elated and depressed mood states are associated with activation of orbitofrontal cortex and associated subcortical structures, activity in distant cortical areas may be modulated activity in this system, through direct cortico-cortical connections or indirectly through subcortical ascending systems.

29.04 DISSEMINATED SCLEROSIS OF THE BRAIN - DIAGNOSIS AND DYNAMIC EXAMINATION BY MRI.

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Purpose. The aim of this study was to define relations between neurological and MRI data, possibilities of MRI in the diagnosis and dynamic examination (6-24 monthes) of brain disseminated sclerosis (DS).

Materials and Methods. All MRI were obtained on the resistive MR-tomograph Tomikon BMT 1100 R23 (Bruker, Germany). The technique of examination was based on three principles - we used: 1). Both T_1-weighted (T_1W) and T_2-weighted (T_2W) MRI; 2). 3 planes: sagittal , axial and coronary; 3). Heavy T_1W MRI for demyelination lesions size determination. This report based on 151 cases (both sexes, 14-70 years old):I group (I gr.)- 69 patients had primary clinical diagnosis "DS"; II group (II gr.)- 82 patients had another diagnosis.

Results. The main specific MRI character of DS was the present of foci with sizes (without edema region) 1-25 mm. This foci were not topical related with brain blood suply basin and had low MRI-signals on T_1W and high - on T_2W MRI. Often diffusion edema of DS foci and lateral brain ventricles was established. MRI had shown that from 151 patients: DS was in 23 (I gr.) and 50 (II gr.) cases (in 8 (I gr.) and 32 (II gr.) cases it was combined with another desease); in 16 (I gr.) cases there was another process; in 30 cases (I gr.) - there was not any lesions (during dynamic examination in 2 cases DS was appeared). In 51 cases during dynamic examination we had seen positive changes.

Conclusion. MRI is effective in diagnosis and dynamic examination of brain disseminated sclerosis. MRI and neurological data correlation was high (0.87).

29.05 HIGH RESOLUTION ^{1}H-NMR SPECTROSCOPY IN CEREBROSPINAL FLUID AND THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM.

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This study was carried out to find new ways in the diagnosis of patients with inherited metabolic disease. Cerebrospinal fluid (=CSF) samples were obtained from 40 neurological patients suspected clinically to suffer from inherited neurometabolic disease. High resolution single pulse ^{1}H-NMR spectra were recorded on a Bruker 600 MHz spectrometer. Protein was removed from the samples and these were routinely concentrated by a factor 3-4. H_2O was replaced by D_2O and the pH was standardized. Quantitative data derived from these spectra correlate well with data measured with existing techniques. Resonances from 26 known metabolites were found in the various CSF samples using ^{1}H-NMR spectroscopy. Furthermore 15 unknown resonances were recorded in these samples. Only six of these were also observed in an earlier study on plasma samples. The other nine may be specific for CSF. Some of the unknowns are present in all CSF samples while others are only found in a minority of cases. The presence of these sporadic unknowns may be related with the age of the patients or with the medication used. Alternatively the underlying disease of the patient may cause their presence. Data are presented on the concentration of betaine in CSF, which is of importance for the remethylation of homocysteine in the brain. Betaine cannot be measured readily with other techniques. Also included in the study were CSF samples from patients with known inborn errors of metabolism. Among these were patients with non-ketotic hyperglycinaemia and histidinaemia respectively. ^{1}H-NMR spectroscopy is characteristically non-selective. It can detect and quantify the majority of H-containing compounds that are present in the micromolar and millimolar range. Therefore it may be possible to find as yet unknown errors of metabolism. In conclusion ^{1}H-NMR spectroscopy can be used to measure quantitatively many metabolites in CSF that are of interest for the study of inborn errors of metabolism.

29.06 NOVEL MRI METHODS IN STROKE RESEARCH.

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Recent developments in magnetic resonance imaging (MRI) have opened up new opportunities for the study of stroke-related brain injury. Novel MRI techniques, like diffusion-weighted (DW) MRI, dynamic susceptibility-contrast MRI and blood oxygenation level dependent (BOLD) contrast MRI, are becoming increasingly important in experimental stroke research and are currently also being adapted for clinical research in stroke.

DW MRI has shown to be a powerful tool for assessing the acute response to ischemia. Retarded diffusion of brain tissue water, presumably reflecting cytotoxic edema, is detected within minutes post-ischemia when damage is still reversible.

Rapid MRI techniques, sensitized to magnetic susceptibility effects, yield information on brain perfusion status. First, the first passage of an intravenously injected bolus of susceptibility contrast agent through the brain vasculature can be tracked with subsecond time resolution. Tracer-kinetic analysis allows estimation of various perfusion parameters (e.g., relative CBV and CBF indices). Second, these techniques are also able to detect differences in blood oxygenation. In this way the vascular response to hemodynamic perturbations (such as during anoxia, hypercapnia or vasodilatation) can be studied providing direct information on autoregulatory response of the brain vasculature.

In conclusion, novel MRI techniques considerably contribute to pathophysiological and pharmaceutical stroke research since they allow for rapid, non-invasive and simultaneous monitoring of several parameters critically involved in the development of brain ischemia.

30.01 SITE DIRECTED MUTAGENESIS OF THE M2 MUSCARINIC RECEPTOR BINDING SITE: EXPERIMENTAL PROBING OF THE THEORITICAL MODEL.
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Recently three-dimensional models of the acetylcholine binding site of muscarinic receptors have been proposed. In brief, the positively charged head group present in all muscarinic ligands, is supposed to form ion-ion interactions with a well conserved negatively charged aspartate. This interaction is stabilized by both hydrogen bonding and the presence of an hydrophobic cleft created by four aromatic residues. In this study amino acids that were postulated to be involved in ligand binding were systematically exchanged to alanine by site-directed mutagenesis in the human m2 muscarinic receptor subtype. The different receptor mutants were then transciently expressed in human embryonic kidney 293 cells and a complete pharmacological and functional characterization was performed.
First results on the aspartate 103 (ion-ion interaction), asparine 404 (hydrogen bonding), and tryptophane 99 (hydrophobic interaction) mutants are in good agreement with the theoretical model. Mutation of those three residues, postulated to be in the binding site, lead to a significant decrease in the affinity of ligands. However, the correct expression of the mutant receptors which show modified and/or no interactions with ligands needs to be assessed by immunodetection techniques. To that aim, constructs harbouring the Flag sequence (D Y K D D D D K) at the N-terminal part of the human m2 receptor were constructed. We have shown that the presence of that tag sequence does not affect the ability of ligands to bind to the expressed receptors when compared with wild type constructs.
These preliminary experimental results demonstrate the qualitative value of molecular models. Nevertheless, further investigation, which are underway, have to be done to validate the theoritical model.

30.02 MUSCARINIC RECEPTORS MEDIATE THE STIMULATORY EFFECT OF ACETYLCHOLINE ON CALCIUM OSCILLATIONS AND RELEASE OF POMC-DERIVED PEPTIDES OF *XENOPUS LAEVIS* MELANOTROPES
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Melanotrope cells of the pars intermedia of *Xenopus laevis* are involved in background adaptation by secretion of α-MSH, a peptide derived from the precursor protein pro-opiomelanocortin (POMC). In this study we have examined the effect of acetylcholine (ACh) *in vitro* on intracellular calcium oscillations and secretion of POMC-derived peptides of the melanotropes of *X. laevis*. Administration of ACh to superfused melanotropes induced a dose-dependent stimulation of the release of radiolabelled peptides. This action of ACh could be mimicked by muscarine but not by nicotine. Pharmacological characterization using selective muscarinic receptor antagonists indicates that the effect of ACh is mediated through a M1 muscarinic acetylcholine receptor. Studies on intracellular calcium in single melanotropes revealed that ACh and muscarine can stimulate calcium oscillations. Nicotine had no effect on intracellular calcium dynamics. Using a monoclonal antibody against the muscarinic receptor in combination with the immunofluorescence technique we demonstrated muscarinic receptor-like immunoreactivity in the pars intermedia. We also studied the possibility that the melanotrope cells are a source of ACh. Dissociated melanotropes incubated in the presence of [^{3}H]choline appear to synthesize [^{3}H]ACh. We propose that ACh in the *Xenopus laevis* pars intermedia serves as an autocrine factor stimulating α-MSH secretion.

30.03 THE NITRIC OXIDE / CYCLIC GMP PATHWAY IN RAT STRIATUM: COUPLED TO GLUTAMATE RECEPTORS ?
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A population of striatal interneurones contain neuronal nitric oxide synthase (nNOS). However, the function of nitric oxide (NO) in the striatum is unclear. We have investigated the coupling of glutamate receptors to NO synthesis and subsequent cGMP production using intact striatal slices prepared from adult rats. Briefly, slices were prepared with a vibroslice and incubated at 37°C prior to the addition of drugs. Slices were inactivated by boiling and the cGMP content measured using a scintillation proximity assay. All experiments were performed in the presence of the phosphodiesterase inhibitor IBMX (1 mM, 15 min). Basal cGMP levels (4.78 ± 0.58 pmol cGMP / mg protein; n = 20 slices) were inhibited by 55 % in the presence the nNOS inhibitor N$^{\omega}$-nitro-L-arginine (3 μM, 15 min) but not by the NMDA receptor antagonist AP5 (100 μM), the AMPA receptor antagonist NBQX (30 μM) nor in the absence of calcium. However, NMDA (2 min exposure) elevated cGMP in a concentration dependent fashion ($EC_{50} \approx 6$ μM). The maximal response was seen at 100 μM NMDA which caused a 2-fold increase in cGMP levels. The response to NMDA (100 μM) was augmented by preincubating with L-arginine (by ≈ 50 % at 30 and 100 μM). Inhibition of the NMDA response was seen both in the presence of AP5 (100 μM) and the nNOS inhibitor N$^{\omega}$-nitro-L-arginine (10 μM, 15 min). Removing extracellular calcium for 5 min abolished the cGMP response to NMDA without affecting the 10-fold increase in cGMP seen with the NO donor nitroprusside (300 μM, 5 min). Application of AMPA (10 μM, 1 min) did not significantly alter the basal cGMP levels. These results indicate that NMDA receptors but not AMPA receptors are coupled to the NO / cGMP pathway in the rat striatum.

30.04 DIFFERENTIAL EXPRESSION OF AMPA RECEPTOR SUBUNITS IN NOS POSITIVE NEURONS OF CORTEX, STRIATUM AND HIPPOCAMPUS.
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AMPA receptor subunits expression was studied in NOS-positive neurons of the adult rat cortex, striatum and hippocampus by a double-labeling approach, combining non-radioactive in situ hybridization and immunohistochemistry.
The majority of cortical and hippocampal NOS-positive neurons were characterized by a predominant expression of GluR-A and -D mRNAs and low or undetectable expression of GluR-B and -C mRNAs. In the striatum all AMPA receptor subunit mRNAs were expressed at low levels; particularly the paucity of GluR-D subunit expression contrasted with its high expression in the hippocampus. A substantial correspondence between mRNA and protein levels was found as revealed by GluR-A and -B in situ hybridization when combined with GluR-A and -B/C immunohistochemistry, respectively. Thus, AMPA receptor subunits expression in NOS positive neurons appears to be differently regulated in specific regions, mainly at the mRNA level. Further evidence for the regional diversity of NOS-positive neurons is derived from our studies analyzing the expression of GAD-65 and -67 mRNAs: NOS positive neurons expressed high levels of GAD-65, but not -67 in the cortex, high levels of both GAD-65 and -67 in the hippocampus and low or undetectable levels of both mRNAs in the striatum.
The different expression profile of AMPA receptor subunits and GAD isoforms in the NOS-positive neurons might be related to their specific function in different neuronal circuits; in particular, different levels of GluR-A and -D subunits might influence the properties of excitatory postsynaptic currents (EPSC) in different areas. Despite their diversity, NOS positive neurons in the three regions share the common feature of low GluR-B expression, suggesting the presence of AMPA receptor channels with high Ca^{2+} permeability, regardless of the regional location.

30.05 Ca^{2+}-DEPENDENT ACTIVATION OF A mGLUR MODULATES THE AMPA-RECEPTOR AND TRANSIENTLY BLOCKS LTP IN RAT PIRIFORM CORTEX.
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In mammalian neurons, the newly established class of metabolically (G-protein)-coupled glutamate receptors (mGluR) mediate slow second-messenger events. They are currently subdivided into three groups (mGluR 1,5; mGluR 2, 3, 8; and mGluR 4, 6, 7) which are linked to two distinct second-messenger pathways: the IP_3/Ca^{2+}/DAG system, and the adenylate cyclase pathway, respectively. We have investigated some properties of mGluRs in the rat piriform cortex.
Intracelluar recordings were obtained from pyramidal neurons in a slice preparation of the rat piriform cortex. Application of 50 μM *t*-ACPD depolarized the membrane, increased the input resistance and evoked membrane oscillations. The iontophoretically evoked AMPA-response increased during and after the application of ACPD, while the NMDA-response increased only during the time course of the depolarization. This suggests that the AMPA-receptor was modulated by a mGluR, while the increase of the NMDA-response was secondary due to the relief of the Mg^{2+}-blockade. AP-3, a blocker of IP_3-turnover in the hippocampus, did not antagonize the ACPD-induced effects. Ni^{2+}, however, a calcium channel blocker, effectively abolished the depolarization and the accompanied membrane oscillations, as well as the increase in resistance and the modulation of the AMPA-receptor.
L-AP4 and ACPD both reduced the field EPSP evoked by stimulation of the lateral olfactory tract. However, after long-term potentiation (LTP) was established (the induction of LTP was not blocked by MCPG), the reduction of the EPSP was much higher compared with control, leading to a transient blockade of LTP. This suggests that the expression of LTP is, at least partially, controlled by a presynaptic mechanism.
We conclude that in rat piriform cortex at least two mGluR subtypes are present which may be located pre-and postsynaptically. Supported by RO1 NS 23807.

30.06 ELECTROPHYSIOLOGICAL CHARACTERIZATION OF SOMATOSTATIN EFFECTS MEDIATED THROUGH DIFFERENT RECEPTOR SUBTYPES ON HYPOTHALAMIC NEURONES IN PRIMARY CULTURE.
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Somatostatin (SRIF) receptor subtypes, mostly sst1 and sst2 (59% and 33% of total mRNAs specific of the five SRIF receptor subtypes respectively) are strongly expressed in hypothalamic neurones, as shown by quantitative PCR. We have investigated possible differential effects of both subtypes on modulation by SRIF of neuronal responses to Glutamate (Glu). The effect of octreotide, a specific sst2 agonist, was compared to that of SRIF-14, an agonist common to all subtypes. Neurones from 16 day old mouse embryos kept for at least 17 days in culture were voltage-clamped at -80mV in the presence of 2mM Mg2+ in order to activate only AMPA/Kainate receptors. Glu (5mM) was pressure applied and octreotide (10nM) or SRIF (100nM) were perifused. Octreotide decreased the response to glutamate in 27% of the studied cells (-21±6%). In contrast to the effect of octreotide, that of SRIF was dual : it induced either a 30% increase of the response to glutamate in 27% of the tested cells, or a 30% decrease in the remaining 73%.
These data suggest that the effects of SRIF on glutamate responses are always inhibitory when they are mediated by the sst2 receptor subtype ; in contrast, SRIF when acting by another subtype, possibly sst1, potentiates the glutamate response.

30.07 ALPHA SCORPION TOXINS BINDING ON RAT BRAIN AND INSECT SODIUM CHANNELS REVEAL DIVERGENT ALLOSTERIC MODULATIONS BY BREVETOXIN AND VERATRIDINE

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At least six topologically separated neurotoxin receptor sites have been identified on sodium channels, that reveal strong allosteric interactions among them. We have studied the allosteric modulation induced by veratridine, binding to receptor site 2, and brevetoxin PbTx-1, occupying receptor site 5, on the binding of alpha-scorpion toxins at receptor site 3, on three different neuronal æsodium channels: rat brain, locust and cockroach synaptosomes. We used ^{125}I-AaH II, the most active alpha scorpion toxin on vertebrates and ^{125}I-LqhαIT, shown to have high activity on insects, as specific probes for receptor site 3 in rat brain and insect sodium channels. Our results reveal that brevetoxin generate three types of effects at receptor site 3: 1) Negative allosteric modulation in rat brain sodium channels; 2) Positive modulation in locust sodium channels and 3) No effect on cockroach sodium channel. However, PbTx-1 activates sodium channels in cockroach axon similarly to its activity in other preparation. Veratridine positively modulates both rat brain and locust sodium channels but had no effect on cockroach. The dramatic differences in allosteric modulations suggest structural differences in receptor sites for PbTx-1 and/or at the coupling regions with alpha scorpion toxins receptor sites in the different sodium channels, that can be detected by combined application of specific channel modifiers, and may elucidate the dynamic gating activity and the mechanism of allosteric interactions among various neurotoxin receptors.

30.08 PROPOFOL AND FLURAZEPAM ACT SYNERGISTICALLY TO POTENTIATE $GABA_A$ RECEPTOR ACTIVATION IN HUMAN RECOMBINANT RECEPTORS.

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Propofol (2,6-di-isopropylphenol) is an increasingly popular intravenous general anesthetic which is frequently combined with a benzodiazepine, either to enhance anesthesia or to alleviate anxiety. We have investigated the interaction between propofol and flurazepam on human recombinant $GABA_A$ receptors expressed in *Xenopus* oocytes. Combinations of cRNAs encoding the $\alpha1\beta2\gamma2L$ or the $\alpha2\beta2\gamma2L$ subunits of the $GABA_A$ receptor were injected into *Xenopus* oocytes, and the effects of GABA and modulation of GABA-evoked currents by propofol and benzodiazepines were measured using standard two-electrode voltage-clamp recordings 2-10 days after cRNA injection. Propofol (0.5-20 μM) produced a concentration-dependent increase in membrane currents activated by GABA. When flurazepam (0.5 μM) was combined with propofol, the resulting current in the presence of 3 μM GABA was significantly greater than that predicted from an additive effect. This synergism between propofol and flurazepam was evident over the whole range of concentrations (0.5-20 μM) of propofol examined. There was a strong concentration dependence to this effect; higher concentrations of GABA or flurazepam failed to produce this synergism. In contrast, the cyclopyrrolone derivative, zopiclone, which is classified as a full agonist at the benzodiazepine site of the $GABA_A$ receptor, failed to act either synergistically or additively with propofol. Our studies suggest that the synergism observed between benzodiazepines and propofol *in vivo* can be acounted for by an interaction between these two drugs at the $GABA_A$ receptor. It is also suggested that zopiclone acts at a site which is distinct from the site of binding of classical benzodiazepine agonists, since the

31. Poster Session: Neurotransmitters, modulators, receptors II

31.01 MELATONIN REDUCES POTASSIUM-INDUCED DOPAMINE RELEASE FROM STRIATUM IN THE FREELY-MOVING RAT: A MICRODYALISIS STUDY.

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Melatonin (aMT) has been suggested to modulate motor activity, since this hormone inhibits spontaneous neuronal activity in rat striatum. In order to further characterize the hypothetical inhibitory role of aMT in the striatum, we have studied the effect of aMT on the release of striatal dopamine (DA).

For this purpose male Wistar rats (250-300g) under equithesin anesthesia, were implanted in the right striatum with concentric dyalisis probes 24h before the experiment (length 3mm; diameter 200μm). Following 2 basal samples (sample = 20min, 1.5μl/min; ACSF K^+4mM), elevated K^+ACSF (75mM) was perfused for 3 consecutive 20min periods. aMT (200nM) was also perfused in the 2nd period of K^+stimulation. At the end of the stimulation two more samples were collected.. Analysis of DA and its major metabolites DOPAC and HVA was performed by HPLC-ED.

As expected, 75mM K^+ significantly increased DA levels above basal ($P<0.01$). However, if aMT (200mM) is added to the second K^+ perfusate the effect on DA was attenuated ($P<0.05$), but DA levels still remained elevated from baseline ($P<0.05$). After aMT, DA returned to K^+ stimulation levels. After removing K^+, striatal levels of DA recovered, but DOPAC and HVA increased above K^+ stimulation levels. These results support the inhibitory role of aMT on DA release in the striatum.

31.02 REGIONAL AND ULTRASTRUCTURAL IMMUNOLOCALIZATION OF CU,ZN-SUPEROXIDE DISMUTASE IN RAT CENTRAL NERVOUS SYSTEM.

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Superoxide dismutases (SODs) are a family of metalloenzymes that catalyze the dismutation of $O^{2-\bullet}$ to H_2O_2. Mammalian cells possess three forms of SODs, namely extracellular SOD (EcSOD), manganese SOD (MnSOD) and copper-zinc SOD (CuZnSOD). We examined the immunocytochemical distribution of CuZnSOD in adult rat central nervous system, using an affinity-purified polyclonal antibody (experiments were carried out according to 86/609/EEC).

The enzyme appears exclusively localized in neurons, while no immunoreactivity is seen in non-neuronal cells. The staining intensity is variable, depending on the brain region and the neuron type. High degrees of immunoreactivity are detectable in cortical and hippocampal interneurons, in neurons of the reticular thalamic nucleus, and in Golgi, stellate and basket cells of the cerebellar cortex. Other neurons, namely pyramidal cells of the neocortex and hippocampus, Purkinje and granule cells of the cerebellar cortex, and neurons of many thalamic nuclei show a much weaker staining. Immunoelectron microscopy performed on the neocortex, hippocampus, reticular thalamic nucleus, and cerebellar cortex shows a cytosolic, as well as nucleoplasmic labeling of the positive neurons. Furthermore, single-membrane-limited immunoreactive organelles, measuring 0.2-0.3 μm in diameter, and resembling peroxisomes, are often found.

Our results suggest a differential expression in nervous cells of specific antioxidant enzymatic systems, depending on the cell type (neuronal/non-neuronal) and on the various neuronal populations. Moreover, our data strongly suggest that in nervous tissue CuZnSOD, besides being located in the cytosol and the nucleoplasm, is also present in peroxisomes.

31.03 THE NMDA RECEPTOR CHANNEL COMPLEX: A COMMON SITE OF ACTION OF GENERAL ANAESTHETICS?

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It has been suggested recently that the common mode of action of general anaesthetics consists in a disturbance of short-term plastic processes controlled by the NMDA synapse (Flohr, 1995).

Accordingly, in the present study the activity state of the cortical NMDA system was determined in different forms of general anaesthesia (barbiturate, ketamine, and ethanol anaesthesia) by means of a newly developed autoradiographic technique that allows to quantify the NMDA receptor activation under *in vivo* conditions.

Adult, male Sprague-Dawley rats were anaesthetized by a) ketamine (120-180 mg/kg), b) Na-pentobarbital (90-120 mg/kg), and c) ethanol (4 g/kg). Control animals were awake. [^{3}H]-MK-801 was used as an open channel marker to label the ion channel under non-equilibrium conditions.

[^{3}H]-MK-801 was injected systemically (600 μCi/kg); animals were sacrificed 1 min after administration of the indicator. The brains were rapidly removed and frozen. Frozen sections were washed by TRIS-maleate buffer (pH 7,2) and air-dried. The sections were juxtaposed with [^{3}H]-Hyperfilm (Amersham, Buchler) for 62 days.

Cortical [^{3}H]-MK-801 uptake was significantly different between awake and anaesthetized states. In anaesthesia [^{3}H]-MK-801 binding was homogeneously *reduced* in all cortical areas.

These results indicate that the NMDA system is critically involved in different forms of general anaesthesia. They support the hypothesis that general anaesthetics may have a common operative mechanism: they directly or indirectly affect the functions of the cortical NMDA system.

References

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31.04 ACUTE VIGABATRIN-PHENOBARBITONE INTERACTION IN THE EXPLORATORY BEHAVIOUR OF RATS.

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Vigabatrin (gamma-vinyl GABA an anti-epileptic) is an irreversible inhibitor of the enzyme GABA- transaminase which is responsible for the catabolism of the major inhibitory neurotransmitter **GABA** in the brain. Vigabatrin causes several fold increases in brain **GABA**. Previously, both vigabatrin and phenobarbitone have proved to produce anxiolytic-like effects through enhancement of **GABA**-ergic mechanisms. In the present study, the acute treatment of rats with vigabatrin (100 mg/kg, i.p.) has produced anxiolytic-like effect presented by the increase in the time spent on the open arms of the elevated plus-maze model of anxiety. Whereas phenobarbitone sodium (20 mg/kg, i.p.) increased the locomotor activity in addition to the anxiolytic effect in the same model. However, when these two drugs are used together, both the anxiolytic and the increase in locomotor activities were no longer observed. This is in contrast to the significant potentiation which was observed upon combination of diazepam (1.5 mg/kg) and vigabatrin in plus-maze test. The mechanism involved in the peculiar interaction between vigabatrin and phenobarbitone should be further elucidated, since both drugs are supposed to reinforce the **GABA** hypothesis of anxiety.

31.05 **ACTIONS OF LEAD ON KAINATE RECEPTORS EXPRESSED IN XENOPUS OOCYTES**
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The potent neurotoxin lead (Pb^{2+}) is a blocker of NMDA-activated ion channels. The aim of the present investigation was to analyze the actions of Pb^{2+} on the function of the non-NMDA receptors kainate (KA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) by use of mRNA-injected oocytes of Xenopus laevis.

Membrane currents of oocytes microinjected with mRNA from rats' brains were measured by the two-electrode voltage-clamp technique; holding potential: -30 to -90 mV. Substances were administered by a concentration-clamp device; application time: 60 sec. KA (50 and 100 µmol/l) and AMPA (50 µmol/l) were first administered to the oocytes separately and then simultaneously with Pb^{2+} (0.01-100 µmol/l).

The investigations revealed the following: 1. Pb^{2+} reduced membrane current responses to KA but not those to AMPA. 2. The Pb^{2+} effect appeared with a threshold concentration of about 0.1 µmol/l; at a potential of -70 mV the concentation needed for a 50% reduction of the KA response was more than 50 µmol/l. 3. The reduction of the KA response was reversible and voltage-dependent. 4. The effects of Pb^{2+} was not dependent on the KA concentration used.

The results show that Pb^{2+} is a potent, reversible and selective blocker of KA-activated ion channels. Thus, Pb^{2+} effects on KA-activated ion channels may contribute to neurotoxic symtoms.

31.06 IDENTIFICATION OF ACETYLCHOLINE RECEPTORS ON *HELIX POMATIA* Br NEURONE
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In our previous investigation it was found that acetylcholine (Ach) induced inward current on identified Br neuron of snail *Helix pomatia*. A single electrode voltage-clamp was used in our experiments. Acetilcholine was iontophoreticaly applied. The amplitude if inward current induced by Ach was dose dependent. The effect of Ach blockers : d-tubocurarine (10^{-4}M) and atropine (10^{-4}M) was tested on Ach induced inward current. It was found that both blockers decreased the amplitude of Ach induced current which implied that there were two types of acetylcholine receptors (muscarinic and nicotinic) on Br neuronal membrane. However the atropine effect was more pronounced which sugget that muscarinic receptor type dominated.

31.07 δ-OPIOID RECEPTOR BINDING IN MOUSE BRAIN: DEVELOPMENT OF HETEROGENEOUS BINDING SITES
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In this study we investigated the characteristics of binding sites with which high selective δ-opioid receptor ligands interact in brain homogenates of C57BL mice, of different ages. The analyses of the homologous displacement curves showed high affinity single site binding at all ages for [^{3}H]DELT-II ([D-Ala^2]deltorphin II, Kd = 2.0 nM), for [^{3}H]NTI (naltrindole, Kd = 0.1 nM) and for [^{3}H]DPDPE (Kd = 4.5 nM). There was a significantly higher Kd value for [^{3}H]DELT-I between earliest age (day 10: Kd=1.54 nM) and all later ages (Kd=0.8 nM). The binding capacity (B_{max}) labelled by [^{3}H]NTI was 40% lower than those of [^{3}H]DELT-I, [^{3}H]DELT-II and [^{3}H]DPDPE at all ages. DPDPE produced a biphasic inhibition of specific [^{3}H]DELT-I binding, from 15 days age onwards. The relative percentage of high and low affinity sites was 72% and 28% in 15 days, 69% and 31% in 25 days and 30% and 70% in 60 days old mice. The portions of high- and low-affinity sites recognized by DELT-II in adult mice brain labelled by [^{3}H]DELT-I was 71% and 29%. DELT-I and DPDPE produced monophasic inhibition of specific [^{3}H]DELT-II binding to brain homogenates of adult mice. These data confirm the existence, in the brain of adult mice, of δ-opioid receptor subtypes with different affinities for DELT-II and DPDPE, but the some affinity for DELT-I: there is a late development of a sub-population of δ-sites, recognized by DELT-I, with low affinity for DPDPE.

31.08 THE CELLULAR AND SUBCELLULAR LOCALIZATION OF METABOTROPIC GLUTAMATE RECEPTOR 5a IN THE RAT CEREBELLAR CORTEX
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The cellular and subcellular localization of the inositol phosphate (IP) second messenger linked metabotropic glutamate receptor (mGluR) mGluR5a was studied in the rat cerebellar cortex using preembedding immunoperoxidase and immunogold techniques.

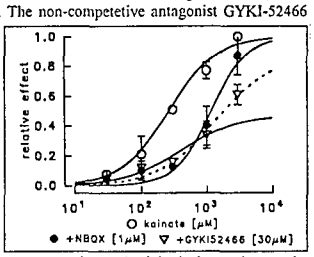
Light microscopic observations revealed an abundant, Golgi-like labeling of a population of interneurons. Although Lugaro, and Golgi cells exhibited the strongest mGluR5a immunoreactivity (ir), some interneurons in the molecular layer were also found to be mGluR5a immunopositive. In addition to a dense plexus of immunoreactive dendrites in all three layers of the cerebellar cortex, axonal processes of mGluR5a immunopositive Golgi cells were also labeled in the granular layer.

At the ultrastructural level strong mGluR5a-ir was present in neuronal elements postsynaptic to axon terminals of different morphology. Using preembedding immunogold method, we found that in the neuropil mGluR5a-ir was in association with plasma membranes, both at the periphery of the postsynaptic specializations, as well as extrasynaptically.

These findings provide further morphological evidence of the involvement of IP-linked mGluR5a within circuits of the cerebellar cortex.

31.09 EXAMINATION OF NBQX AND GYKI-52466 ON KAINATE-INDUCED RESPONSES IN CULTURED CORTICAL CELLS USING A CYTOSENSOR
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The AMPA/kainate-antagonists NBQX and GYKI-52466 were investigated on responses induced by kainate (30 - 3000 µM) in cultured cortical cells. pH-changes from the resulting modulation of the metabolic activity were measured using a Cytosensor Microphysiometer. The results were compared with those of patch-clamp experiments in identical cultures. In the Cytosensor the competetive antagonist NBQX (1 µM) reduced the kainate-induced responses and the concentration/response relation of kainate was shifted to the right; the EC_{50} was changed from 269 µM to 1185 µM. The non-competetive antagonist GYKI-52466 (30 µM) reduced the maximal inducable response of kainate. The non-linear regression through the single data points of kainate 30 - 1000 µM resulted in a curve with an EC_{50} of 399 µM and a maximum of 0.46, which is comparable to electrophysiological experiments. The data points of the experiments with kainate 3000 µM failed to follow the curve (shown by the dashed line). An explanation for this could be that in contrast to electrophysiological experiments the responses in the Cytosensor are the results of a cascade of events (e. g. depolarization, opening of voltage-gated channels, removal of magnesium block) triggered by the the opening of the kainate-gated channel.



31.10 ANXIOLYTIC ACTIVITY OF FLUOXETINE AND ITS INFLUENCE ON MEMORY AND LOCOMOTOR FUNCTION.
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The purpose of this paper is to observe some activities of fluoxetine, the known antidepressant, on some central nervous system functions.

Memory was tested using the inhibitory avoidance test, the anxiolytic activity was investigated using Crowley's "two compartment exploratory test", and locomotor activity was determined in the "PAN-licensed activity meter". Wistar rats, fluoxetine hydrochloride - Eli Lilly and Co (Indianapolis, IN) and MK-801 (Merck, Sharpe and Dohme, Inc. US) were used.

It was shown, that fluoxetine does not influence the memory of the animals. The drug also by itself had no influence on locomotor activity, but it enhanced significantly the hyperactivity induced by MK-801 (on NMDA receptor antagonist). Fluoxetine had a distinct anxiolytic effect, which disappeared, however (in long term experiments) already after 7 days of treatment.

CONCLUSION: the effects mentioned above may participate in the antidepressant activity of the drug.

31.11 LHRH- IMMUNOREACTIVE (IR) NEURONS IN THE NERVOUS SYSTEM OF THE MOLE RAT (*CRYPTOMYS*). QUANTITATIVE ASPECTS.

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Investigated six neonate, juvenile and non-reproductive adult specimens (4f, 2m) of the African mole rat (*Cryptomys* spec.) by cryotomy and immunocytochemistry.

In these animals, some variability is found with respect to the number of „genuine" LHRH-ir neurons (see below). The terminalis nerve (n.t.) comprised 104-239 neurons (average: 162) while in the central nervous system there were 351-964 LHRH-ir neurons (average: 540). In most cases, there was good correspondence between the left and right side as to the number of neurons in the n.t. and brain. The majority of the LHRH-ir neurons were bipolar (average of 74% in the n.t. and of 80% in the CNS) while the rest were irregular in shape.- In three specimens, additional LHRH- immunoreactivity was found in so-called „dark spot" (DS) cells in the parafascicular nucleus (range: 661-1113; average: 836) in the form of 1-3 heavily labeled vacuoles of different size. These vacuoles seem to be restricted to adult non-reproductive animals. The identity of these „spot cells" so far has not been determined.

During the postnatal period, the amount of LHRH-ir material does not show a developmental trend; with the exception of the DS cells, the number of genuine LHRH-ir cells and fibers seems to be more or less constant from the neonate to the adult stage. The DS cells are not found in adult reproductive animals (females); here, the vacuoles are no longer detectable.

31.12 SIMULTANEOUS DETECTION OF TYROSINE-HYDROXYLASE IMMUNOREACTIVITY AND VASOPRESSIN mRNA IN NEURONS OF THE HUMAN PARAVENTRICULAR AND SUPRAOPTIC NUCLEUS.

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Our previous studies indicated that in the developing and adult human paraventricular (PVN) and supraoptic (SON) nucleus a large proportion of neurons are tyrosine-hydroxylase immunoreactive (TH-IR). Using a double immunohistochemical procedure we showed that in the PVN and SON of the neonates the majority of TH-IR neurons contains also vasopressin (VP) while in the adults only few TH-IR perikarya were visualized to colocalize VP (1). Since antemortem factors appear to influence the immunohistochemically detectable amounts of both TH and VP in the human PVN and SON (1)- thus affecting the results of the double immunohistochemical procedure- we further investigated this colocalization by combining *in situ* hybridization for the detection of VP-mRNA with immunohistochemistry for the localization of TH-IR neurons in the same tissue section. Paraffin sections of 4 control cases (2 adults and 2 neonates) were first hybridized with a ^{35}S-labelled oligonucleotide probe for VP mRNA and subsequently stained for TH using avidin-biotin-peroxidase complex and diaminobenzidine as a chromogen. Sections were then dipped in emulsion and developed to detect the labelled probe. By combining *in situ* hybridization for VP mRNA with TH-immunohistochemistry we observed a larger proportion of TH-IR neurons synthesizing VP than that visualized with the double immunohistochemical procedure. In the neonate the number of double stained neurons was much larger than that observed in the adult where many single-stained cells for TH or VP mRNA were evident. Our findings confirm the presence of TH-immunoreactivity in VP-synthesizing neurons of the human PVN and SON (1) and extend this observation to a larger sample of neurons than previously reported.

1. Panayotacopoulou M., Raadsheer F. and Swaab D., Dev. Brain Res. 83 (1994) : 59

Brain material was obtained from the Netherlands Brain Bank , Amsterdam, (coordinator Dr. R. Ravid).

31.13 A ROLE FOR THE NITRIC OXIDE/CYCLIC GUANYLATE CYCLASE SIGNAL TRANSDUCTION PATHWAY IN THE HISTAMINERGIC NERVE SYSTEM OF THE RAT BRAIN

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To investigate a possible role of the nitric oxide/cyclic guanylate monophosphate signal transduction pathway in the histaminergic nerve system, an immunocytochemical method was used. This method visualizes cyclic guanylate monophosphate production in tissue slices. Upon stimulation with histamine an enhanced cyclic guanylate monophosphate production was found in the suprachiasmatic nucleus and the medial preoptic area of the rat brain. This effect was completely abolished when the nitric oxide synthase inhibitor L-nitro arginine methyl ester was applied to the tissue. The nitric oxide donor sodium nitroprusside gave an enhanced cyclic guanylate monophosphate production in the entire section.

These results indicate a role for the nitric oxide/cyclic guanylate monophosphate transduction pathway in the histaminergic signal transduction in the rat brain. However, extensive research is necessary to quantify these effects and to identify the histaminergic receptor subtypes involved in this process.

31.14 DALARGIN ALTERS LH SECRETION WHEN INJECTED INTO THE BRAIN.

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Enkephalin analogue Dalargin (= D-ala$_2$-leu$_5$-arg$_6$-enkephaline) was developed for the use in some clinical cases, e.g. treatment of peptic ulcer disease and skin wound healing. Little is known about its endocrine effects. In a series of experiments we examined Dal effects on LH secretion when it is injected both systemically and intracerebrally. Adult castrated male and female miniature pigs were provided with intrahypothalamic tubings. Animals received one of the following treatments in 2 - 3 day intervals: 30 or 60 ng/2 µl microinjections (mic) of Dal; 10 µg/kg intravenous injections of Dal; 2 µl mic of saline or served as non-treated controls. Blood samples were withdrawn for 90 min before to 180 min after treatments in 10 min intervals. Dalargin mics into the anterior preoptic area and mediobasal hypothalamus resulted in a (P at least < 0.05) decline in plasma LH levels. No dose- or sex-dependent effect was seen. Intravenous administration of Dal also significantly (P at least < 0.05) lowered plasma LH levels. Females reacted to i.v. injections within 10 min. Reaction of males was delayed. Although it remains to be ruled out, whether Dalargin exerts its effect after i.v. application exclusively via receptors within the anterior pituitary, we assume, that its action is mediated via hypothalamic receptors.

31.15 NORADRENERGIC INNERVATION OF CORTICAL MICROVASCULATURE. AN ULTRASTRUCTURAL IMMUNOCYTOCHEMICAL ANALYSIS IN THE RAT VISUAL CORTEX.

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Pharmacological and biochemical data accumulated to date indicate that noradrenalin (NA)-containing neurons in the brain regulate cerebral blood flow and vascular permeability, and influence the availability of the brain energy substrate, via adrenergic receptors present in intraparenchymal microvessels and perivascular astroglia. The present study provides an ultrastructural analysis of the NA fiber system relationships with the intraparenchymal blood vessels in the rat visual cortex. For this purpose, immunocytochemistry with an antiserum against NA was employed. The immunoreaction end product was gold toned according to the gold-substituted silver peroxidase technique.

Electron microscopy revealed that intracortical vascular profiles of various caliber, identified as capillaries and microarterioles, were among the targets of the NA fiber system. A plethora of fine NAergic varicose fibers, closely associated with the blood vessel wall, was identified. Serial section examination revealed that these NA fibers, separated from the parenchymal basal lamina by the intervening perivascular neuroglia, outlined the contours of the capillaries and microarterioles. Contacts between the NA fibers and the capillary endothelial basal lamina or the basal lamina of a pericyte, associated with a capillary endothelial cell, were established at sites where the continuity of astrocytic end feet interrupted. NAergic boutons engaged in such vascular associations were found to measure from 0.4µm to 1.4µm in diameter. No junctional specializations were ever observed between neuronal elements and the parenchymal basal lamina or the interposed perivascular neuroglia.

The present ultrastructural findings may provide the anatomical substrate for the control exerted by the NAergic fiber system over the cerebral cortex microcirculation.

31.16 REGULATION OF THE EXPRESSION OF ß-ADRENERGIC RECEPTORS AND ITS REGULATORY PROTEINS ß-ADRENERGIC RECEPTOR KINASE AND ß-ARRESTIN.

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A general feature of G protein-coupled receptors is that their acute or sustained activation leads to a loss of receptor responsiveness, a process termed desensitization.The ß-adrenergic receptor (ßAR)-adenylyl cyclase system has been used as a prototypic model for the study of the molecular mechanisms of desentizitation. Short-term ßAR regulation involves receptor uncoupling by the regulatory proteins ß-adrenergic receptor kinase (ßARK) and ß-arrestin, whereas long-term modulation is based on changes in protein and mRNA levels. Very little is known about the regulation of the expression of ßAR ,and specially about that of the expression of ßARK and ß-arrestin. In order to explore this issue, we have selected as experimental models primary cultures of rat astrocytes and the rat perinatal period, a physiological situation characterized by a dramatic surge in plasma catecholamines and a active regulation of ßAR in peripheral tissues (García-Higuera I. and Mayor F, jr. (1994). J. Clin. Invest. 93, 937-943).

The mRNA and protein levels of ßARs, ßARK and ß-arrestin have been investigated by a sensitive RNase protection assay and by inmunobloting with specific antibodies or radioligand binding, respectively. Our results show transient changes in the brain mRNA levels of these proteins during the first hours after delivery, which are similar to those observed in cultured astrocytes challenged with ß-agonists. Moreover, the expression of ßARK in a peripheral, highly irrigated tissue such as liver is very high at birth compared to the values attained during postnatal development and in the adult , thus suggesting a very important role for this kinase during the perinatal period. The combined use of these "*in vivo*" and "*in situ*" experimental models may prove useful in order to understand the coordinated regulation of receptors and regulatory proteins and its physiological roles.

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31.17 BEHAVIOURAL AND NEUROCHEMICAL EFFECTS OF EARLY EXPOSURE TO FLUMAZENIL IN FEMALE AND MALE MOUSE PUPS

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Flumazenil (Ro 15-1788), is a benzodiazepine antagonist which has intrinsic properties. Clinically, flumazenil is used to treat overdosing of benzodiazepines and to terminate sedative effects of the agonist when used as a preanaesthetic. This work has examined the effects of two doses of flumazenil (10 and 20 mg/Kg) on several behavioural measures; righting reflex, body weight and body temperature, and on the concentration of different biochemical brain constituents (proteins, cholesterol and phospholipids). Twenty one male and twenty one female mouse pups (1 to 5 days after birth) of the CD1 strain, were used for behavioural measures and 15 animals of each sex, from the same strain, for biochemical determinations. Litters were adjusted to have 3 males and 3 females with an animal of each treatment group (Saline or Flumazenil). The results show that the neonatal administration of flumazenil does not have effects on righting reflex, body weight or body temperature but changes significantly proteins, cholesterol and phospholipid concentrations of the whole brain.

31.18 EARLY POSTNATAL DIAZEPAM (DZ) EXPOSURE FACILITATES PARENTAL BEHAVIOR

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In this work we study the effects of early DZ treatment on the induction of parental behavior, endocrine secretion and its correlation with accesory olfactory bulb (AOB) morphological alterations. Our rationale is as follows: 1) perinatal DZ exposure eliminates morphological differences in the AOB. 2) peripartum progesterone high levels provoque increase in the affinity and decrease in the density of the GABA/BDZ receptors,and prenatal DZ treatment has the same effects on this kind of receptors. 3) the AOB and other vomeronasal structures inhibit induced parental behavior (PB) in rats.

Twenty five male rats divided in two groups. A) Untreated (UT, N=15) and B) 2.5 mg/kg of DZ (DZ, N=10). Maternal behavior (MB) test was initiated at the age of 90 days following the MBR software. After MB test blood samples were collected for analysis and animals were transcardially perfused; olfactory bulbs were removed, histologically processed and mitral cells of the AOB counted.

DZ treatment significantly increased the following MB patterns: nest building quality ($p<0.0001$); contact time ($p<0.04$); percentage of animals reaching sensibilization ($p<0.0001$). Mitral cell number was signifficantly lower in DZ treated males vs. control males ($p<0.002$), while no signifficant differences were found in the plasmatic levels of E2, T, Progesterone, Corticosterone, Prolactine ($p>0.05$ in all cases).

Our results clearly indicate that the increase in the opening frequency of the GABA/BDZ CL^- channels facilitates the induction of maternal behavior. This may be attributed to induced permanent receptor alterations, as no changes have been found in endocrine secretion. Another factor can be the neuronal loss of the AOB, which could not exert its fully inhibitory action of MB.

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31.19 PHARMACOLOGICAL STUDY OF NON-NMDA-INDUCED EXCITOTOXICITY ON RAT MESENCEPHALIC NEURONS.

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Excitatory amino acids have been implicated in diverse neurodegenerative processes. *In vitro*, for example, glutamic acid exerts toxic effects on mesencephalic cultured neurons. We have studied the effects of multiple excitatory amino acid agonists and antagonists with a special focus on the pharmacological aspects of non-NMDA neurotoxicity using [^{3}H]dopamine uptake as an index of cell viability. Cultured rat ventral mesencephalic neurons (from E15 embryos) were exposed to the toxic agent for 24h, and the capacity of the culture to uptake [^{3}H]dopamine was then measured. Kainic acid and domoic acid (100 µM) were the most toxic compounds reducing by 60 and 50 %, respectively, the level of [^{3}H]dopamine uptake. The effect of AMPA or quisqualic acid (100 µM) is by itself very weak (reduction of 15 % of the [^{3}H]dopamine uptake capacity of the culture), but could be potentiated strongly by cyclothiazide (50 and 100 µM). Cyclothiazide did not potentiate the effect of kainic or domoic acid. Competitive, such as YM90K or CNQX (10 µM), as well as non-competitive, GYKI 52466 (100 µM), non-NMDA antagonists are protective against kainic acid- or AMPA + cyclothiazide-induced toxicity. As reported in other models when AMPA is added to kainic acid, the toxic effect of kainic acid is reduced (30 % of reduction in [^{3}H]dopamine uptake instead of 60 %). This model could be useful for the evaluation of excitotoxicity and new neuroprotectors *in vitro*.

31.20 THE GLUTAMATE TRANSPORTER ACTS AS A PRESYNAPTIC RECEPTOR IN PHOTORECEPTORS.

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The glutamate-elicited current in photoreceptors has been attributed to either a glutamate receptor coupled to a Cl^- channel or to a glutamate transporter. We further characterized the current and its physiological role in isolated cones.

Noise analysis of the glutamate-elicited current fluctuations showed that the current is gated by a channel with an estimated single channel conductance of 0.7pS and an open time of 2ms. The channel carries Cl^- because the current reverses at E_{Cl} and is completely suppressed when Cl^- was removed from both the internal and external solutions. The receptor gating this Cl^- current had been shown to have a pharmacology similar to that of glutamate transporters (Tachibana and Kaneko, 1988; Eliasof and Werblin, 1993). We showed further that this receptor has a ionic requirement (Na^+, K^+) similar to that of glutamate transporter. Finally we observed spontaneous pulse-like glutamate-elicited current in isolated photoreceptors that were highly reminiscent of miniature postsynaptic currents.

These observations indicate that the glutamate-elicited current is carried by a Cl^- channel that might be gated by a glutamate transporter. Furthermore they suggest that photoreceptors respond to their own glutamate release. The transporter-gated Cl^- conductance appears therefore to enable photoreceptors to monitor glutamate release in a negative feedback loop.

31.21 CLONIDINE-INDUCED LOCOMOTOR HYPOACTIVITY IS REDUCED BY DEXAMETHASONE IN MICE.

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The effects of dexamethasone pretreatment on clonidine-induced locomotor hypoactivity were investigated in mice. Dexamethasone administered intraperitoneally (1 mg/kg) 15 min before clonidine did not change clonidine-induced hypoactivity, whereas administered 30 or 60 min before clonidine, it reduced clonidine effects in the activity cage. A lower dexamethasone dose (0.1 mg/kg) administered 30 min before clonidine was not able to change clonidine-induced effects, while higher dexamethasone doses (0.5 and 10 mg/kg) reduced clonidine-induced hypoactivity. Dexamethasone administered centrally (1, 5 and 10 ng) 30 min before clonidine was also able to reduce clonidine-induced locomotor hypoactivity. The glucocorticoid receptor antagonist RU-486 administered centrally at the dose of 1 ng did not change clonidine-induced effects, whereas it was able to block dexamethasone effects on clonidine-induced locomotor hypoactivity. These results suggest that dexamethasone effects on clonidine-induced locomotor hypoactivity depend on the central effects that dexamethasone exert *via* the glucocorticoid receptor in the brain.

31.22 CONFOCAL MICROSCOPY ANALYSIS OF EGb 761 EFFECT ON DYNAMIC CHANGES IN IPSILATERAL RETINOGENICULATE FIBRES.

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We studied with a fluorescent tracer (DiI), the setting of terminal retinal arborizations in the dorsolateral geniculate nucleus (DLGN) at 0, 3, 7 and 15 days of postnatal development (D0, D3, D7, D15) in the C57BL/6J mouse. We compared controls and animals which were monocularly deafferented at birth and used the same methods on animals treated with a free radical scavenger (EGb 761, IPSEN France).

The confocal microscopic analysis was focused on the variation of the ipsilateral projections and especially permitted us to follow the growth of individual fibres. At birth, few collateral fibres lead off perpendicularly from the superficial optic tract in direction of the visual neuropil. They are numerous at D3, scarce at D7 and missing at D15. Up until D7, the retinofugal fibres show many varicosities which thereafter start to regress and at D15 are sparse both in the control and deafferented animals. We observe two distinct types of varicosities : large and small. The large varicosities are located on the emergence of collaterals, they increase in the enucleated animals. The small ones are numerous in the visual neuropil, with an increase observed in the animals treated with EGb 761 (100 mg/kg/po). Our results suggest that the size, morphology and location variability of varicosities may be correlated to the remodelling and refinment that occur during the axon development and that EGb 761 may play a role in the axoplasmic transport of cytomembranes concerned by the formation of terminal arbors.

31.23 ATP MODULATES PHOSPHOINOSITIDE-LINKED HYPOXIC SIGNAL TRANSDUCTION IN THE CAT CAROTID BODY

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The carotid body (CB) is a sensory organ that mediates the ventilatory response to hypoxia. Previous work showed that the activity of the phospholipase C degrading phosphatidylinositol-4,5-bisphosphate (PIP_2-PLC) is enhanced in the hypoxic CB. In the present study we investigated whether ATP could be a regulator of the hypoxic PIP_2-PLC enhancement. We addressed this issue by comparing the effects on the PIP_2-PLC of 0 mM, 0.25 mM, and 1 mM ATP added to the homogenate of CB dissected from anesthetized cats preexposed in vivo to the contrasting conditions of normoxia (PaO_2=90 mmHg) and hypoxia (PaO_2=20 mmHg) for 20 min. The PLC activity was assessed from the measured formation of radioactive IP_3 from [^{3}HPIP_2] used as an exogenous substrate. We found that ATP stimulated appreciably the PLC activity over its basal level in the normoxic CB; the effect being stronger at 0.25 mM ATP. The stimulation was about 3-fold greater in the hypoxic CB. We conclude that ATP is a cytosolic regulator of the phosphoinositide-underlain chemotransduction in the carotid body.

31.24 LIPOSOMAL MORPHINE ON INTESTINAL INFLAMMATION IN MICE.

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The aim of the present study was to evaluate the antitransit effects of liposomal morphine (MS-LP) in a model of intestinal inflammation induced by croton oil (CO) in mice. Male swiss CD-1 mice, received 0.05 ml of p.o. CO or saline (SS) 3 hrs prior to the study and gastrointestinal transit evaluated 20 min afterwards with a charcoal meal. In both groups, peak/duration of antitransit effects, potency (ED_{50}) and antagonism by naloxone (NX) were established for morphine (MS) and MS-LP.

Peak effect for MS and MS-LP was 30 and 40 min respectively. MS-LP had an increased and more prolonged effect that MS both in SS and CO groups evaluated by the AUC. The ED_{50}'s of MS and MS-LP (at peak times) in both experimental conditions are shown in the table. The effects of MS and MS-LP were NX-reversible.

GROUP	TIME(min)	SS	CO	RATIO(SS/CO)
MS ED_{50} (mg/kg)	30	1.2±0.06 a	0.42±0.06 b	3.0
MS-LP ED_{50} (mg/kg)	40	1.1±0.08 a	0.12±0.03 c	9.2
RATIO (MS/MS-LP)		1.09	3.5	

Mean values ± SEM. N=10 animal per dose. Different letters indicate significant differences ($p<0.05$) between groups.

Our results demonstrate that the potency of MS-LP is 3,5 higher than that of MS during inflammation, while it has the same potency in control animals. In addition, the presence of inflammation increases the potency of MS 3 times, while that of MS-LP is increased 9,2 times. The results suggest that during inflammation, the uptake or inclusion of liposomal morphine into macrophages could behave as a drug-delivery system to the inflamed sites.

31.25 [3H]NISOXETINE - A NOVEL RADIOLIGAND FOR NORADENALINE (NA) REUPTAKE SITES: CORRELATIONS WITH INHIBITION OF [3H]NA UPTAKE AND LOSS OF NA NERVE TERMINALS AFTER DENERVATION.

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[3H]Nisoxetine has previously been used to label NA uptake sites (Tejani-Butt et al., Eur.J.Pharmac.,191,239.1990). We have compared the potency of monoamine reuptake inhibitors to inhibit [3H]nisoxetine binding and [3H]NA uptake in rat frontal cortex. Also studied was the effect of progressive lesioning of noradrenergic neurones with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) on the number and affinity of cortical [3H]nisoxetine binding sites.

Ki (inhibition constant) values for [3H]nisoxetine binding (1 nM) and [3H]NA uptake (10 nM) were determined using cortical membranes and synaptosomes respectively. For lesioning studies, DSP-4 (10-100 mg/kg ip) was given and 72h later cortices were removed for receptor binding assays. Depletion of cortical NA was determined by HPLC with electrochemical detection (HPLC-ECD). [3H]Nisoxetine binding was of high affinity, fitting a single site binding model and was potently inhibited by the selective NA uptake inhibitors desipramine (Ki 1.6 nM) and protriptyline (Ki 4.2 nM). Good correlation was seen between the ability of 25 monoamine reuptake inhibitors both to inhibit [3H]nisoxetine binding and to inhibit [3H]NA uptake ($r = 0.89$, $p< 0.001$). DSP-4 dose-dependently depleted cortical NA levels (51-100%) with no effects on 5-HT or dopamine. These depletions were associated with a dose-related decrease in [3H]nisoxetine sites (20-97%) with no change in binding affinity. Furthermore, a good correlation existed between cortical NA and binding site number ($r = 0.87$, $p< 0.001$). These data demonstrate that [3H]nisoxetine binds to a single population of homogenous sites associated with the NA transporter complex.

31.26 RELEASE OF AMINO ACIDS IN CULTURED RETINAL CELLS UNDER PEROXIDIZED AND CHEMICAL ISCHAEMIA CONDITIONS

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The effect of ascorbate/Fe^{2+}- induced peroxidation on the release of endogenous amino acids was investigated in retinal cells in culture and compared to the release induced by chemical hypoglycemia and/or anoxia (ischaemia) conditions. In the presence of 5 mM ascorbate/100 μM Fe^{2+}, at pH 6.5, we observed an increase in the release of aspartate, glutamate and taurine, whereas glycine, alanine and GABA release was not significantly affected. K^+-evoked release of aspartate and glutamate was significantly enhanced after ascorbate/Fe^{2+} treatment, whereas no alteration in GABA release was observed. Hypoglycemia and/or anoxia conditions significantly increased aspartate, glutamate and glycine release, whereas taurine, alanine and GABA release was not affected. Hypoglycemia and/or anoxia- induced aspartate release was similar as compared to peroxidized conditions. Peroxidized or ischaemia conditions did not induce cellular depolarization, as determined by the uptake of TPP^+. The Na^+-dependent transporter release for aspartate, glutamate, glycine and GABA was significantly reduced after peroxidation, although it was not affected by chemical anoxia. Moreover, the Na^+-dependent release of alanine and taurine was not affected by peroxidation. These results indicate that aspartate, glutamate, glycine and GABA transporters are significantly affected by oxidative injury. Furthermore, the results suggest that, although free radicals production has been associated to occur during ischaemia conditions, the mechanisms associated with the release of amino acids may be different in both conditions.

31.27 EFFECTS OF IMMOBILISATION STRESS ON ALPHA$_2$ AND BETA ADRENOCEPTORS IN RAT LYMPH NODES AND SPLEEN: AN AUTORADIOGRAPHIC STUDY.

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Changes underwent by α_2 and β-adrenoceptors in both lymph nodes and spleen of immobilisation-stressed rats were studied by means of autoradiographic techniques. Comparisons in binding to each subtype receptor in both lymph nodes and spleen were performed by using rats immobilised for 2 hours, rats that rested for 1 hour after being immobilised for 2 hours and non-immobilised animals.

Autoradiography of β-adrenoceptors was made using [^{125}I] cyanopindolol as a radioligand. The specific β_1 and β_2 adrenergic antagonists ICI 89406 and ICI 118551 respectively were used to characterise the relative binding to these subtype receptors. Propranolol was utilised to determine the non-specific binding. The α_2-adrenoceptors were labelled with [^{3}H] bromoxidine being the non-specific binding determined by using both phentolamine and adrenaline.

No changes in [^{125}I] cyanopindolol binding were found neither in any of the structures studied nor in any of the different subtype β-adrenoceptors while striking drops in [^{3}H] bromoxidine binding were detected in spleen (up to 77%) but not in lymph nodes. The animals that rested for 1 hour after being immobilised also showed a remarkable decrease in [^{3}H] bromoxidine binding values (up to 58%). It is concluded that only circulating cells are involved in the type of stress here studied.

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31.28 DISTRIBUTION OF SEROTONIN IMMUNOREACTIVE FIBERS IN THE MEDIODORSAL NUCLEUS OF THE MACAQUE THALAMUS AND COMPARISON WITH THE PATTERNS OF ACETYLCHOLINESTERASE STAINING

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The mediodorsal nucleus (MD) of the macaque thalamus is biochemically heterogeneous as revealed by acetylcholinesterase (AChE) histochemistry and other markers. In the same vein, previous studies in the squirrel monkey have shown a notable heterogeneity in the distribution of serotonin immunoreactive (5HT-ir) fibers in MD. We have studied the serotoninergic innervation of MD using immunohistochemistry and have compared the patterns of 5HT-ir fibers with those revealed by AChE staining in *Macaca nemestrina*. AChE was selected because it has been proposed as a template marker for analysis of the chemical architecture of the thalamus (Cavada *et al.*, J. Chem. Neuroanat., in press).

The 5HT-ir fibers are morphologically diverse. We have classified them according to their diameter sizes as thick, intermediate and thin. Thick fibers (~1μm in diameter) have no varicosities and show either straight or spiral trajectories. Thin fibers (~0,5μm in diameter) typically show irregular trajectories and varicosities. Intermediate fibers are less numerous and show no varicosities.

Dense plexuses of 5HT-ir fibers are present in all sectors of MD, and no definite correspondences were observed between the distribution and density of the 5HT-ir fibers, and the heterogeneous patterns of AChE activity. Thus, the serotoninergic innervation of the macaque MD is denser and more homogeneously distributed than previously described in primates. Considering the heterogeneous distribution of cholinergic markers in the nucleus, it appears that specific and diverse architectural principles apply to the serotoninergic and cholinergic innervation of MD, suggesting different interactions between these neurotransmitters in the various sectors of MD.

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31.29 HIGH RESOLUTION IMMUNO-LOCALISATION OF A PRESYNAPTIC METABOTROPIC GLUTAMATE RECEPTOR (mGluR) RESTRICTED TO THE SITE OF GLUTAMATE RELEASE IN THE HIPPOCAMPUS.

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The release of glutamate from nerve terminals is depressed by G-protein coupled presynaptic mGluRs. At least 8 mGluRs have been cloned and they differ in their pharmacology and transduction mechanisms, and some of them were found to have a very selective distribution (Baude et al., Neuron 1993. 11, 771; Ohishi et al. Neuron, 1994, 13, 55). In order to gain insight into their roles in the cortical neural network, high resolution immunocytochemical analysis was carried out using an antibody that was developed to an amino acid sequence of mGluR7. The antibody reacted with mGluR7 expressed in cultured mammalian cells, but not with mGluR4 or 6; in immunoblots it recognised 2 closely migrating protein(s) with apparent mol. w. of around 100 kD from brain and an expression system.

Immunoreactivity with antibody to mGluR7 was dense in all dendritic layers of the hippocampus; some elements of the neuropil having a very high density of labelling. Electron microscopic immunogold localisation revealed an exclusively presynaptic distribution of immunoreactivity in hippocampal nerve terminals that formed type 1 (asymmetrical) synapses. *Immunoparticles were restricted to the presynaptic membrane specialisation at the synaptic junctions.* Different populations of glutamatergic synapses differ in the density of presynaptic mGluR7.

In conclusion, the results demonstrate that there is a compartmentalised distribution of mGluRs in the plasma membrane of glutamatergic nerve terminals; mGluR7 immunoreactivity is restricted to the presynaptic membrane specialisation where the receptor may interact with the vesicle fusion apparatus and/or with calcium channels. The restricted and strategic location of some mGluRs to the presynaptic grid suggests that they participate in dynamic changes in the release of glutamate.

31.30 BRAIN MONOAMINE TRANSPORTER GENES IN DIABETES MELLITUS.

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In diabetic animals and in humans, altered neurotransmission in dopaminergic (DA), noradrenergic (NA) and serotoninergic (5-HT) systems have been found in the brain. Synaptic transmission of these monoamines is modulated by membrane transporters, known also as target sites for the action of tricyclic antidepressants and the response to treatment with these drugs is impaired in diabetic animals and in humans. We have investigated the expression of DA-, NA- and 5-HT-transporter mRNAs in the brain of rats with streptozotocin-induced diabetes, using in situ hybridization with ^{35}S labelled synthetic oligonucleotides. With the duration of diabetes, the expression of DA-transporter gene slowly decreses in the substantia nigra+ventral tegmental area and increases in the arcuate nucleus, reaching statistical significance 4 weeks after the induction of diabetes. Over the observed time course of diabetes, the expression of NA-transporter gene is unchanged in the locus coeruleus, increased in the brain stem A1 cell group in 1 week-lasting diabetes and decreased in the brain stem A2 cell group 4 weeks after diabetes induction. The expression of 5-HT-transporter gene in dorsal raphe nuclei gradually increases, reaching statistical significance 4 weeks after the induction of diabetes. Thus, expression of brain monoamine transporters is altered in diabetes mellitus, particularly of longer duration and it is likely to contribute to DA, NA and 5-HT dysfunction and related cerebral disorders seen in long-lasting diabetes mellitus.

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31.31 AMPHETAMINE-INDUCED DOPAMINE RELEASE IN UNILATERAL 2-METHYL-NORSALSOLINOL LESIONED RATS.

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The TIQ derivative N-methyl-norsalsolinol (2-MDTIQ) was found in lumbar cerebrospinal fluid and brains of patients with Parkinson's disease. Since 2-MDTIQ is a methyl-phenyl-tetrahydropyridine-(MPTP)-like compound, the question is raised wether 2-MDTIQ is responsible for cell death in Parkinson's disease.

Female wistar rats were stereotactically lesioned by unilateral injections of 2-MDTIQ (8 µg/3 µl) or 6-hydroxydopamine (6-OHDA, 8 µg/3 µl) into the left medial forebrain bundle (A 4.3; L 1.9; V 3.0). During the following weeks behavioural changes were not observed in 2-MDTIQ treated rats. There were also no differences in spontaneously performed rotations between the groups.

Three weeks after lesioning, application of amphetamine (0.1 mg/kg s.c.) induced only a slight tendency of ipsiversive rotation in sham operated control rats within the first hour. A marked ipsiversive circling was found in 2-MDTIQ and 6-OHDA treated rats (78 ± 4 and 82 ± 3 circlings/min as a percentage of total rotations). In comparison to sham operated rats as well as to 6-OHDA treated rats, the total number of rotations (left and right) was significantly decreased in rats lesioned by 2-MDTIQ. Only in 6-OHDA treated rats a contraversive rotation was induced by apomorphine (0.6 mg/kg s.c.).

These results suggest that (1) 2-MDTIQ affected nigrostriatal neurons leading to a reduction of dopamine release ipsilateral to the lesion and (2) that nigrothalamic neurons, that are responsible for regulation of both nigrostriatal dopaminergic pathways, were also impaired by 2-MDTIQ.

31.32 ALTERATIONS OF AMINO ACID OUTFLOW IN THE LOCUS COERULEUS OF CONSCIOUS RATS BY ACUTE STRESS AND BARORECEPTOR ACTIVATION

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Electrophysiological studies have demonstrated that the activity of locus coeruleus (LC) neurons in conscious animals is increased by various types of stress. On the other hand, baroreceptor activation seems to inhibit LC cells. In the present study we examined directly by push-pull perfusion in conscious rats the effects of cardiovascular and noxious stimuli, as well as that of restraint stress on the amino acid release in the LC.

The LC was perfused with artificial cerebrospinal fluid at a rate of 28 µl/min. The amino acids (AA) GABA, taurine, glutamate (GLU), aspartate (ASP) and arginine (ARG) were quantified in perfusates collected in time periods of 3 min by HPLC and fluorimetric detection. Intravenous infusion of noradrenaline increased blood pressure (BP) by 60 mm Hg. This pronounced baroreceptor activation increased the release rate of GABA in the LC and did not influence the release of GLU, ASP, ARG and taurine. Similarly, a rise in blood volume (30%) by blood infusion enhanced only GABA release rate in the LC. Lowering BP (-50 mm Hg) by intravenous infusion of nitroprusside, as well as a reduction in blood volume (-15%) by haemorrhage led to slight increases in the outflow of GLU and ASP in the LC. GABA, taurine and ARG were not influenced. Tail pinch for 3 min increased the release rates of GLU and ASP profoundly and led to slight increases in GABA and taurine outflow. These effects were strongly attenuated during superfusion with tetrodotoxin (1µM). Immobilization stress for 9 min elevated GLU, ASP and GABA concentrations in the LC perfusates. Only slight, transient increases were observed in the outflow of taurine and ARG.

The results show that baroreceptor activation increases the release of the inhibitory AA GABA in the LC. Noxious stimulation increases preferentially the release of the excitatory AA GLU and ASP. Decreases in BP and blood volume, regarded as physiological stressors, exert only slight effects on LC AA release. On the other hand, strong emotional stress by immobilization increases GLU, ASP, as well as GABA levels in the LC. Hence, various stimuli influence differently the outflow of AA in the LC of conscious rats.

31.33 Abstract withdrawn

31.34 DISTRIBUTION OF NADPH-DIAPHORASE IN RELATION TO CATECHOLAMINERGIC NEURONAL STRUCTURES IN THE BRAIN OF THE LIZARD *GEKKO GECKO*.

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A recent study of the distribution of NADPH-diaphorase (NADPH-D) in a turtle brain (Brüning et al., JCN 348: 183-206, 1994) has revealed that this enzyme is not only widely distributed throughout the brain, but also seems to be colocalized with other classical neurotransmitters, such as catecholamines (CA) and acetylcholine. The main goals of the present study were: 1) to assess primitive and derived traits of the NADPH-D distribution in the brains of reptiles, and 2) to determine sites of colocalization of NADPH-D and TH (as marker for CA). For that purpose, single (NADPH-D) and double staining (NADPH-D and TH) techniques were applied to the brains of four adult gekkos (*Gekko gecko*). The NADPH-D reaction involved an incubation in a medium of 1 mM ß-NADPH, 0.8 nM nitro blue tetrazolium and 0.06% Triton X-100 in 0.1 M phosphate buffer at 37°C for 1-2 h. TH immunohistochemistry was performed, after the NADPH-D reaction, with a mouse anti-TH serum (Incstar, diluted 1:1000, for 48-60 h) and diaminobenzedine (DAB) as chromogen.

The distribution of NADPH-D in *Gekko* was largely comparable to that in turtles which implies involvement in certain functions of this enzyme. Colocalization was observed in numerous cells of the ventral tegmental area and the substantia nigra. In other CA cell groups, e.g. the locus coeruleus, TH immunoreactive cells and NADPH-D positive cells were closely intermingled, but not double-stained. Supported by DGICYT (PB93-0083) and Junta de Castilla-Leon.

31.35 RELEASE AND EXTRACELLULAR METABOLISM OF ATP IN THE RAT HABENULA BY LOW FREQUENCY ELECTRICAL STIMULATION.

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The release and extracellular metabolism of ATP and ADP, the putative central neurotransmitters were studied in the rat habenula by the combined luciferin-luciferase and creatine phosphokinase assay and by high performance liquid chromatography with UV-detection (HPLC-UV). Endogenous ATP is released under resting condition and by low frequency electrical stimulation (2 Hz, 2.5 msec, 360 shock) and ADP the primary metabolite of ATP could be also detected in the effluent. The relative amount of ADP in the total ATP+ADP content decreased after stimulation indicating that the majority of the released compound is ATP in response to stimulation. ATP is decomposed to ADP and AMP in the extracellular fluid by the ectoATPase enzyme as shown by HPLC-UV technique (K_m= 811 ± 68 μM, v_{max}= 23.1±2.75 nmol/min/prep.). Inhibition of voltage-dependent Na^+ influx by tetrodotoxin (1 μM) reduced the majority of the evoked release of ATP. Similarly, ω-conotoxin GIVA (0.01-0.1 μM), ω-Agatoxin IVa (0.05 μM), inhibitors of N- and L-type Ca^{2+} channels and the inorganic Ca^{2+} channel blocker, Cd^{2+} (0.02 mM) exhibited inhibitory effect on the outflow.

In conclusion, our results demonstrate the stimulation-dependent release and extracellular enzymatic breakdown of ATP in the rat habenula and support the electrophysiological observations that endogenous ATP functions as fast neurotransmitter in this brain area.

31.36 CO-LOCALIZATION OF VASOACTIVE INTESTINAL POLYPEPTIDE (VIP) AND γ-AMINOBUTYRIC ACID (GABA) IN RAT CEREBRAL CORTEX.

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Inhibitory local circuit neurons in rodent cerebral cortex use GABA as their main transmitter. In recent years, it became obvious that a large portion of these GABAergic neurons co-localize neuropeptides like somatostatin, neuropeptide Y, among others. It has been hypothesized that such neuropeptides are co-released and exert modulatory effects on GABAergic inhibition. Although several physiological studies have shown that VIP is able to potentiate GABA-mediated inhibition in sensory cortices, no conclusive evidence has been obtained for the co-localization of both substances in rodent cortical neurons. Therefore, we examined this issue with the mirror-section method in series of alternate vibratome sections immunostained with antisera against either VIP or GABA in brains of male rats. The experimental animals were deeply anesthetized with nembutal and perfusion-fixed with a 1% glutaraldehyde/2.5% paraformaldehyde solution. From 104 VIP-immunoreactive neurons encountered so far, all showed co-localization with GABA in the corresponding sections. The cells were mainly of the bipolar/bitufted variety and located in layers II-IV, but also in layers V and VI. The largest sample came from the primary somatosensory cortex (Par1) containing the barrel field. Additional observations in primary auditory (Te1) and secondary visual (Oc2MM, Oc2ML, Oc2L; for nomenclature see: Zilles [1985], The cortex of the rat, Springer Verlag) cortices. These data suggest a complete co-localization of the two neuroactive substances VIP and GABA. Accordingly, the prominent population of bipolar and bitufted VIP-immunoreactive interneurons with their conspicuos columnar dendritic and axonal organization consitutes a subset of the GABAergic interneurons. Such knowledge aids the functional interpretation of the input-output relationships of these VIP-cells we are currently studying. Supported by DFG and OKTA.

31.37 ENHANCED SPECIFIC ANORECTIC ACTIVITY OF THE NITRIC OXIDE SYNTHETASE INHIBITOR, L-NAME, IN OBESE ZUCKER RATS.

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The presence of a nitric oxide synthetase (NOS) was demonstrated in the rat brain. It has been recently shown that administration of NOS inhibitors reduces food intake in mammals. These results suggest that NO might be involved in the mechanisms controlling feeding behavior. To test this hypothesis, we administered L-NAME (L-N^G- Nitro Arginine Methyl Ester) intraperitoneally (IP) and intracerebroventricularly (ICV) at dark onset in obese Zucker rats, a genetic model of hyperphagia and obesity. Lean Zucker rats served as controls. The feeding behavior was recorded via a complete automatic system. L-NAME (IP, 0, 10, 25 and 50 mg/kg) induced a dose-dependent decrease in food intake in the obese rats (Minimal Effective Dose: 0.50 ± 0.06 mg/kg ; Effective $Dose_{50}$: 3.50 ± 0.46 mg/kg), but remained ineffective in the lean rats whatever the dose used. These anorectic properties were well-translated into the picture of the microstructure of feeding behavior. L-NAME (IP) induced decreases in meal duration (-85 %), in meal number (-64 %) and in time spent to eat (-93 %) in the obese rats. In the lean rats, decreases in meal duration (-46 %), in meal number (-44 %) and in time spent to eat (-65 %) were balanced by an increase in meal size (+62 %), leaving food intake unaffected. ICV L-NAME (10 μg) reproduced the same effects in the obese rats, but lean rats still remained insensitive. This study clearly demonstrates that the activity of the NOS inhibitor L-NAME is enhanced in the obese Zucker rat and that this action is most probably located into its brain. This indicates that NO could be implicated into the expression of hyperphagia.

31.38 IMMUNOCYTOCHEMICAL STUDY OF MGluR1a RECEPTOR IN THE PURKINJE CELLS OF MOUSE CEREBELLUM TREATED WITH METHYL AZOXY METHANOL

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Metabotropic glutamate receptor mGluR1a plays a crucial role in the excitatory neurotransmission. This receptor is characteristically present in the dendritic spines of Purkinje cells receiving the massive parallel fiber input. Early postnatal - PN days 0/1 and 5/6 - treatment of developing mice with methyl azoxy methanol (MAM) results in the partial loss of granule cells decreasing also the number of parallel fibers. In the present study we compare the morphological changes and the presence of the mGluR1a receptor in the dendritic spines of Purkinje cells in MAM treated and control mice 30 days PN. The numerical density of the Purkinje dendritic spines was 99.12 ± 18.29 x 10^6 spines /mm^3 in the control, somewhat lower (91.72 ± 12.87 x 10^6 spines/mm^3) in the cerebella of PN 5/6 and moderately increased (109.59 x 10^6 spines/mm^3) of PN 0/1 days treated mice. The density of Purkinje cells was the lowest in the control group (679 ± 49 cell/mm^3) and has significantly increased in both MAM treated experimental groups (PN 5/6 = 952 ± 52 cell/mm^3 and PN 0/1 = 1,287 ± 81 cell/mm^3), respectively. The number of spines belonging to 1 Purkinje cell, however, was reduced by about 33 % in PN 5/6 (96,891 ± 17,129 spines) and by about 37 % in PN 0/1 (91,662 ± 16,662 spines) days treated animals, in comparison to the control (145,680 ± 22,373 spines/Purkinje cell) cerebella, respectively. The proportion of the "vacant" synaptic spines was about 39 % in the controls, was similar in the PN 5/6 days treated mice (42 %) but increased in the PN 0/1 days treated animals (55 %). In the MAM treated cerebella large, climbing fiber-like axonterminals, pleomorf-ovoid vesicle containing axon endings as well as mossy fiber-like terminals appeared, replaceing the missing parallel fiber afferents. The presence of mGluR1α receptor was detected by DAB immunocytochemical method on ultrathin sections. The proportion of the immunopositive spines labelled with electrondense precipitate was the same (about 80 % of all Purkinje spines) both in the treated and in the control cerebella. Although the innervation deficit can be characterised by several morphological changes, the expression of the mGluR1a receptor was not influenced by the reduced glutamatergic parallel fiber input.

31.39 PHARMACOLOGICAL CHARACTERIZATION OF [^{3}H]ZOLPIDEM LABELLED ω_1/BENZODIAZEPINE$_1$ (BZ_1) RECEPTOR SUBTYPES IN THE RAT CEREBELLUM.

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Although a heterogeneity of ω/benzodiazepine (BZ) receptors is generally accepted, the rat cerebellum was thought to contain a homogenous population of the zolpidem-sensitive ω_1/BZ_1 subtype. In view of recent evidence of ω_1/BZ_1 receptor heterogeneity (Ruano et al., Brain Res., 1993 ; Schoemaker et al., Neurosci. Abs. 1994), we now report on their pharmacological identity.

Extensively washed rat (Sprague-Dawley) cerebellar membranes were incubated for 45 min at 0°C with 2 nM [^{3}H]zolpidem in a 50 mM Tris-citrate/200 mM NaCl buffer (pH = 7.4), nonspecific binding defined by the presence of 1 μM diazepam.

In the presence of 0.2 μM GABA , [^{3}H]zolpidem binding was monophasically inhibited by diazepam and triazolam (IC_{50} = 13 and 0.74 nM, respectively). However, inhibition curves by zolpidem (IC_{50} = 2.8 and 64 nM) and CL 218,872 (IC_{50} = 12 and 490 nM) were biphasic, each phase representing approximately 50 % of total specific binding. In the additional presence of CL 218,872 (50 nM) to mask the population of [^{3}H]zolpidem binding sites recognized with high affinity by CL 218,872, residual [^{3}H]zolpidem binding was displaced monophasically (nH ≈ 1) with a pharmacological profile (diazepam, IC_{50} = 25 nM ; CL 218,872, IC_{50} = 180 nM ; zolpidem, IC_{50} = 52 nM and triazolam, IC_{50} = 0.7 nM) similar to that described for the ω/BZ receptor subtype obtained by coexpression of $\alpha_1\beta_x\gamma_2$ subunits of the $GABA_A$ receptor complex (Luddens et al., Mol. Pharmacol., 1994).

In conclusion, the present study shows that in the presence of 0.2 μM GABA, [^{3}H]zolpidem labels a heterogenous population of binding sites in the rat cerebellum, one of which, studied in the presence of 50 nM CL 218,872, may represent the native $\alpha_1\ \beta_x\ \gamma_2$ containing ω/BZ receptor subtype.

31.40 INVOLVEMENT OF NMDA AND AMPA TYPE GLUTAMATE RECEPTORS IN SEGMENTAL SPINAL REFLEXES; AN ANALYSIS IN CATS.

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The relative contribution of AMPA-type and NMDA-type glutamate receptors in spinal segmental reflexes were studied by investigating the effects of specific blockers on polysynaptic and monosynaptic reflexes, in cats. Flexor reflex responses were investigated by electrically stimulating one hind paw and recording responses from the anterior tibial muscle, myographically. In the patellar reflex studies responses were evoked by tapping the patellar tendon with an electronically controlled hammer, and the contractions of the thigh muscle were measured with a force-displacement transducer. Reflex potentials evoked by electrical stimulation of the tibial nerve were recorded directly from the exposed lumbar ventral roots, in spinal animals. Both competitive (NBQX, and LY293558) and non-competitive AMPA antagonists (GYKI 52466 and several other 2,3-benzodiazepines) inhibited flexor reflex responses dose-dependently. A complete blockade was achieved with relatively low doses of the non-NMDA antagonists, while only partial with the competitive NMDA antagonist LY233053 (up to 20 mg/kg i.v.). The effect of the 2,3-benzodiazepine compounds was not antagonized by the benzodiazepine antagonist Ro 15-1788. The ED50 values for inhibition of the polysynaptic flexor and the monosynaptic patellar reflexes by GYKI 52466 were very similar (ED50s: 0.9 and 1.0 mg/kg, i.v., respectively). Also, in the spinal root reflex potential experiments, mono- and polysynaptic responses were inhibited by practically the same doses of the tested 2,3-benzodiazepine AMPA antagonists. We concluded that the role of AMPA receptors in mediation of mono- and polysynaptic reflexes is equally important, and more significant than that of NMDA receptors.

31.41 THE POSSIBLE ROLE OF NITRIC OXIDE IN MEDIATING BEHAVIOURAL ACTION OF SOME NEUROPEPTIDES. Telegdy G*. and Kokavszky K. Department of Pathophysiology, Albert Szent-Györgyi Medical University, Szeged, Hungary

During the last few years it has been shown that some neuropeptides can improve learning and memory formation in different learning tasks.It was shown by us and also be others that most of the peptides can influence their action via neurotransmitters.The new discovery of nitric oxide (NO) as possible transmitter arose the question that whether No can play any role in the action of neuropeptides influencing learning and memory processes. In the present paper the possible role of NO was tested in behavioral action of some neuropeptides. The learning task was a one-way passive avoidance paradigm. The peptide was injected into the lateral brain ventricle immediatelly after the learning task, nitric oxide synthase inhibitor nitroarginine was administered into the lateral ventricle 3o min before the peptide administration. The following peptides were tested: ANP, BNP, vasopressin, and ACTH. Nitric oxide inhibitor in the dose applied did not influence the passive avoiodance learning, however could block or attenuate the facilitated learning caused by ANP, BNP vasopressin or ACTH administration.The results indicate that in the neuropeptide facilitated learning processes No could also be an important mediator.

31.42 DIFFERENTIAL CHANGES IN STRIATAL PREPRODYNORPHIN GENE EXPRESSION AND DOPAMINE RELEASE PERSIST LONG AFTER TWO TYPES OF MORPHINE TREATMENT: CHRONIC VS. INTERMITTENT

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In addition to the acute euphoric effects, drugs of abuse such as opiates and psychostimulants have been known to induce long-lasting behavioral sensitization. The expression of this phenomenon is dependent on the temporal pattern of drug administration (e.g. intermittent versus chronic) and may be involved in the acquisition/maintenance and relapse of drug-seeking behaviour. However, little is known about long-term neuroadaptive processes which may form the neurobiological substrate of these enduring behavioral effects. In this regard, endogenous opioid and mesolimbic dopamine (DA) systems may play an important role. For instance, cocaine treatment has been reported to increase the striatal preprodynorphin (PPD) gene expression and the responsivity of DA neurons. However, it remains unclear whether this involves a long-lasting adaptation and may be generalized to other drugs of abuse such as morphine. Therefore in this study we determined changes in depolarization-induced DA release and PPD gene expression in caudate putamen and nucleus accumbens in male Wistar rats treated intermittently or chronically with morphine.
Our results show that both intermittent and chronic morphine induced an decrease in striatal PPD gene expression and electrically evoked DA release 1 day after the last administration of the drug. However, a clear increase in PPD expression and DA release was found 3 weeks after intermittent, but not chronic morphine. In contrast, DA release was still depressed 3 weeks after chronic morphine treatment with no significant effect on PPD gene expression. These results are discussed in relation to the locomotor sensitizing effects of morphine and suggest that enduring adaptive changes in PPD gene regulation and excitability of dopaminergic neurons may be involved in the long-lasting behavioral effects of drugs of abuse.

31.43 IMMUNOCYTOCHEMICAL EVIDENCE FOR CO-TRANSMISSION BY GABA AND GLYCINE AT INDIVIDUAL SYNAPSES IN RAT SPINAL CORD. A.J. Todd[1]*, R.C. Spike[1], C. Watt[1] and W. Sieghart[2]. [1]Laboratory of Human Anatomy, University of Glasgow, Glasgow G12 8QQ, U.K. and [2]University Clinic for Psychiatry, Department of Biochemical Psychiatry, Währinger Gürtel 18-20, A1090 Vienna, Austria.

GABA and glycine are the main inhibitory transmitters in the spinal cord and many axons show significant enrichment of both compounds, suggesting that they may act as co-transmitters. In order to look for further evidence of co-transmission, we carried out pre-embedding immunocytochemistry on spinal cord sections with antibodies directed against the β3 subunit of the $GABA_A$ receptor and the glycine receptor-associated protein gephyrin, and combined this with post-embedding detection of GABA and glycine. With light microscopy, reaction product corresponding to $GABA_A$ receptor β3 subunit had a punctate appearance in all laminae and at the ultrastructural level it was found to be present mainly at synapses. At most β3-immunoreactive synapses (84 out of 90) the presynaptic axon was GABA-immunoreactive. By using a double-labelling method we were able to show that the $GABA_A$ β3 subunit and gephyrin were sometimes present at the same synapse, and in these cases the two proteins could either be intermingled or else partially separated. At 32 out of 40 synapses where both proteins were detected, the presynaptic axon was enriched with both GABA- and glycine-immunoreactivity. These results suggest that $GABA_A$ and glycine receptors may both be present at certain synapses in the spinal cord, but that they may be at least partially segregated to different parts of the active site. They provide strong support for the suggestion that GABA and glycine act as co-transmitters at some synapses in the spinal cord.
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31.44 CHARACTERISATION AND MAPPING OF OPIOID RECEPTORS IN BRAIN TISSUE AND IN PRIMARY CULTURES BY MONOCLONAL ANTIBODY OF KAPPA-2-SUBTYPE SPECIFICITY

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The majority of published data can be rendered to kappa-1-subtype opioid receptors e. g. pre-synaptic regulation of transmitter release. The recent molecular cloning results did not solved the problem of kappa-1 and kappa-2 receptor subtypes, because pharmacologically the cloned receptors belong to the kappa-1 subtype.
Our laboratory developed a monoclonal antibody (mAb) with established kappa-2 subtype selectivity (KA8, IgG1,k) (J. Neurochem. 56, 1991, 1887). The mAb shows some agonist character, it can effectively displace opioid ligands in radio assays in frog and in chick brain (Neuroscience 58, 1993, 459). Double immunocytochemistry by this mAb and proper cell-markers showed kappa-opioid receptor-like labelling (κ-2-ORLI) on developing neurons and type-2 astrocytes in primary cultures of chick, rat and human by light and electron microscopy. K-2-ORLI was marking neuronal and astroglial plasma-membrane, ribosomes and polyribosomes, sometimes in close vicinity to the membrane. In neurons κ-2-ORLI was present in dendrites to be associated with micro tubules and in synaptic specializations always post-synaptically.
These results show that kappa-2-opioid receptors may play function in developing and adult neurons and glial cells, however, this can be different from that of the kappa-1-opioid receptors with established pre-synaptic localisation, contrary to the post-synaptic, extra-synaptic and glial expression of kappa-2-opioid receptors presented here. To know this function, however, needs further studies.

31.45 COLOCALIZATION OF NPY AND TH IN THE SUPRACHIASMATIC NUCLEUS OF *XENOPUS LAEVIS*

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The South African clawed toad *Xenopus laevis* is able to adjust its skin color to a dark background by releasing α-MSH from the melanotrope cells in the pars intermedia (PI) of the hypophysis. *In vitro* superfusion experiments with neurointermediate hypophyseal tissue revealed that neuropeptide Y (NPY), dopamine (DA), γ-aminobutyric acid (GABA) and noradrenaline have an inhibitory effect on α-MSH release, whereas corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) are stimulatory. CRH and TRH are released from nerve endings in the pars nervosa and are thought to originate from the magnocellular nucleus. NPY, DA and GABA coexist in synaptic contacts on the melanotropes of the PI. Retrograde tracing studies showed that the PI is innervated by projections from the locus coeruleus, magnocellular nucleus and suprachiasmatic nucleus (SC). Furthermore, the SC receives direct input from the retina as was shown by filling the optic nerve with an anterograde tracer. Using immunocytochemistry combined with confocal laser scanning microscopy we identified a small number of neurons located laterally in the SC, close to the optic chiasm, simultaneously stained for NPY and TH. Beside these neurons there are other neurons situated more medially in the SC, close to the third ventricle, stained either for TH or for NPY. With c-FOS immunocytochemistry individual neurons within the SC and in other parts of the brain are being studied that are involved in the regulation of background adaptation. In the PI Fos expression is induced when the toad is transferred from a white to a black background.

31.46 MESENCEPHALIC CELL CULTURE: A USEFUL MODEL TO STUDY METHAMPHETAMINE NEUROTOXICITY.

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The psychostimulant methamphetamine is believed to elicit its action by interacting with the central monoaminèrgic neurons. This stimulant is able to block dopamine uptake potently and to release cytoplasmic dopamine as well. There is also abundant evidence demonstrating the neurotoxic effects of methamphetamine with an extensive damage to dopamine terminal regions. Recent reports indicate that dopamine overflow in some way is responsable for the lesioning action of the stimulant. In order to reach more insight into the mechanism of methamphetamine neurotoxicity we studied the effects of the stimulant on a simple in vitro system such as mesencephalic cell cultures. Methamphetamine at the dose of 100 uM produced a significant increase in lactate dehydrogenase (LDH) activity within the culture medium, indicating a minimal cell lesion. A dose response curve of this effect was obtained and direct correlation with the methamphetamine-induced dopamine release and metabolism was performed on day 5 to 12. Changes in dopamine release and metabolic pattern were observed in cultures with or without glial cells, indicating a substantial role of glia in dopamine disposition and neuronal lesion. Our findings suggest that the tissue culture model of fetal mesencephalic cells provides a useful tool for the study of methamphetamine neurotoxicity

31.47 THE EFFECTS OF LOW DOSAGES D-CYCLOSERINE ON POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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In the past years, interest in the role of excitatory aminoacids and their receptors, like the N-Methyl-D-Aspartate (NMDA) receptor, in the pathofysiology of schizophrenia is rapidly increasing. It has been suggested that stimulation of the NMDA receptor could reduce both positive and negative symptoms of schizophrenia. D-cycloserine is a partial agonist of the glycine recognition site of this receptor. As a partial agonist, the effects of D-cycloserine are twofold: in the lower dose range it acts as an agonist whereas in higher dosages it has antagonistic properties. In this study, the hypothesis will be tested that low dosages of D-cycloserine reduce schizophrenic symptoms. In an open dose-effect study, 10 patients with schizophrenia (DSMIII-R), between 18 and 50 years old, will participate after written informed consent has been given. Following a drugfree period of two weeks, treatment with D-cycloserine is started. After an initial period of 4 days of placebo, D-cycloserine will be given in increasing doses of 15mg, 25mg, 50mg, 100mg and 250mg daily, each administered for 4 days. At the end of each period, patients will be evaluated using the Positive and Negative Symptom Score (PANSS), the Clinical Global Impression Scale (CGI) and the Extrapyramidal Symptom Rating Scale (ESRS). Furthermore, neuropsychological tests will be performed and plasmalevels of D-cycloserine will be determined. Preliminary results indicate that D-cycloserine might reduce negative symptoms of schizophrenia. Further results of this study will be discussed.

31.48 EFFECTS OF γ-MSH-LIKE PEPTIDES ON CARDIOVASCULAR PARAMETERS IN CONSCIOUS RATS: STRUCTURE-ACTIVITY STUDIES.

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The melanotropin γ_2-Melanocyte-Stimulating hormone (γ_2-MSH) causes a dose-dependent increase in mean arterial blood pressure (MAP) and heart rate (HR) after i.v. administration to conscious rats. The recent discovery of melanocortin receptors prompted us to investigate the amino acid sequences within the γ_2-MSH structure essential for potency and intrinsic activity with respect to the effects on MAP and HR.

Several γ-MSH analogues containing the MSH-core (=γ-MSH-(5-8)=His-Phe-Arg-Trp), and varying in the length of the C- and N-terminal part of γ_2-MSH were i.v. administered to conscious rats, and MAP and HR were measured. In addition, the cardiovascular effects of the endogenous γ_2-MSH, Lys-γ_2-MSH, were investigated. The ED_{50}- and E_{max} (α) values were used to express the degree of potency and intrinsic activity, resp.

The MSH-core and γ-MSH-(3-8) had a slight effect on MAP. The C-terminal fragments γ-MSH-(2-12), -(3-12), -(4-12), -(5-12) and -(6-12) were as potent as γ_2-MSH (=(1-12)) (ED_{50}= 20 nmol/kg; E_{max}= 50 mm Hg) or slightly less potent. Lys-γ_2-MSH induced similar increases as γ_2-MSH. The N-terminal fragments Lys-γ-MSH-(1-10) and -(1-8) had no significant effect on MAP. A similar structure-activity relationship was observed for the effects on HR.

In conclusion, these data suggest that (1) the MSH-core within γ_2-MSH is the minimal sequence which increases MAP and HR, (2) the N-terminal part of γ_2-MSH is essential for potency, and (3) the C-terminal part of γ_2-MSH is required for intrinsic activity. The results will be discussed in light of receptor classification.

31.49 STRESS-INDUCED HYPERTHERMIA IN INDIVIDUALLY HOUSED MICE: A METHODOLOGICAL STUDY.

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Measurement of stress-induced hyperthermia (SIH) in group-housed mice requires a large number of animals and is time-consuming. We therefore adapted this method to be used in individually housed mice as a screening model.

The effect of various stressors on the rectal temperature of individually housed mice was tested. Repeated, but not a single disturbance of the animals in their home cage resulted in a strong hyperthermic response within 10 minutes. Similar hyperthermic responses were observed if the stressors were immobilization for 1 min or rectal temperature measurement itself. An acoustic stimulus or repeated footshocks were not stressful enough to induce a temperature change.

Repeated temperature measurement at a 10 min interval was chosen since this enabled measurement of basal temperature and hyperthermic response in each animal within a short time. The maximal hyperthermia is reached after 30 min, but 70 % of the response is reached after 10 min. When the animals are repeatedly used in separate experiments both the basal temperature and the temperature measured 10 min later gradually increase.

Prior injection of the animals also results in a modest hyperthermia, that is no longer observed if the animals are treated 60 min prior to the first temperature measurement. Both the anxiolytic diazepam and the putative anxiolytic 5-HT_{1A} agonist flesinoxan dose-dependently suppressed the stress-induced hyperthermia. The antidepressant amitriptyline lowered temperature levels but did not affect the hyperthermic response. In conclusion the stress-induced hyperthermia model in individually housed mice is a fast and reproducible screening test for anxiolytic activity. The major advantages of this model compared to that described in group-housed mice are the reduction in time and animals needed for an experiment. The predictive validity of this screening model still has to be further elucidated.

31.50 BENZODIAZEPINES MODULATE THE $GABA_A$ RECEPTOR ACCORDING TO A TWO-SITE MODEL

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We determined the effects of diazepam, midazolam and oxazepam on [^{3}H]TBOB binding to rat brain membranes, containing μM quantities of endogenous GABA. [^{3}H]TBOB labels the convulsive site of the $GABA_A$ receptor.

The three benzodiazepines displaced [^{3}H]TBOB according to a two-site model with a nM and a μM affinity. In the presence of the GABA antagonist bicuculline-methochloride the nM affinity site is not demonstrable (tested with diazepam (1)). The benzodiazepine antagonist flumazenil shifted the curve of the nM affinity site to the right (tested with midazolam and oxazepam).

The effect of nM concentrations of benzodiazepines is known to be a potentiation of the effect of GABA. The μM effect may result from an interaction with a second specific binding site on the $GABA_A$ receptor complex or it may result from an allosteric negative cooperation between two interdependent receptor sites.

We suppose that in vivo the slight slopes of the dose-response curves of benzodiazepines (2) camouflage a two site model. Indeed in a detailed in vivo study a two site effect of midazolam has been reported (3). Flumazenil fails to antagonize the effect of high concentrations midazolam in that study. This indicates the clinical relevance of a low affinity effect of benzodiazepines.

1) Van Rijn et al., J. Receptor Res. in press; 2) Haefely, W.E. et al. in: The benzodiazepines, ed: E. Costa, Raven Press, 1983, p21; 3) Hoogerkamp, A., Thesis 1992, Leiden University, The Netherlands p157.

31.51 EFFECTS OF LYS-CONOPRESSIN ON AN IDENTIFIED CENTRAL NEURONE IN LYMNAEA STAGNALIS. P. F. van Soest and K. S. Kits Graduate School Neurosciences Amsterdam, Faculty of Biology, Vrije Universiteit, De Boelelaan 1087, 1081 HV Amsterdam, The Netherlands.

Lys-Conopressin is a vasopressin-related neuropeptide found in various molluscan species, among which is the pond snail *Lymnaea stagnalis* (L.). A number of neurones responsive to conopressin have been identified in the anterior lobe of the right cerebral ganglion. We focused on one of these cells, which exhibits a steadily beating firing pattern, and shows a prolonged depolarisation, accompanied by strongly enhanced spiking activity, upon application of conopressin. We have been able to isolate this cell from the nervous system. Under these conditions, the spontaneous firing patterns are more variable than those in the isolated nervous system, but the strong excitatory action of conopressin is preserved.

Under voltage clamp conditions, this neurone exhibits a prominent sustained inward current upon depolarisation, which is reminiscent of the pacemaker currents found in several molluscan cell types. The steady-state current-to-voltage relation invariably shows a characteristic region of negative slope resistance at voltages more positive than -40 mV. This voltage-activated steady-state inward current appears to be carried mainly, but not exclusively, by Ca^{2+}.

Application of conopressin not only increases the peak amplitude of the total steady-state inward current, but expands the voltage range of negative slope resistance as well. The effect of conopressin on the peak current amplitude can be reduced, but not abolished, by application of extracellular Cd^{2+}, suggesting that two or more ionic currents contribute to the response. In contrast, the effect on the voltage dependency does not appear to be modified by Cd^{2+}. The observation that the current induced by conopressin both has a different voltage dependency as well as a different reversal potential, leads us to believe that conopressin does more than increasing the voltage-activated steady-state inward current.

31.52 FALSE TRANSMISSION BY SEROTONIN IN DOPAMINERGIC NERVES MAY BE STUDIED BY USING THE HYPOTHALAMO-PITUITARY PATHWAY AS THE MODEL TISSUE. Vanhatalo S* and Soinila S: Deparment of Anatomy, Division of Biomedicine, P.O.Box 9, 00014 University of Helsinki, Finland

False transmitter is defined as any transmitter substance that is taken up, stored, and released by a nerve terminal that does not synthesize it. A number of recent studies have shown that many amines may function as a false transmitter in both the peripheral and the central nervous system (CNS), and false transmission may be related to a wide variety of physiological and pathophysiological phenomena. In order to study the properties of false transmission mediated by serotonin (5-HT), we have characterized both *in vivo* and *in vitro* our model tissue, the central dopaminergic periventriculo-pituitary intermediate lobe (IL) pathway, and shown that it contains 5-HT as a false transmitter. We first demonstrated that these fibers co-store dopamine and 5-HT and are destroyed by neurotoxin (6-OHDA) specific for catecholaminergic systems, but not affected by neurotoxin specific for 5-HT-ergic neurons (PCA). Secondly, we showed that they do not synthesize 5-HT, but take up exogenously synthesized 5-HT, which is subsequently released by both exocytotic and transporter-mediated mechanisms. Finally, these nerve fibers comprise almost all of the nerves present in the IL. Thus, IL contains a rather homogenous CNS nerve terminal population exhibiting false transmitter action for 5-HT and, as an isolated part of the brain, offers an ideal model to study false transmission phenomenon in the CNS at the terminal level.

31.53 EFFECTS OF CHRONIC MORPHINE ADMINISTRATION ON GLIAL CELLS IN THE CENTRAL NERVOUS SYSTEM

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During brain development activation of glial cells, neuronal proliferation and differentiation and simultaneous celdeath has been demonstrated. Exogenous opiates can produce specific or generalized neurotoxic effects during brain development and in the adult rat brain. In opioid tolerant/dependent rats, attention has mainly been focused on neuroadaptive effects and only little is known about the effects of opioids on the different types of glial cells. Therefore we have studied the effect of chronic morphine treatment on the microglial cells and the effect on astroglial cells in the developing brain and adult brain in vivo.
Chronic morphine was administered subcutaneously to pregnant Wistar rats three times a day starting at gestational day 16 and to adult male rats during 6 days with increasing doses of 5, 10, 20, 30, 40, 50 mg/kg respectively. The rats were sacrificed one day after the last morphine injection and the fetuses and male rats were perfused intracardially with Bouin fixative. The 50 μm vibratome sections were stained using immunocytochemistry with the astrocytic marker GFAP, glutamine synthase and the microglial cell marker isolectin-B4. In fetal rats morphine significantly inhibited differentiation of ameboid microglial cells into ramified microglial cells. Thus throughout the circumventricular regions ameboid microglial cells were abundant in morphine fetuses, while in control fetuses the microglial cells at this stage already have differentiated into ramified microglial cells. In the adult male rats, morphine induced GFAP expression in the interpeduncular nucleus and increased the GFAP immunoreactivity in the hippocampus. These alterations in GFAP levels can reflect astrocytic proliferation or morphologic differentiation and can be indicative of neural trauma or injury.

31.54 CHANGES OF STRIATAL PROENKEPHALIN AND DINORPHIN mRNAs AFTER CHRONIC TREATMENT WITH AMPHETAMINE, PHENCYCLIDINE AND HALOPERIDOL: *IN SITU* HYBRIDIZATION STUDY. S.Vukosavić*, S.Kanazir, R.Veskov, S.Ruždijić, Lj.Rakić
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This study was designed to evaluate the effects of chronic treatment with high doses of psychostimulants amphetamine (AMPH) and phencyclidine (PCP), and neuroleptic haloperidol (HAL) on the proenkephalin (pEnk) and dinorphin (Din) mRNA expression in the rat striatum. Six groups of adult rats were treated during seven days with 1.AMPH; 2.PCP; 3.HAL; 4.AMPH+HAL; 5.PCP+HAL in 5mg/kg/day doses on 12h intervals. Striatal sections (12μm) were used for *in situ* hybridization histochemistry with ^{35}S-labeled riboprobe for pEnk and Din. Quantification of hybridization signals were performed using the PhosphorImager and software package Image Quant. *In situ* hybridization study revealed that chronic administration of AMPH induced significant increase of both pEnk (30% over the control) and Din (20%) striatal mRNAs, while PCP treatment caused increase of pEnk mRNA (30%) and decrease of Din mRNA (15%) in rat striatum. Interestingly, HAL induced 85% increase in striatal pEnk while Din mRNA was decreased (10%). In AMPH+HAL group level of Din mRNA was as in the control striatum, but pEnk mRNA was strongly increased (70%). Both Din and pEnk mRNAs in PCP+HAL group showed decreased expression. Our results demonstrated that chronic administration of AMPH, by blocking dopamine reuptake, induced more pronounced increase of both Din and pEnk striatal mRNAs then PCP, a non-competitive NMDA antagonist, which caused increase of pEnk mRNA, while its action on Din mRNA expression was opposite. HAL, dopamine receptor antagonist, induced impressive increase of pEnk mRNA.

In conclusion, these results showed stronger involvement of dopaminergic system in alteration of striatal opioides after treatments with psychostimulants, so they may contribute to the dopaminergic hypothesis of schizophrenia.

31.55 THE RESPONSE OF SUPRACHIASMATIC NEURONS TO GABA APPLICATION IN VITRO IS DETERMINED BY CIRCADIAN TIME.

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The numerous GABAergic inputs to the suprachiasmatic nucleus (SCN), as well as its large number of intrinsic GABAergic neurons and their extensive outputs to the hypothalamus and beyond, suggest that inhibitory pathways play a major role in the generation of circadian rhythmicity.

In the present study, freshly prepared rat hypothalamic slices (300-500μm) were used. Single unit activity was recorded using current-follower mode with an ACSF-filled patch electrode. The instantenous frequency was calculated from the reciprocal of the interspike interval, averaged over 30secs. The value of the cell's response to each concentration of bath-applied GABA (10-1000μM) was determined by averaging instantenous frequency over a period of 5mins. The responses of 46 cells from 20 animals were examined during subjective day and 20 cells from 7 animals during subjective night. During the day, 43% of the cells showed an increase in firing rate, 48% of the neurons did not respond and in only 9% the firing rate decreased in response to GABA at concentrations of up to 300μM. On the other hand, during subjective night 30% of the neurons showed a decrease in firing rate, 56% of the cells did not respond and only 19% showed increased firing rate. The average dose-response curve of the day shows an increase at concentrations as low as 10μM. The maximum increase was observed at 400μM (47±30%). At night the average dose-response curve shows only a decrease in response at concentration as low as 50μM. Since the increase in firing rate during subjective day was blocked by either picrotoxin or bicuculline (100μM; n=3), the response appears to have been mediated via $GABA_A$ receptors.

These experiments demonstrate bimodal responses of SCN neurons to GABA application, the mode of response depending on the circadian time of the nucleus. We hypothesize that either the sensitivity or the distribution of GABA receptors on SCN neurons undergoes circadian alterations.

31.56 NADPH-DIAPHORASE ACTIVITY IN ASTROCYTES AND PYRAMIDAL NEURONES OF THE AGING HUMAN BRAIN.

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NADPH-diaphorase is colocalised with nitric oxide synthase in both neurones and activated astrocytes in the brain (Wallace & Bisland, Neurosci.59:905,1994).The NADPH-diaphorase is a very stable enzyme and we have used it to study potential nitric oxide production in the brains of subjects who had bequeathed their bodies to medical science. Postmortem delay was 8 - 28 h. and following bilateral canulation of the internal carotids, brains were perfused with 4 litres of 4% paraformaldehyde in phosphate buffer (pH 7.4) over a period of 6 - 16 h. Blocks of brain were immersed in 30% sucrose for 24 h. They were frozen in a jet of solid carbon dioxide and sectioned at 30 μm in a cryostat. Sections were taken from a variety of neocortical areas and the hippocampus. Sections were stained for NADPH-diaphorase, Nissl substance, myelin and acetylcholinesterase. Some sections were also stained for the astrocyte marker glial fibrillary acidic protein (GFAP), and the calcium binding protein parvalbumin.

Multipolar neurones with high NADPH-diaphorase activity were observed in all cortical areas - most commonly at the white matter border - and there was a plexus of densely stained fibres. In all areas except the precentral gyrus, there was no evidence of any diaphorase staining in pyramidal neurones. However within layer V of the motor cortex the giant pyramidal neurones of Betz contained moderate NADPH-diaphorase activity. Furthermore in the hippocampus of one brain there were crystalline deposits of what appeared to be calcium salts in a perivascular location within stratum lacunosum-moleculare of the CA1 field. Surrounding these deposits, and at no other location, there were activated astrocytes which demonstrated high levels of NADPH- diaphorase activity. Thus we conclude that both the Betz cells and activated astrocytes in the human brain are able to release nitric oxide in what may be a neuroprotective roleand in the absence of any pathology.

31.57 VASOACTIVE INTESTINAL POLYPEPTIDE (VIP) IN HUMAN HYPOTHALAMUS

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The number of VIP expressing neurons was determined in the human suprachiasmatic nucleus (SCN) in relation to sex and aging. Between 10 and 40 years of age the male SCN contained, on average, twice as many VIP neurons as the female one. This difference reversed by a drop in VIP cell numbers in males between 40 and 65 years of age, whereas after 65 years of age no sex difference was found. When men and women were considered separately, there was no significant age-related alteration in the number of VIP expression cells between middle-aged and aged subjects. While in homosexual men the vasopressin cell number in the SCN was twice as large as in heterosexual men, no difference was found in VIP cell numbers in the SCN. Current research is directed towards VIP differences in other parts of the human hypothalamus in relation to gender (male, female) and gender problems (transsexualism).

Brain material was obtained from the Netherlands Brain Bank (coordinator Dr. R. Ravid).

D.F. Swaab et al., Dev. Brain Res. 79 (1994) 249-259.
J.-N. Zhou et al. Brain Res. 672 (1995) 285-288.
J.-N. Zhou et al. Neurobiol. Aging (1995) (in press).

31.58 A-RECEPTOR MEDIATED EFFECTS OF CHOLECYSTOKININ ON LATERAL GENICULATE (LGNd) NEURONS OF RATS. U.Zippel* and D. Albrecht. Inst. Physiology, Dep. Neurophysiol., Charité, Humboldt-Univ., 10117 Berlin, FRG

In earlier experiments we found about 1/3 of the LGNd neurons to be responsive to the iontophoretically applied cholecystokinin octapeptide CCK-8S. Most of the influenced neurons were excited, but also some inhibited (11%). Using specific CCK-A and CCK-B receptor antagonists it became evident that beside the B-receptors common in the brain A-receptors must be involved, too. Since both antagonists were able to block excitatory as well as inhibitory effects of CCK on geniculate neurons the question arose whether the two CCK receptors mediate the same or opposite effects on the discharge rate. In the present study the type of CCK-receptors existing in the LGNd was directly investigated using the selective CCK-A receptor agonist A71378 and the selective CCK-B receptor agonist Suc-Trp-N(Me)Nle-Asp-Phe-NH_2 (both synthetized by P. Henklein, Charité). The maintained activity was changed by more than 50% in 21/38 neurons by the CCK-A agonist and in 19/28 neurons by the CCK-B agonist. Thus the responsiveness to the two drugs was not very different. Furthermore 14/24 neurons tested with both drugs responded even to both, whereas 5/24 selectively responded to one agonist. Interestingly, neurons which changed their activity to both agonists mostly (10/14) developed a qualitatively equal response (9 excitations, 1 inhibition). If we assume that B-receptors mediate excitation and A-receptors inhibition then all excitations elicited by the A-agonist and all inhibitions elicited by the B-agonist should be mediated via the GABAergic local circuit neurons. Therefore we tried to prevent the CCK effects of 12 neurons with the GABA-A antagonist bicuculline. Beside results consistent with the above mentioned assumption 4 CCK-A evoked inhibitions were abolished by bicuculline. This can only be interpreted as an excitatory effect of the CCK-A agonist on LGNd-interneurons. It seems that the A-receptor can mediat excitation as well as inhibition.

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32.01 SPIRAL GANGLION ALTERATIONS AFTER ISCHEMIA

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The ultrastructural pathomorphological study analyzes qualitative and quantitave changes in the rat spiral ganglion neurons after 30 min global brain ischemia with subsequent 3 days survival.

Neuronal changes included a decrease in the endoplasmic reticulum, peripheral cytoplasmic vacuolation and the presence of lamellar myelinoid bodies. Nuclei of neurons contained nucleoli located close to the karyolema with a frequent incidence of coiled bodies. An increase in lipofuscin granules with different morphological characteristics in neurons and satellite cells was noticed. Quantitative analysis showed 28% increase in the cell and nuclear volume compared to the control.

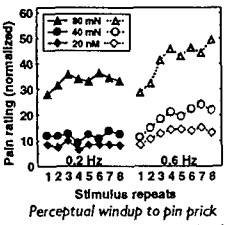
The results of qualitative and quantitative study showed slow dynamics of neuronal alterations of auditory neurons and thereby offer some possibilities for the treatment of structural and functional lesions induced by ischemia.

32.02 SUMMATION OF PAIN SENSATION ('WIND-UP') IN NORMAL SKIN AND AREAS OF SECONDARY HYPERALGESIA

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Skin injury triggers an enhanced pain sensitivity in surrounding uninjured skin (secondary hyperalgesia) due to heterotopic central sensitization. Repetitive stimulation of nociceptors at frequencies > 0.5 s^{-1} induces a homotopic response facilitation in dorsal horn neurons ('wind-up'), which is thought to contribute to central mechanisms of hyperalgesia. In our study we examined the expression of perceptual wind-up in normal skin and areas of secondary hyperalgesia to elucidate whether it contributes to heterotopic sensitization.

Secondary hyperalgesia was induced by i.d. injection of capsaicin (40 µg). Sensitivity to mechanical stimuli using cotton balls, calibrated von Frey hairs and pin pricks was tested at 15 mm distance from the injection site. Blunt von Frey hairs were used to determine S/R functions for pricking pain. Stimulus repetition at 0.2 and 0.6 s^{-1} was used to test for perceptual wind-up.



Perceptual windup to pin prick

In normal skin significant perceptual wind-up was only observed at the 0.6 s^{-1} frequency and limited to pin prick stimuli independent of their strength (20-80 mN) (see Fig.). Capsaicin evoked strong burning pain and a leftward shift of S/R function (> factor 3) in the area of secondary hyperalgesia. Though pain ratings increased, the extent of wind-up to repetitive stimulation in the area of secondary hyperalgesia remained unchanged.

This suggests that secondary hyperalgesia (heterotopic facilitation) and wind-up (homotopic facilitation) may be independent phenomena.

32.03 INFLUENCE OF HYPERBARIC OXYGEN ON RETINAL DEGENERATION OF C3H MOUSE

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Morphological and electrophysiological analogies have been described between retinal degeneration of C3H mouse and human retinitis pigmentosa. We have choosen the mouse in order to verify the effectiveness of hyperbaric oxygen administration in retinitis pigmentosa. **Methods.** The experimental protocol was carried out in accordance with the ECCD (86/609/EEC). 20 litters were divided into three groups. The first one was used as control; the second one was exposed to a +0.5 atm hyperbarism for the first 10 days of life; the third one received the same treatment with a continuous flow of humidified supplemental oxygene (FiO_2 = 50%). At days 17, 27 e 50 some mice were sacrified for histologic examination of the retinas, some other underwent to electroretinography. **Results.** At histological examination, the first group showed a marked reduction of the thickness of outer nuclear layer and photoreceptor's layer with the increasing of age. On the other side the two treated groups showed thick retinas, with a good preservation of outer nuclear layer and photoreceptor's cellular rows. In those groups we observed a delayed appearance of degenerative lesions. At electroretinography, treated groups showed an improvement of b-wave size and implicit time. **Conclusions.** At histology, our results show some effectiveness of hyperbarism and oxygen supplementation in order to delay retinal damage of C3H mice. Further studies will be necessary to fully understand the electrophysiological parameters of the treated groups.

32.04 FUNCTIONAL RELATIONSHIP BETWEEN CELLS LOCATED IN SUPRAGRANULAR LAYERS OF VISUAL AREAS 17 AND 18 IN THE CAT.

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Feedback connections from area 18 to area 17 in the cat are well known on the basis of anatomical studies. Furthermore, supragranular layer cells in area 18 seem to be selectively connected to supragranular layer cells in area 17, and a similar relationship has been observed between deep layers (Henry et al. 1991). Previous investigations carried out in our lab have explored the functional role of these feedback connections in deep layers, by mean of lignocaine blockade. (Alonso et al. 1993). Our present study is focused on the functional role of feedback connections between cells located in layers II/III in both visual cortical areas.

Experiments were performed on adult cats, anesthetized with halothane in 70% N_2O and 30% O_2, and paralyzed with gallamine (10 mg/kg/h). Multi-barrelled micropipettes were used to record single unit activity within layers II/III of area 18 and iontophoretical ejection of GABA. Activity of retinotopically matched cells within layers II/III of area 17 was simultaneously recorded by mean of metal microelectrodes. For all cell pairs each receptive field was mapped and studied in the orientation and direction domains.

Focal reversible blockade of area 18 resulted in significant changes in orientation domain in 78% (35/45) cells in area 17. Area 17 cells showed statistically significant increased [40% (18/45) cells] or decreased [38% (17/45) cells] responses to one or more orientations or directions during area 18 blockade. Likewise, statistically significant changes (increase or decrease) in banwidth were observed. These effects were found in both simple and complex cells in similar proportions.

These data support the fact that parallel processing of visual information occurs within the cortex, particularly between cortical areas 17 and 18. This functional link could be mediated by long excitatory connections and local inhibitory processes related to the observed changes in orientation and direction domain.

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Alonso JM, Cudeiro J, Perez R,Gonzalez F, Acuña C (1993). Exp Brain Res 96: 212-220.

32.05 A REINVESTIGATION OF THE RETINO-RECIPIENT DORSAL THALAMUS OF LIZARDS

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1. Visiting Scientists of the Sechenov Institute; Russian Acad. Sci.; 44 Thorez pr., Saint Petersburg (Russia); granted by the Spanish Ministry of Education and Science

To clarify the organization of the lacertilian dorsal retino-recipient (DRR) thalamus we have studied its cytoarchitecture, retinal afferents, main efferents and the distribution of NPY and GABA, in a lizard, *Podarcis hispanica*. Our results confirm the presence of four DRR thalamic nuclei displaying different organization and projections: the rostral nucleus ovalis (OV), the dorsal lateral geniculate nucleus (GLD), the intergeniculate leaflet (IGL) and the caudal part of the dorsolateral anterior nucleus (DLA).

OV shows a laminar organization with a lateral retinorecipient neuropile (where most GABA cells are found) and a medial cell plate, the neurons of which project to the ipsilateral ventral visual thalamus. Retinal fibers enter the caudal edge of the DLA, but DLA cells may receive an additional visual input onto distal dendrites that enter the IGL and GLD. DLA projects to the cortex. GLD displays a rough neuropile/cell plate organization. Neurons projecting to the telencephalic pallial thickening are mainly found in the medial part of the nucleus (where cell density is higher) and extend long dendrites into the dorsolateral (retino-recipient) neuropile, where most GABA cells are found. So, our GLD "cell plate" corresponds to the intercalate optic nucleus of Bruce & Butler ('84; JCN 229:585-601). The IGL displays a high density of big NPY neurons (some of them grouped in clusters) and GABA cells. Caudally the IGL is interposed between the GLD and GLV. It receives an important retinal afferent and projects to the suprachiasmatic area and opposite ventral thalamus, thus being related to the ventral rather than dorsal thalamus. The IGL coincides in location with the DRR intercalate optic nucleus of Northcutt ('78; Neurology of Lizards), and with the NPY-rich perirotundal belt of Medina et al. ('92; JCN 319:387-405). *Supported by the Spanish DGICyT (PB 91-0643) and IVEI.*

32.06 CHANGES IN THE CGRP INNERVATION SYSTEM OF THE SUPERIOR COLLICULUS DURING POSTNATAL DEVELOPMENTIN NORMAL AND UNILATERALLY ENUCLEATED RATS.

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In paraformaldehyde fixed sections of superior colliculus (SC) CGRP inmunopositive ($CGRPI^+$) structures were stained with a polyclonal antibody (Cambridge antibodies, England).

In this study normal and neonatally enucleated Sprague-Dawley rats of several ages (P1, P2, P4, P7, P10, P15) and adults were used. In adults animals visual layers of SC were innervated by thin fibers with dense boutons. Scattered somata were weakly satined in these layers and stratun griseum intermedium (SGI). During the first postnatal week fibers and neuronal somata $CGRPI^+$ arranged in circular patches increasingly appeared in stratum opticum and SGI. The intensity of labelling of these $CGRPI^+$ structures diminished progresively after the second postnatal week and by P20 they were not visible.

Unilateral enucleation was followed by an increase of $CGRPI^+$ fibers and a dissappearance of $CGRPI^+$ somata in contralateral SGS. Currently it is unknown the significance of $CGRPI^+$ structures in SC during development and in adult animals. The increased of $CGRPI^+$ fibers on SGS postenucleation would contribute to the sprouting of collicular afferents.

32.07 COLOCALIZATION OF GLYCINE AND GABA AT GEPHYRIN-IMMUNOREACTIVE SYNAPSES ON POSTSYNAPTIC DORSAL COLUMN NEURONS. D.J. Maxwell*, A.J. Todd and R. Kerr. Laboratory of Human Anatomy, Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow G12 8QQ, U.K.

Glycine and GABA are both involved in inhibition of neurons in the spinal dorsal horn and these transmitters are colocalized in many boutons in this region. The purpose of the present investigation was to determine if spinomedullary neurons belonging to the postsynaptic dorsal column (PSDC) system receive synapses from such boutons. PSDC neurons were retrogradely labelled with horseradish peroxidase in adult cats and were prepared for combined light and electron microscopy. Postembedding immunogold reactions were performed with antisera which recognize GABA or glycine. Analysis of series of ultrathin sections revealed that many of the boutons which formed synapses onto these cells were enriched with both GABA- and glycine-immunoreactivity, while others showed only one type of immunoreactivity or were not immunoreactive. Pre-embedding immunocytochemistry was performed on sections containing labelled cells with a monoclonal antibody which recognises the glycine receptor-associated protein, gephyrin. Many synapses onto postsynaptic dorsal column neurons were associated with gephyrin-like immunoreactivity and these typically contained irregularly shaped vesicles. Immunogold reactions showed that synaptic profiles apposed to gephyrin-immunoreactive junctions frequently contained both GABA and glycine. It is likely that at least some of the boutons containing GABA and glycine originate locally, since many interneurons in the dorsal horn contain both transmitters. These results suggest that glycine is a neurotransmitter at synapses on PSDC neurons and that it is often colocalized with GABA.

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32.08 Reticular activation modulates intracortical synchronization M.H.J.Munk*, P.R.Roelfsema, P.König, A.K.Engel, and W.Singer
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Activating the ascending reticular system is known to transform EEGs dominated by low frequencies into fast, »desynchronized« activity. However, more recent studies using intracerebral recording techniques have uncoverewd that adequate sensory stimulation evokes high frequency oscillations in the gamma frequency range (>30Hz) often accompanied by millisecond-precise synchronization of spike discharge. Synchronization of sensory responses in neurons of the visual cortex was shown to depend on the global configuration of the visual stimulus and is particularly strong between neurons that respond to features of a single coherent object. This led to the binding-by-synchronization hypothesis. In this study we show that reticular activation induces gamma frequency oscillations in the local field potential of the cortex and increases synchronization of visually evoked spike responses in pairs of multi-unit recording sites, even across different hemispheres. The term »desynchronization« seems therefore to be inadequate to describe the effect of reticular activation of the cortex: it does reduce synchronization of low frequency signals, but at the same time increases coherence in the gamma frequency range.

32.09 ARE SYNCHRONOUS OSCILLATIONS IN THE LATERAL GENICULATE NUCLEUS OF RETINAL ORIGIN? S. Neuenschwander* and W. Singer. Max-Planck-Institut für Hirnforschung, Frankfurt a.M., Germany.

Synchronization of neuronal activity has been postulated as a mechanism to enhance the saliency of selected neuronal responses and to define relations among them. In the present study we have investigated the occurrence of synchronous firing in the dorsal lateral geniculate nucleus (LGN).

Recordings were made in anesthetized cats by means of a pair of electrodes placed in different LGN laminae. Cross-correlation analysis revealed that geniculate cells may show strongly synchronous oscillatory activity in response to a visual stimulus. Stationary flashed bright or dark spots or bars were more effective in inducing oscillatory responses than drifting gratings or bars. Synchronized responses were seen most often for recording sites located within the same lamina and between different laminae receiving inputs from the same eye (between lamina A and C, and rarely between lamina A1 and A or C). The fact that laminae receiving inputs from the same eye were more likely to show correlated activity suggests a retinal mechanism for synchrony. To further test this possibility, we have made recordings from different LGN laminae of the two hemispheres. This method allows us to follow simultaneously the synchronization behavior for cell pairs located in different hemispheres and receiving inputs from the same or different eyes. Confirming our hypothesis, we have observed that cell pairs between lamina A1 of one hemisphere and lamina A or C of the opposite hemisphere (inputs from the same eye) were more likely to show correlated activity than cell pairs between lamina A and lamina C of the opposite hemisphere or homologous laminae (inputs from different eyes).

We conclude that the synchronous oscillations we observed are *unlikely* to be mediated by cortico-cortical connections, since they are induced by stimuli that are far from being optimal in activating cortical neurons. The intra- and interhemispheric correlation we describe in the LGN may be better understood in terms of retinal interactions.

32.10 Abstract withdrawn

32.11 TACTILE AGNOSIA - A CASE REPORT

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Impaired tactile object recognition (TOR) and naming can be due to a variety of impairments including basic and intermediate somatosensory dysfunctions, supramodal spatial disturbances, modality specific anomia, and tactile agnosia aside from attentional, intellectual and linguistic deficits.

Tactile agnosia (left hand) was documented with a 51 year-old man who had a right parietal meningeoma centered over his postcentral and supramarginal gyrus surgically removed. Cognitive and sensorimotor abilities were largely preserved. Finger sensation for touch, pain, temperature, vibration, position sense, uni- & bilateral stimulation, 2 point dicrimination, discrimination and matching of weight, texture, size, 2D and 3D form, and of thermal properties (1 mistake with L hand) were unimpaired. However, the pat. could not tactually recognize 8 out of 17 common objects with his left hand in spite of preserved tactual after-selection, tactual-visual matching and visual recognition. 3D motion analysis showed normal abilities for fastest repetitive finger movements while manipulative finger movements during TOR were reduced for the agnostic left hand.

32.12 CHRONIC MOTOR CORTEX STIMULATION AS TREATMENT OF NEUROPATHIC PAIN.

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Chronic motor cortex stimulation, first described by Tsubokawa in 1990 has been reported to be effective for central pain (post-stroke pain).

We report our experiences in a serie of 14 patients between May 1993 and December 1994. Eight of them had central pain as sequelae of cerebrovascular disease (CVD), five patients had chronic pain due to injury of the trigeminal nerve after trigeminal ganglion thermocoagulation and the remaining patient had a medically refractory pain secondary to quadriplegia.

These patients were treated by chronic electrical stimulation with a quadripolar plate epidural electrode surgically inserted on the motor cortex area. Central sulcus was located by stereotactic tomography and per-operatively with somatosensory evoked potentials (the reversal of the N20 wave). The stereotactic procedure was performed under local anesthesia using the Leksell frame and clinical effect of motor cortex stimulation was tested per-operatively.

Pain complaints were quantified by an analogical and functional scale. The patients with CVD obtained pain reduction estimated to 50% in 6 cases and 20% in the 2 remaining cases. The 5 patients with trigeminal neuropathy enjoyed definite pain relief varying between 70% and 95%. The relief of pain was quasi complete in the last patient with quadriplegia.

No sensory trouble, abnormal movement nor epileptic seizure were observed under cortical stimulation during per-operative tests nor after permanent implantation. In only one patient (CVD) the stimulation effect gradually decreased. Chronic motor cortex stimulation appears to be a promising possibility of pain treatment.

32.13 THE EYE IN THE HEAD ON THE SHOULDER: THE INFLUENCE OF EYE AND HEAD POSITION ON DETECTION THRESHOLDS. Podvigin N[1], Stoerig P[2], Bobrova-Evpiatjeva EV[1], Kulikova SV[1], Pöppel E[2]*, Pavlov Institute of Pysiology, Russian Academy of Science, St.Petersburg, Russia[1], and Institute of Medical Psychology, Ludwig-Maximilians-University, 80336 Munich, FRG[2]

To see whether a misalignment of eye, head, and body axes would affect visual sensitivity in normal observers, we measured increment thresholds monocularily in 10 subjects, using three conditions: 1) 20° between head and eye; 2) 20° between head and shoulder; 3) 20° between eye and head, and another 20° between head and shoulder. Increment thresholds were measured at +10, 0, and -10° eccentricity on the horizontal meridian, with a 10', 200ms white stimulus on a 10 cd/m^2 white background. Mean sensitivity (n=15) was calculated and compared to the zero position where eye, head, and shoulders were aligned. The difference amounted up to 60% in individual cases. With the eye deviated, sensitivity decreased in 83%; with the head deviated, it decreased in 45%. An overall increase in sensitivity was observed in conditions 2) and 3) for the foveal position. The eye that was tested affected the results only in condition 3), where the left eye's sensitivity increased in 88% in the deviated position, whereas the right eye's decreased in 80%. These results show that a misalignment of visuomotor maps can markedly influence detection thresholds, for better or worse. The effect may be mediated by both subcortical (colliculur) and cortical (parietal) representations of visuomotor space and is most pronounced when eye and head are both deviated.

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32.14 IMPLICIT PROCESSING IN PATIENTS WITH VISUAL EXTINCTION : EVIDENCE FROM THE REDUNDANT TARGET EFFECT.

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A group of patients with left visual extinction as a result of right hemisphere damage was tested on a redundant target effect. LED - generated brief flashes were randomly presented to the left or to the right or bilaterally in the visual field. Subjects were asked to press a key as fast as possible following either bilateral or unilateral (right or left) stimulus and after each press to report on the number of the stimuli seen. As previously found in normal subjects, double stimuli evoked faster reaction times than single stimuli, this speeding of response providing evidence of a 'Redundant target effect' (RTE). In extinction patients we found an RTE not only for correctly detected double stimuli but also in trials in which they extinguished the stimulus on the left. This result suggests the presence of visual processing of the extinguished stimulus. In order to verify the probabilistic o neural nature of the RTE in our patients, we applied Miller's inequality to the cumulative distribution of reaction time frequencies. We found that RTE for correct bilateral stimuli was attributable to a probabilistic mechanism, whereas the RTE for extinguished stimuli could be ascribed to a neural one.

32.15 EVALUATION OF FUNCTIONAL CHANGES OF DECOMPRESSED LUMBO-SACRAL ROOTS USING DERMATOMAL SOMATOSENSORY EVOKED POTENTIALS (DSEP).

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Forty-one patients aged from 22 to 53 years with prolapsed disc who underwent discectomy by fenestration were investigated by dermatomal somatosensory evoked potentials (DSEP) prior to, two weeks and three months after surgery. The intraoperative and MRI assessments of the structural changes of the spine and nerve roots were correlated with functional abnormalities of individual sensory roots detected by DSEP. Following electrical stimulation of L3, L4, L5, S1 dermatomes potentials were recorded from the scalp electrodes placed at Cz' refered to Fpz. DSEP abnormalities were defined as: an absence of potential, delayed latency of first positive peak P40 and/or pathologically decreased amplitude, prolonged side to side latency differences.

Consistently with compressed spinal roots by prolapsed disc dermatomal potential were not obtained in four patients, whereas after surgery DSEP gradually improved. Pathological results of the same roots were obtained in 56% of patients examined prior to surgery. The consistency of pathological findings was less in DSEPs performed two weeks after surgery and comprising only 49% of cases. In the remaining patients some abnormalities of potentials were found in roots contralateral or adjacent to the decom- pressed spinal root. Total recovery of latency and amplitude of DSEP were obtained in 62% of patients three months after disectomy. In remaining 38% of patients abnormal DSEP were detected on different levels and sides to decompressed spinal nerve root despite clinical improvements. We assumed that these discrepancies were due to different directions and dimensions of prolapsed discs, period of compression, oedema of surrounding tissue and impairment of endoneurial capillary blood flow which may induce varying degrees of conduction delay of spinal nerve roots.

32.16 USE-DEPENDENT RHYTHM TRANSFORMATION OF HEAT RESPONSE IN FELINE C-FIBER CUTANEOUS NOCICEPTORS BY LIDOCAINE AND N-PROPYLAJMALINE. S.Revenko*, L.Baidakova, D.Borovikov, V.Ermishkin. National Cardiology Research Center, Moscow 121552, Russia.

Subcutaneous application of tertiary amine lidocaine (LID 0.1%) and quaternary amine N-propylajmaline (NPA, 0.01%) modified the responses to pulse or ramp heat stimuli of C-axon mechano-heat (CMH) polymodal sensory units in narcotized cats. After drug application only low-frequency discharges of CMH-units could be elicited even by strong (noxious) heat stimuli (up to 52^{o}C). Such discharges are similar to that elicited by non-noxious chemical stimulation (Revenko et al., 1992) or that evoked by non-noxious heat stimuli (Torebjork, 1984). Both NPA and LID deformed frequency-temperature (FT) relationships obtained with ramp heat stimulation which decreased risk of receptor sensitization. Having negligible effect upon temperature threshold and initial rising phase of FT-curve, NPA strongly suppressed discharges at higher temperatures resulting a selective high-frequency inhibition of CMH heat responses. In addition to similar effect, LID enhanced the temperature threshold by about 2-4^{o}C. The effects of both drugs developed more rapidly under repetitive heat stimulation or even during the prolong first stimulus. The inhibitory effect was partially reversed during a pause in stimulation. These features strongly suppose the use-dependent nature of NPA and LID action upon CMH units. The selective use-dependent high-frequency blockade of nociceptive sensory units may be thought of as a way to prevent their high-frequency bursts in chronic pathological conditions (i.e. inflammation). It may moderate or eliminate peripheral pain but still preserve the informational pathways between a deceased tissue and brain.

32.17 PERIGENICULATE GABAergic CELLS OF THE CAT ARE MODULATED BY NITRIC OXIDE. C.Rivadulla*, R.Rodriguez, S. Martinez-Conde, C.Acuña and J. Cudeiro. Dpto. Fisiologia, Univ. Santiago. Dpto Ciencias de la Salud I and Dpto. Psicologia, Univ. de La Coruña, SPAIN.

Acetylcholine (ACh) has both excitatory and inhibitory effects in the thalamus, dependig upon the type and localization of the postsynaptic cell. In the cat dLGN, ACh directly excites relay neurons and has exactly opposite effects on local and perigeniculate (PGN) GABAergic cells. Interestingly, it has been shown, that cholinergic axons from the brainstem also stain positively for NADPH-diaphorase, a marker for nitric oxide synthetase (NOS)[1]. Moreover, we have suggested that nitric oxide (NO) acts in concert with the cholinergic input and enhances dLGN relay cells activity permitting full expression of NMDA evoked activity [2,3]. Here we try to answer the following questions: (a) Does NO influences PGN cell's activity? (b) If this is the case, are NMDA receptors involved.?

Experiments were carried out on anaesthetized (halothane in 70% N_2:30%O_2) and paralyzed (gallamine, 10 mg/kg/h) adult cats. Seven barrelled micropipettes were used for extracellular unit recording and iontophoretic ejection of drugs. The effects of application of N^G-nitro-L-arginine (L-NOArg, an inhibitor of NOS), L-arginine (L-Arg, the physiological substrate of NOS), D-Arginine (the inactive isome), S-Nitroso-N-acetylpenicillamine (SNAP, a NO donor) and sodium nitroprusside (SNP, another NO donor) were tested on resting discharge, visual evoked responses and NMDA evoked excitation of PGN cells. All cell tested showed marked response reductions to either visual stimulation or NMDA application during iontophoretic ejection of L-NOArg. This effects were prevented by simultaneous application of L-Arg but no by D-Arg. Ejection of either SNAP or SNP significantly increased spontaneous activity and NMDA evoked responses. This data show that NO modulates PGN cells activity very much like it does at the level of dLGN relay cells.

(1) Bickford et al., *J. Comp. Neurol* 334:410-430 (1993).
(2) Cudeiro et al., *J. Neurophysiol.* 71:146-149 (1994).
(3) Cudeiro et al., *Neuropharmacol.* 33:1413-1418 (1994).

32.18 ANALGETIC PROPERTIES OF "OF-743"

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The aims of the research are to study the analgetic properties of one of sydnoneimine derivatives - "OF-743"." OF-743", psychostimulator and antidepressant, having cholinolytic activity. showed also rather significant antiulcer effects. Our study was fulfilled on rats and mice. using the termal ("Tail-flick", "Hot plate") and chemical (acetic asid writching test) nociceptic stimulation. We discovered that "OF-743" have really analgetic properties Maximum analgetic effect exerts in 20-40 minutes after intraperitonal injection of 15-20 mg/kg and may continue till 60-120 minutes. Minimum effectiv dose is about 5 mg/kg. "OF-743" increases morphine analgesia, but not analgin anesthesia. Possible mechanisms of "OF-743" analgesic effects (influence on bioamine and cholinergic sistems) are under discussin.

32.19 INTEGRATION OF VISUAL INFORMATION AND DIRECTION OF GRAVITY IN PRESTRIATE CORTEX OF THE AWAKE BEHAVING MONKEY.

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We have investigated the effect of body tilt on mechanisms of contour processing in the visual cortex of the alert monkey. The responses of single neurons were studied while the monkey performed a visual fixation task. The animal worked either in the upright position or with its body tilted about the naso-occipital (roll) axis by ±25-30 deg. We plotted the response fields of 51/117 neurons with light or dark bars in the upright position and in 1-2 tilted positions and compared the preferred stimulus orientations of the neurons in these body positions.

In striate cortex, most neurons (25/30) were of a non-compensatory type showing a change in the preferred orientation according to the body tilt and the estimated counterrolling of the eye. By contrast, about 40% of the neurons (8/21) in prestriate cortex (areas V2 and V3/V3A) were of a compensatory type preferring similar orientations in all body positions. For each neuron, we predicted the orientation preferred in the tilted positions from the orientation preferred in the upright position, assuming orientation constancy in retina centered coordinates and taking into account the conterrolling of the eyes. The difference between the predicted orientation and the actual orientation preferred in the tilted positions was small in non-compensatory cells (mean 6±11 deg) indicating orientation constancy in retina centered coordinates. This difference was significantly larger in compensatory cells (mean 23±2 deg) indicating invariance with respect to the direction of gravity, and thus orientation constancy in space centered coordinates.

In conclusion, our results suggest that information about the direction of gravity is implemented early in visual processing, in the monkey at the level of area V2.

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32.20 CODING OF SOUND SOURCE DIRECTION IN THE TROUT LOWER MIDBRAIN. Nico Schellart*, René Wubbels and Jeroen Goossens, Lab. Med. Physics & Inf., AMC, Univ. Amsterdam, Amsterdam, NL 1105-AZ The Netherlands.

The fish-ear is stimulated by sound causing displacement of the sensory hair cells relative to the otoliths, and by the pressure-into-displacement transforming swimbladder. Together they yield an elliptic stimulus. Binaural convergence, essential for unequivocal spatial hearing[1], occurs in the torus semicircularis (homologue to the inferior colliculus) where extensive auditory processing occurs.

The fish was attached to a 2-D vibrating platform. We examined whether the response features of directional selective units (DSUs) support (one of) the models[1] of directional hearing of fish. The computer-driven platform generated recti-linear or elliptic displacement bursts (0.5 to 100 nm at 172 Hz) of the fish skull (measured with a miniature 3-D accelerometer).

Acoustic units (N = 183), mainly localized in the upper torus, often (34%) are directionally selective. DSUs, which show strong topographic features[2] mostly (75%) show (strong) phase-locking. Direction selectivity is hardly dependent on intensity and encoded by spike density rather than by phase-locking. For a minority of the units the instant of firing is strongly dependent on direction. Occasionally, responses to clock- and anti-clockwise elliptic stimuli are different and distinguishable from those to recti-linear stimuli. The response features of DSUs cannot be incorporated easily in the current directional-hearing-models.

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32.21 "DELTA RESPONSE" IN COGNITIVE EVENT-RELATED POTENTIALS (ERPs): HINTS AT A FUNCTIONAL DIFFERENTIATION OF ERP FREQUENCY COMPONENTS. Martin Schürmann*, Canan Başar-Eroglu[1], Erol Başar. Institut für Physiologie, Medizinische Universität zu Lübeck, 23538 Lübeck, Germany; [1]Institut für Psychologie und Kognitionsforschung, Universität Bremen, 28334 Bremen, Germany

On the basis of a working hypothesis [Başar E: EEG Brain Dynamics. Amsterdam 1980] event-related potentials (ERPs) are interpreted as *stimulus-induced EEG rhythms*. In the present study healthy subjects were watching a checkerboard pattern. Stimuli A (checkerboard reversal; occurrence: 75%) and B (reversal with displacement; 25%) were applied in pseudo-random order. The subjects payed attention to stimulus B (TARGET stimuli).

TARGET stimuli elicited a P300-like response. Frequency domain analysis showed marked maxima in the delta-theta (0.5–5 Hz) range in responses to TARGET stimuli. This is in accordance with auditory P300 measurements. For occipital electrode positions, filtered ERP responses to TARGET stimuli show an early alpha (8–15 Hz) response maximum followed by a delta-theta (0.5–5 Hz) response maximum (around 400–500 ms). Delta-theta responses to TARGET stimuli were clearly visible even in unfiltered single EEG-ERP epochs.

Both the established cognitive role of P300 responses and previous studies – based on intracranial EEG/ERP measurements in primary sensory areas of the cat brain – imply a *functional differentiation of alpha and delta-theta responses*: the ERP alpha component might be predominantly involved in primary sensory processing, the delta-theta component might be correlated with cognitive processing and decision making.

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32.22 SOME DATA ON AVIAN LDA NUCLEUS WITH GOLGI AND PREEMBEDDING GABA-EM METHOD

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In the avian visual system the nucl.dorsolateralis ant. (DLA) thalami receives input from the contralateral retina and relays it bilaterally to the visual Wulst. This system was comparable to mammalian dorsal lat. geniculate nuclas (LGN). In his EM study, Watanabe found that also the synaptic organization in DLA nucleus is similar to that in mammalian LGN. Also GABA-ergic relay neurons were found in DLA. Two kinds of relay neurons, one excitatory and the other inhibitory were suggested to be in DLA. We examined the neuron types with Golgi method in DLA of chicken. To see the maturation process of the neurons, too, one-day-old and one-month-old chicken neurons were compared. The results showed basically two main types of neurons. 1.Large neurons with long axon; they are projection neurons. 2. short axon neurons with smaller perikarya and dendritic tree. They are local circuit neurons. The projection (large) neurons have two subtypes - they differ in shape from perikaryon, and dendritic arborization pattern. All types and subtypes of neurons have spiny dendrites. The interneurons are GABA positive proved by preembedding GABA EM method.

32.23 SYMPATHETIC-SENSORY COUPLING IN DORSAL ROOT GANGLIA: ULTRASTRUCTURE. Vera Shinder*, Shula Cohen and Marshall Devor, Institute of Life Sciences, Hebrew University, Jerusalem, 91904, Israel.

After sciatic nerve injury, sympathetic postganglionic axons sprout within the corresponding dorsal root ganglia (DRG) and form basket-like structures around large diameter axotomized sensory neurons. Sympathetic stimulation can activate such neurons. The site of the sympathetic-sensory coupling in the DRG is unclear. Tyrosine hydroxylase (TH) immunostaining was used to visualize sympathetic endings in the DRG at the ultrastructural level. In normal rats the few endings observed are associated with local blood vessels. Several weeks to months after sciatic nerve section there was prolific sprouting of TH-positive fibers, some of which formed dense baskets around sensory somata, particularly large diameter, light neurons. Serial sections with three-dimensional reconstruction of large neurons with baskets were made to determine the nature of apposition of TH-positive fibers to the neuronal soma. Results showed that TH-positive fibers ran on onion bulb-like layers of satellite cells that sprout around the axotomized neurons. The closest apposition obtained to the neuron soma was 0.5 µm. TH-positive fibers did not enter the cleft between the satellite cell sheath and the neuron. No synaptic endings occurred on neurons. We conclude that sympathetic-sensory coupling in DRGs is via non-synaptic noradrenaline release from sympathetic axons and diffusion of neurotransmitter to adrenoreceptors associated with the sensory soma.

32.24 DIRECT VISUAL INPUT TO PREMOTOR CORTEX FROM SUPERIOR PARIETAL CORTEX (AREAS V6 & V6A) IN THE MACAQUE MONKEY

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Premotor cortex has a distinct visual modality to its functional properties, but has not previously been shown to receive input from an area of cortex that is regarded as primarily visual. We have discovered one such source of input to premotor cortex by making injections of WGA-HRP into the caudal face of the superior parietal gyrus (SPG) in 5 anaesthetised macaque monkeys. In three of these we also obtained the pattern of interhemispheric connections (by staining for degenerating terminals after transection of the corpus callosum), and were able to show that the injection sites lay inside the callosally defined perimeter of visual area V6[1]. Subsequent analysis of the local laminar patterns of labelled cells and axon terminals persuaded us that callosal V6 was better regarded as two separate areas V6 and V6A – a conclusion that is also consistent with visual physiological data from this very region[2, 3]. The connections we describe here originate chiefly from area V6A, which lies immediately dorsal to V6 on the caudal aspect of the SPG.

V6A receives ascending visual input from V6, and also from areas V5, V3A and V3. Its frontal projections are to dorsal premotor cortex (but not the frontal eye fields) and terminate within the posterior bank of the arcuate sulcus (AS), and on the frontal gyrus just medial to the AS. V6A is also heavily interconnected with visual areas V5A/MST and 7a, and with visual/somatosensory association areas such as VIP, MIP and 7m. The latter include regions which have been characterised[4] as later stages in the somatic pathway for the limbs and trunk (as opposed to head, face and neck); provisionally V6A, or at least the region we injected, is responsible for visuomotor integration concerning locomotion and posture. V6A is also known to possess cells with visual fields expressed in craniocentric coordinates[5], a property that is also a reported feature of premotor physiology, and further indicative of the proposed role of V6 and V6A in spatiomotor behaviour.

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32.25 APPARENT MOTION ACROSS A SCOTOMA: AN IMPLICIT TEST OF BLINDSIGHT. Stoerig P[1]* and Fahle M[2], Institute of Medical Psychology, Ludwig-Maximilians-University, Goethestr.31, D-80336 Munich[1], and University Eye Hospital, D-72076 Tübingen, FRG[2]

In a patient who suffered a post-geniculate trauma, we measured apparent motion direction discrimination across the wedge-shaped field defect. Performance with two points flanking the field defect on its upper and lower border, was compared with performance when an additional third point appeared between these two. This third point fell within the defect, and thus made a perceptual difference only in the normal hemifield used for control purposes. With a MacIntosh IIci computer and 14" colour monitor, we tested at 15° eccentric positions in both fields, with the two or three points aligned parallel to the vertical meridian. Blue and red stimuli of 20' (normal field), 1° (both fields) and 2° (affected field) were used, and presentation times and intervals were varied to determine a range where upward vs downward direction discrimination was above the 50% chance level. This range included time constants short enough to require motion mechanisms for direction discrimination. To ensure comparability, presentations in the two-point condition were temporally separated by an interval that matched the presentation time of the third point in the three-point condition.

Results show that the additional third point significantly improved the patient's performance in the normal hemifield, and in the affected hemifield if the two visible stimuli were 1° in diameter. When 2° stimuli were used in a later session, the difference did not reach significance, although the middle point was 2° in both cases. We conclude that a) a F-motion mechanism can bridge a visual field defect, and b) a summation effect can be demonstrated under certain spatiotemporal conditions.

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32.26 STUDY OF THE SYNAPTIC CONFIGURATION OF IC NEURONS USING A COMPARTMENTAL MODEL.
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Information processing in the auditory midbrain was studied by using a simulation of a single-unit model.

The inferior colliculus (IC) neuron was modeled as a relatively small compartmental structure, in which known morphological and electrophysiological characteristics of real IC neurons were combined. An active compartment with ion channels expressed by Hodgkin-Huxley type equations imitated soma. The dendritic tree was constructed from passive compartments. Inputs from other auditory structures and IC neurons were described by suitable point processes.

The experimental data were obtained in anaestethized guinea pigs by extracellular recordings of single-unit activity. Tones at characterictic frequencies were used for stimulation of neuronal activity.

The effect of synaptic configuration on spike-discharge activity was investigated by systematic variation of variable synaptic parameters - the number of excitatory and inhibitory synapses, their position and their strength. A complex set of characteristics was constructed for both experimental and simulated data to give a base for evaluation of agreement between simulated activity and those recorded. Especially in the presence of both, excitatory and inhibitory inputs, the simulated activity closely resembled the observed.

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32.27 CHANGES IN THE NADPH-DIAPHORASE REACTION IN THE AUDITORY PATHWAY OF THE RAT AFTER NOISE EXPOSURE. J. Syka* and R. Druga, Institute of Experimental Medicine, Academy of Sciences of the Czech Republic and Institute of Anatomy, 1st Medical Faculty, Charles University, Prague, Czech Republic.

The NADPH-d / NOS positive neurons in the CNS of mammals are localized in many subcortical and cortical structures and their distribution is not identical with any other neurotransmitter system. Partial colocalization of NADPH-d/NOS has been found, however, with some peptides and with the ChAT. The expression of NADPH-d /NOS *de novo* has been described in neurons as a result of axotomy, chronic algic stimulation and damage of the nervous tisssue. The cochlear nuclei and the nuclei of the superior olivary complex in the intact rat do not contain NADPH-d positive neurons (Druga and Syka, 1993). After noise exposure (third-octave band noise at 16 kHz for 1 hour, intensity 105 dB SPL) expressions of NADPH-d in neurons of the cochlear nuclei and in some nuclei of the superior olivary complex were found in pigmented rats (weight 250-300 g). The histochemical reaction for NADPH-d according to Scherer-Singler et al. (1983) was used. NADPH-d expression first occurred 24 hours after exposure in the dorsal cochlear nucleus, the LSO, the MSO, the SPO and the MTB. Later positive perikarya appeared in the ventral cochlear nucleus. The NADPH-d positivity produced in the brainstem auditory nuclei by noise exposure gradually disappeared and 4 weeks after exposure the positivity remained only in the VCN and the MTB. The results demonstrate that exposure of the rat to noise may result in transitory NADPH-d positivity in neurons of the acoustical brainstem nuclei, which under normal conditions are NADPH-d negative

R. Druga and J. Syka: NeuroReport, 4, 999-1002, 1993.

32.28 INFLUENCE OF CCK-8 AND CLONIDINE ON SUPRASPINAL MODULATION OF NOCICEPTIVE PROCESS.
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Experiments were carried out on rabbits with permanently implanted electrodes into motor-sensory cortex (MSC), ventro-lateral posterior thalamic nuclei (NVPL), hippocampus (HIP), and lateral reticular formation (LRF) where additionally a cannula was implanted. CCK-8 in doses 100ng and 200ng/rabbit and Clonidine (in concentr. 5mg/ml) were administered locally. Nociceptive stimulation (NS) was performed by means of electrical pulses (60Hz, 8mA, 5s) applied to the front paw. Bioelectrical activity (BA) before and after NS was analyzed by means of spectral analysis (FFT), Autoregressive Method (AR) and directed transfer functions (DTF).

NS changed power spectra of BA in analyzed structures and increased the synchronism between NVPL and MSC, HIP and MSC and between HIP and NVPL. NS after CCK-8 in a dose 100ng had no significant influence on BA nor did influence the synchronism between structures. NS after the dose of 200ng produced significant changes in BA of MSC and NVPL and increased synchronisation between NVPL and MSC and between HIP and MSC. NS after Clonidine changed power spectra of BA only in MSC and increased the synchronism between HIP and MSC and between NVPL and HIP. NS after administration of Clonidine together with CCK-8 in both doses changed BA in MSC. We observed increased synchronism between NVPL and MSC and between HIP and MSC after the dose of CCK-8 of 100ng. After the dose of 200ng CCK-8 increased the synchronism only between NVPL and MSC.

These results suggest that either Clonidine or CCK-8 (more significantly in the 100ng dose) administered to LRF separately have inhibitory effect on nociceptive process. Administration of Clonidine together with CCK-8 (mainly in the 100ng dose) have oposite effect and even enhance the pain transmission.

32.29 SYNAPTIC RESPONSES AND EFFECT OF PHYSIOLOGICALLY AND ANATOMICALLY IDENTIFIED DOUBLE BOUQUET CELLS IN CAT VISUAL CORTEX. G. Tamás*, E. H. Buhl and P. Somogyi, Medical Research Council, Anatomical Neuropharmacology Unit, Oxford Univ., Mansfield Rd. Oxford, U. K.

In the heterogeneous population of cortical GABAergic neurones *double bouquet cells* (DBCs) of layers II-III are distinct, as they give rise to radially oriented, tight axonal bundles traversing all cortical layers. Previous studies showed that DBCs provide synapses to dendritic shafts and spines, contain calbindin and neuropeptides. However, the identity of postsynaptic cells and receptor mechanism(s) or the sources of their afferent input remain unknown. Recordings were obtained in an *in vitro* slice preparation with biocytin-filled electrodes from putative interneurones of areas 17 and 18. The afferent and efferent connectivity of DBCs was determined with paired intracellular recordings from synaptically coupled pre- and/or postsynaptic neurones. Slices were processed for light and electron microscopy (Buhl et al., Nature 368. 823). Following the recovery of 5 DBCs, the analysis of 3 axons showed that they established 4,600 - 5,500 light microscopically detectable boutons; 9-11% in layer I, 75-85% in II/III, 4-9% in IV, 1-3% in V and 1-2% in layer VI. Electron microscopic random samples of the postsynaptic targets of DBCs (n=2) revealed an efferent output being directed mainly towards dendritic spines (70-82%) the remainder being dendritic shafts. Physiological analysis of DBCs revealed that in response to current injection they fired rapid trains of short-duration (<0.4 ms at half-amplitude) action potentials which were followed by deep short-latency afterhyperpolarizing potentials. In 2 postsynaptic pyramidal neurones DBCs elicited short-latency IPSPs with rise and decay kinetics comparable to those of $GABA_A$ receptor mediated potentials. In turn, one of these DBCs received a fast EPSP from the recurrent axon collaterals of the pyramidal cell. Three DBCs were postsynaptic to GABAergic basket cells, two of which elicited fast IPSPs in DBCs. Two of these 3 DBCs reciprocally innervated the basket cells. In conclusion, we show that GABAergic DBCs are reciprocally connected to pyramidal cells, and elicit fast inhibition through synapses on dendritic shafts and spines, strategically placed for the local control of incoming afferent excitation. Basket and DBCs reciprocally influence each other through $GABA_A$ receptors.

32.30 GOLGI AND EM-GOLGI STUDY ON THE AVIAN TECTUM OPTICUM
Teréz Tömböl
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In the external seven layers of avian tectum, nearly all dendrites of neurons of tectum, and the majority of afferent fibers are present. The optic information from these layers is transferred by the large neurons (ganglion cells) of the 13th layer (using the Cajal nomenclature) to nucleus rotundus, the thalamic visual center. The dendrites of these neurons are extended in a large field (might be 1000 µm or more in dorso-ventral and the same in rostro caudal direction) The number of dendrites is very low, but they are branching by bifurcating numerous times before they enter, as very thin dendrites, into the outer layers of tectum. One group of these dendrites terminates in layers 4-5, the other in layer 3. The optic fibers in these layers develop a very dense, vertically arranged terminal plexus. They contact the terminal section of the dendrites. Large neurons with huge, thick, long dendrites interlace layers 3. and 5. creating a dense network. These neurons and also their EM relations to the optic fibers and ganglion cell dendrites were observed. They might modulate the effect of optic and Ipc as well as Imc fibers.

32.31 BEHAVIOURAL CONTRAST SENSITIVITY IN CATS: DEPENDENCE ON THE VELOCITY OF THE VISUAL STIMULUS.

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The bandwidth and the maximum of the human contrast sensitivity function is not altered by image motion. The effect of increasing the velocity of the grating is to slide the spatial frequency window down the spatial frequency scale. The relevant parameter in perception of a moving grating seems to be the temporal frequency of the stimulus. Electrophysiological recordings in area 18 of the cat have shown similar behaviour. Neurones shift their spatial frequency response characteristics to lower spatial frequencies when the velocity of the stimulus increases. In single units, however, the temporal frequency is not the relevant parameter: when plotting the same data on temporal rather than spatial frequency axis they do not superimpose as it is the case in man. The aim of the present experiment was to determine behaviourally the contrast sensitivity function at various velocities in the cat and to compare the results with those obtained in single units and human subjects. Measurements were performed in 2 cats trained to push either the right pedal in response to a grating of variable contrast, spatial frequency and drifting velocity presented on the monitor screen or the left pedal in response to a blank of equal mean luminance.

The range of visible spatial frequencies at increasing the velocity of the visual stimulus shifts in cats, as in man, toward lower frequencies without major change in the maximum sensitivity. At variance with results obtained in single units, the temporal frequency of the stimulus seems to be the relevant parameter.

32.32 LONG-LASTING EFFECTS OF NEONATAL DESTRUCTION OF SEROTONERGIC AFFERENTS ON MORPHOLOGY AND ACTIVITY OF THE BARREL FIELD IN RAT.

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Recent papers (cf. J. Neurosci. 14:7594-7607) show that serotonin influences development of somatosensory cortex in albino rat. After neonatal lesion of serotonergic axons, at the age >60 days area of the barrel field was shrunk by about 20%. We decided to check these results in another (hooded) strain of rats and to find how the depletion of serotonin during development influences the activity of the barrels evoked by stimulation of vibrissae. On the day of birth pups were pretreated with desipramine and one hour later half of them received injection of 5,7 DHT. The injections were repeated in 24h. At the age of six weeks 2 rats of each group were processed for serotonin immunostaining. In rats injected with 5,7 DHT 70-90% of serotonergic fibers in the cortex were missing. Remaining rats (4 in each group) had their vibrissae clipped on both sides with the exception of row C, were injected with H^3 2-deoxyglucose and had their vibrissae of the rows C on both sides stimulated for 45 minutes. Then animals were killed and quickly perfused. The cortex of both hemispheres was removed, flattened and cut on a cryostat at 40μm. Autoradiograms of the sections were processed with an automatic system and the sections were Nissl-stained. Measurements of the size of barrels of the row C showed that their linear dimensions were 5-10% smaller than in the untreated littermates. The width of the activated zone on the autoradiograms was 10-20% smaller in the serotonin-lesioned rats. These results confirm the previous results and show that the functional deficits due to the serotonin depletion are even larger than the anatomical ones.

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32.33 THE INFLUENCE OF VARIOUS PATTERN OF STIMULATION ON THE CHEMORECEPTORS IN Periplaneta americana (L.).

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Antennal chemoreceptors in Periplaneta americana were investigated using electroantennographic (EAG) method. Chemical stimuli (ethyl acetate) were applied continously with a constant frequency or with a break in stimulation of different duration. The mode of stimulation influenced the parameters of adaptation (in terms of amplitude and duration of the EAG).

The chemoreceptors under the influence of a nonspecific pheromone (Tomodor, Tomicus piniperda) showed a decrease of both amplitude and duration of the EAG compared with the effect of ethyl acetate. The future work will comprise the use of specific pheromones.

32.34 MULLER CELLS IN LIGHT AND DARK ADAPTED RETINAS OF MACACA FASCICULARIS

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In goldfish a major morphological difference between dark and light adapted retinas exists. In light adapted retinas the dendrites of horizontal cells form spinules which protrude into the cone pedicle. The aim of this study was to investigate whether this phenomenon was also present in cynomolgus monkey (Macaca fascicularis). One eye of the monkey was dark adapted and one eye was light adapted as verified with ERG recordings immediately prior to enucleation under infrared illumination. The monkey was transcardially perfused with a glutaraldehyde/paraformaldehyde solution and the retinas were processed for light and electron microscopy.

No obvious differences were observed betweeen the cone pedicles of light and dark adapted retinas. Careful observation revealed a major difference in the ultrastructure of the Müller cells. In the cytoplasm of the light adapted retina many electron dense particles were present possibly representing glycogen. These particles were also present in the cone pedicle, but not in the rod pedicle. Light microscopy using PAS staining revealed that these particles indeed represent glycogen.

The presence or absence of glycogen particles may reflect the difference in metabolic activity of the dark and light adapted retina.

At present a possible difference in glycogen content is investigated in the goldfish.

32.35 RECEPTOR mRNA DENSITIES AND PSYCHOMETRIC MEASURES AS DETERMINANTS OF ANGINAL PAIN.

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This investigation was undertaken in order to explain the variability in symptomatology of patients with significant Coronary Artery Disease, on the basis of psychological and physiological variables. The psychometric variables include the degree of depressiveness and anxiety, subjectively experienced quality of life and coping strategies. Among the physiological parameters are the levels of Adenosine A1 and Bradykinin B1/2 receptor mRNA in the myocardium. The anginal pain characteristics and the psychological parameters were assessed by means of an interview, held approximately three weeks prior to the bypass surgery. During the surgical procedure, the auriculum of the right atrium was withdrawn; from this the RNA was extracted. A semiquantitative Reverse Transcriptase Polymerase Chain Reaction was performed with the aid of which the densities of the abovementioned mRNA types, known to be involved in pain transmission, were measured.

The variability in intensity of the anginal pain cannot be explained by any of the parameters under investigation, in contrast to the variability in quality of anginal pain; patients reporting a type of strangling pain are on the average older and express lower levels of Adenosine A1 receptor mRNA in their myocardium as compared to patients reporting discomfortable anginal pain. The psychometric variables do not differ between these two groups of patients.

32.36 INTERACTION BETWEEN SYNAPTIC ACTIVATION AND INDUCED MEMBRANE POTENTIAL OSCILLATIONS IN NEURONS OF THE VISUAL CORTEX.

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Whole-cell recordings were made from layer 2-3 pyramidal cells in slices of the rat visual cortex. Sinusoidal oscillations of the membrane potential (Vm) were induced by injection of sine-wave currents (10-50 Hz). The modulation of Vm was phase-shifted relative to the injected current reflecting the membrane time constant. If spikes occurred they appeared at the positive peaks of the oscillations. Their phase-shift relative to the injected current depended on Vm and the modulation depth and increased systematically with the number of cycles. Synaptic responses were evoked by electric shocks applied through stimulation electrodes located 0.5-1.5 mm below or lateral to the recording site. Sub-threshold synaptic activation triggered spikes when superimposed on the induced oscillations and the spikes occurred at the peaks of the Vm oscillations irrespective of the timing of afferent stimulation relative to the oscillation cycle. If single EPSPs had a pronounced NMDA-receptor mediated component they evoked a sequence of spikes (>100 ms) which occurred at the peaks of the oscillation and therefore with a frequency corresponding to the oscillation period.

These results indicate that an oscillatory modulation of Vm, which is an emergent property of cortical networks *in vivo*, leads to substantial modification of input-output functions: It synchronizes responses with the oscillation cycle irrespective to the precise timing of the input and generates trains of equally distributed spikes in response to a single EPSP. It is proposed that these properties are exploited to synchronize the responses of distributed cortical neurons.

32.37 EEG-SYNCHRONIZATION SEEMS TO REFLECT FUNCTIONAL PROPERTIES OF THE UNDERLYING CORTICAL NETWORKS IN THE HUMAN BRAIN

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The synchronization of EEG signals, expressed by their amplitude and coherence, seems to reflect characteristics of the stimulus structure as well as of the neuronal ensembles involved in processing. We have found basic differences in EEG synchronization between visual processing and auditory processing, auditory processing leading to an *increase* in synchronization and visual processing leading to a *decrease* in synchronization, in 20 human subjects. We think that these results reflect functional differences between visual and auditory processing: Auditory information is temporal Gestalt and should therefore need some short term storage which may be the reason for longer lasting synchronizations measurable in the EEG. Visual processing, instead, needs good spatial resolution with many and very small ensembles - the Hubel &Wiesel detectors - synchronizing differently and very quickly alternating; these synchronizations do not sum up to be measured in the EEG, but instead lead to a desynchronization of the whole network.
We propose that the activation of different Hubel&Wiesel detectors is the reason for a desynchronization in the summed activity in visual processing. This hypothesis was tested by addressing as many equally oriented Hubel&Wiesel detectors as possible. With more similarily oriented bars in the visual field, more neuronal ensembles should be synchronized and thus higher amplitudes should be measured in the EEG. Visual stimuli with increasing number of equally oriented bars were presented within 4° of a subjects central visual field (1-164 contrasts / 4°) and EEG was recorded above the visual cortex. Indeed, a correlation between EEG amplitude and amount of equally oriented bars / ° seems to exist for distinct frequency ranges.
Thus, EEG gives insight on information processing in the underlying cortical network.

32.38 DYNAMIC STRUCTURE OF THE VISUAL RECEPTIVE FIELDS IN THE TECTO-PARABIGEMINAL COMPLEX OF THE CAT

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The visual receptive field structure of 12 superior colliculus and 5 parabigeminal nucleus cells was examined using single unit extracellular recording. The cells were tested with a light bar moving along horizontal axes of their receptive fields within a limited range of 0.5° to 10°, in several test-zones. The intensity of cell responses and the direction sensitivity indexes varied depending on the locations of the test-zone in the receptive field. Most collicular cells (9) showed structural heterogeneity, six of them had opposite types of responses to stimulus movement within the test-zones when compared to the clear-cut direction sensitive response of a cell for movement throughout the whole receptive field. Three collicular cells, directionally nonsensitive when tested with full length movement along the horizontal axis, showed directional responses to small amplitude movements in different test-zones of the receptive field. The receptive fields of three other collicular cells were homogenous with nondirectional characteristics. All tested parabigeminal cells had a receptive field structure similar to collicular cells with a homogenous response. The parabigeminal neurones required larger summation region for a stimulus movement to evoke their response.

These results suggest that receptive fields of most collicular cells are composed of elements with different characteristics which interact to form a global response and that collicular cells with a nondirectional homogenous receptive field may be a source of projection to parabigeminal nucleus.

32.39 *BARRELLESS* MICE HAVE AN ORDERED WHISKER REPRESENTATION IN THE SOMATOSENSORY CORTEX (SI); A DEOXYGLUCOSE STUDY.

Egbert Welker* and Gilles Bronchti, Institute of Anatomy, University of Lausanne, 1005 Lausanne, Switzerland.

In SI of mice the representation of an individual mystacial vibrissa has a morphological correlate in the form of a barrel in layer IV. *Barrelless* mice lack barrels in SI, but have whisker-related patterns in the lower stations of the pathway. Here, we investigated the cortical whisker representation in *barrelless* (n=8) and normal mice (n=6) using the deoxyglucose method. Adult mice had all whiskers on the left side clipped except those of follicles C1-3, or of follicles B1-3 and D1-3. After the injection of ^{14}C-deoxyglucose mice explored an object-filled cage. Then they were anaesthetised, transcardially perfused and their hemispheres cut tangential to the pial surface above SI. Analysis of DG uptake patterns in layer IV showed that the cortical whisker representation in *barrelless* is topologically organised in an identical manner as in normal mice. A quantitative analysis revealed that areas of stimulus-dependent DG uptake were larger in *barrelless* than in normal mice. We conclude that in *barrelless* the whisker representation in SI is somatotopically organised and suggest that the larger representation of individual whiskers is due to a diminished spatial segregation of the thalamo-cortical afferents in layer IV. Support: Swiss NSF 31-39184.93

32.40 THE REGULATION OF RETINO-CORTICAL SIGNAL TRANSMISSION BY TEMPORALLY STRUCTURED ACTIVITY IN THE LGN.

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The temporal structure of cell responses in the LGN of anesthetized cats has been studied with flashing dot stimulation. During the tonic response multiple peaks, spaced equidistantly, were observed in the inter-spike interval distribution. This behaviour can be explained by a one-to-one transmission from retina to LGN and a superimposed intra-LGN deletion mechanism. The incoming retinal spike train induces the interval peak containing the shortest intervals (*fundamental intervals*), and longer intervals occur as multiples thereof, contributing to the higher order peaks. Different computer models, with varying levels of abstraction have been designed and we predict that the temporal structure observed in LGN cells could in principle subserve several mechanisms: 1) Disambiguate confusing stimulus situations: Due to the surround inhibition of LGN cells a trade off exists between stimulus size and contrast and the mean firing rate is identical for multiple combinations of these stimulus parameters. Time strucure can help to discriminate between these situations. 2) Flow control to the visual cortex: Cortical cells act as coincidence detectors and will only fire if enough input spikes arrive at almost the same time. Deletion inhibition in the LGN, which leads to the observed interval peaks can, therefore, efficiently shut down the input to the cortex. 3) Flow control within the corticofugal feedback loop: The corticofugal activity restructures the observed temporal patterns in the LGN. A primary facilatory influence from the cortex leads to a predominance of the fundamental interval peak in the LGN and to a pronounced synchronisation effect between the cells. 4) Enhancement of the robustness of the thalamocortical pathway. To be able to exert an effect on the LGN the corticofugal feedback loop requires a coincident (synchronous) activity pattern. Random (noisy) inputs will not drive the loop. On the other hand, once active, the loop will also be resistant against a few missing input spikes. Therefore, this system can act like a switch with hysteresis. Statements 1-3 were tested experimentally and the results don't conflict with the predictions of the models.

32.41 ACTIVITY IN THE AUDITORY PATHWAY ELICITED BY ELECTRIC STIMULATION OF THE COCHLEA IN THE RAT: FOS AND DEOXYGLUCOSE DATA.

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Fos-like immunoreactivity (FLI) and 2-deoxyglucose (2-DG) uptake were used to map the activity evoked in the auditory pathway by unilateral electric stimulation of the cochlea (20 μs pulses delivered at 50 Hz in a bipolar apex to base configuration) in an animal model of cochlear implant. After 45 minutes of stimulation followed by immediate sacrifice, FLI was dense in the ipsilateral dorsal cochlear nucleus (DCN), moderate in the contralateral DCN, the posteroventral cochlear nucleus and the lateral lemniscus. Sparse FLI was seen in the superior olivary complex (SOC: mainly in the lateral nucleus), while the anteroventral cochlear nucleus was free of labeling. In the inferior colliculus, FLI was moderate to dense in the external and dorsal nuclei while it was sparse in the central nucleus. In the thalamus, dense FLI was found in the peripeduncular nucleus, the dorsal and medial divisions of the medial geniculate body (MGB) while its ventral division was free of FLI. The same stimulation evoked an increased 2-DG uptake in the cochlear nucleus and SOC, consistent with the distribution of FLI. However, in contrast to FLI, 2-DG uptake was increased mainly in the central nucleus of the inferior colliculus and in the ventral division of the MGB. The general distribution of FLI was maintained when durations of stimulation were shortened (upto 5 minutes), but the number of FLI neurons progressively decreased. The number of FLI neurons augmented for increasing stimulation intensities. Stable FLI was seen in the cochlear nucleus for survival times ranging from 0 to 3 hours, but decreased for longer periods (5 or 6 hours), while in the MGB it was unchanged for such long survival times. The two functional markers FLI and 2-DG labeled different midbrain and thalamic nuclei for the same stimulus, possibly reflecting different, complementary, aspects of the activation of these auditory nuclei.

32.42 DEVELOPMENT OF THALAMOCORTICAL INNERVATION IN THE MARSUPIAL NORTHERN NATIVE CAT (*DASYURUS HALLUCATUS*)

Zoltán Molnár*, Leah Krubitzer[1] John E. Nelson[2] and Colin Blakemore
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Marsupials are born at a stage equivalent to early fetal life in eutherian mammals. We hope to investigate the effects of thalamic and cortical manipulations on forebrain development in an Australian marsupial, the Northern Native Cat (*Dasyurus hallucatus*), whose cortex is divided into a number of distinct physiological and cytoarchitectonic fields. To facilitate comparison with other species we set out to establish the pattern and time-course of thalamocortical innervation. Carbocyanine dyes (DiI, DiA and DiAsp) were used to trace thalamic axons in eight paraformaldehyde-fixed brains of various postnatal (P) ages (one each at P13, 15, 24 and 30; two at P18 and 23). After 4-6 weeks incubation at room temperature, 75-100 µm-thick coronal or horizontal sections were cut, counterstained with bisbenzimide, and examined by fluorescence microscopy. Placement of crystals in the thalamus at P13 and 15 revealed thalamic fibres extending into the internal capsule, but not yet reaching the cortex. At this stage, cells of the cortical plate are beginning to migrate into position, splitting the earlier-generated preplate into marginal zone and subplate. By P18, thalamic fibres have reached and accumulated below the cortical plate but have not yet entered it: at this stage crystals placed in the cortex retrogradely label clusters of thalamic cells. By P30, thalamic axons have entered the lower two-thirds of the thickness of the cortex but not the dense cortical plate (migrating and newly-arrived neurons), which constitutes the upper third. By this time, cortical neurogenesis is close to completion, judged by the rarity of mitotic spindles in the ventricular and subventricular zones. Thus thalamocortical innervation in the Northern Native Cat appears to follow an algorithm of development similar to that in eutherian mammals but with events between P13 and P30 corresponding to those between embryonic day E14 and P2 in the rat.
Supported by the MRC, Merton College Oxford and a Ciba Foundation Bursary to ZM.

32.43 **THE ORGANIZATION OF NEOCORTEX IN THE AUSTRALIAN MARSUPIAL (*DASYURUS HALLUCATUS*).** L. Krubitzer[1,2], J. Nelson[3], and J. Clarey[1]. [1]VTHRC, Dept. of Physiol. and Pharm., University of Queensland, Australia, [2]Centre for Neuroscience and Dept of Psychology, University of California, USA, and [3] Dept. of Ecology and Evolutionary Biology, Monash University, Australia.

The northern quoll is a ground dwelling, nocturnal marsupial of the family Dasyuridae. It has a number of specialized features including striated glabrous hand pads, and wrist, chin and snout vibrissae. In the present investigation we hoped to determine if any of these morphological specializations are reflected in the organization of somatosensory cortex. Using microelectrode recording techniques, neurons were recorded at a number of closely spaced recording sites and stimulus preference, and receptive field size and location were determined. We found evidence for three complete representations of the sensory surface, each of which was coincident with a unique architectonic appearance. The primary somatosensory area, SI, was similar to SI described in other mammals, and a large proportion of this field was devoted to representing the hand pads and specialized vibrissae. The rostral and caudal divisions of the deep somatosensory area (DSr and DSc respectively), contained neurons that preferred a broad, intense stimulus. Most of the representation in DSr and DSc was dominated by inputs from the hand. Finally, a small lateral somatosensory area was identified in the approximate location of SII described in other mammals. This work, as well as observations in a variety of other metatherian and prototherian mammals suggests that the neocortex reflects species specializations, and that multiple somatosensory fields may have been present in our earliest mammalian ancestor.

TUESDAY

33. Poster Session: Behaviour I

33.01 **A ROLE FOR CHICK MEMORY-ASSOCIATED N-CAM FRAGMENTS IN MEMORY PROCESSING IN THE RAT**
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A polyclonal antibody which recognises a specific fragment of neural cell adhesion molecule (N-CAM), raised against chick, and having amnestic action in the chick, was injected in three-month old rats after one trial passive avoidance learning. Intraventricular injections through bilaterally implanted cannulas of 8 µl antibody or saline were made 5.5h post training. There was an amnestic effect of the antibody which was significant for a retention interval of 48h but not 24h. A series of control experiments ruled out an effect due to increased activity as consequence of the treatment. Other experiments showed that the amnesic effect could not be due to stressful handling during training-to-test interval or to increased cerebroventricular volume during injection. In a final replication, there was no effect of preimmune serum, while the antibody produced the expected amnestic effect at 48h. Thus the amnestic effect of the antibody can generalise from chick to rat and reinforces the view that long term memory formation involves synaptic remodeling dependent upon specific membrane glycoprotein synthesis.

Supported by the ESF program on Neural Mechanisms of Learning & Memory

33.02 EVENT-RELATED POTENTIALS DISSOCIATE STEM COMPLETION WITH AND WITHOUT EXPLICIT MEMORY K. Allan* and M.D. Rugg, Wellcome Brain Research Group, University of St. Andrews, Scotland.

This study used event-related brain potentials (ERPs) to investigate the circumstances in which priming in normal subjects is accompanied by explicit memory. Subjects viewed words in two randomly interleaved study tasks, a 'semantic' task (is the meaning of MOTEL pleasant or unpleasant?), and a 'nonsemantic' task (are the vowels in MOTEL in alphabetic order?). At test, subjects were shown a list of three letter word 'stems' (e.g. MOT__), half of which could be completed with studied words. The task was to complete each stem with the first suitable word to come to mind. Priming was measured as the bias to complete word stems with studied words rather than an alternative (e.g. MOTEL rather than *MOTOR*).

Significant priming of completions occurred for words studied in both tasks. The ERPs evoked by completions with semantically studied words showed a temporally extended, frontally maximal enhanced positive shift relative to the ERPs evoked either by completions with non-semantically studied words, or the ERPs evoked by completions with unstudied words. These latter two ERPs did not differ.

The positive shift closely resembles that found in recent ERP studies of recognition and cued recall, where it was linked to explicit memory for the studied words. It is likely therefore that successful completions of semantically studied words were accompanied by explicit memory for their prior occurrence. The absence of the positive shift in the ERPs to stems completed with non-semantically studied words is consistent with other evidence that significant priming can occur in normal subjects without appreciable levels of explicit memory for the studied items.

33.03 MULTISITE OPTICAL RECORDINGS FROM PROCESSES OF INDIVIDUAL INVERTEBRATE NEURONS S. Antic* and D. Zecevic, Institute for Biological Research, Belgrade, Yugoslavia; Yale Univ. Sch. Med., New Haven, USA

The major motivation for developing optical methods for monitoring membrane potential is the possibility of making simultaneous multisite measurements of neural activity. Intracellular applications of voltage-sensitive dyes provide functional visualisation of neural processes where most of the signal integrations take place (Antic et al., J. Neurosci.15, 1392-1405, 1995). This approach was limited to neurons that are anatomically suitable for epifluorescence measurements being positioned in the superficial layer of the ganglion.

Here we demonstrate optical signals obtained from identified neurons with processes located deeper in the neuropil of the suboesophageal ganglion of Helix apersa. Changes of membrane potential were simultaneously detected from multiple sites along all three principal neurites. Best signal-to-noise ratio was 30. Spread of the action potential evoked by microelektrode stimulation was optically followed up to 1000 µm away from the soma. This extension in optical methods to non-superficial cells is based on the improvements in dye injection protocol to increase the concentration of the injected dye, and mechanical removal of superficial cell layer to reduce light scattering. The present approach will facilitate further investigation of signal initiation, spread and summation at the level of processe of individual neurons.

33.04 **DOES REWARDING ELECTRICAL STIMULATION OF LATERAL HYPOTHALAMUS FACILITATE LEARNING OF CONDITIONED NICTITATING MEMBRANE RESPONSE IN RABBITS?** **J. Arikoski*, T. Korhonen, M. Penttonen, T. Ruusuvirta and J. Wikgren, Dept. of Psychol., Univ. of Jyväskylä, P.O. Box 35, SF-40351, Jyväskylä, Finland.**

There are only few observations of rewarding effects of an electrical brain stimulation (ESB) on classical conditioning of nictitating membrane (NM) response in rabbits. There are also a few if not at all such studies in which both the rewarding pre- and post-ESB is present. In this study control rabbits (CC group) were classically conditioned with a tone conditioned stimulus (CS) and an airpuff unconditioned stimulus (US). In test groups, the ESB either preceded (CCpre group) or followed (CCpost group) the CS-US presentation.

Results indicated that during the CS periods of the CS test trials (an unpaired control tone) all the groups showed significant increase in the CR amplitude over days ($F(1.50, 40) = 22.48$, $p < .001$). After five days of conditioning it could be identified that the CCpost group showed faster CR acquisition than the CC group, whereas only a slight CR could be identified from the CCpre group. In this phase a significant Treatment x Day interaction ($F(2.99, 40) = 3.56$, $p < .05$) was observed.

Due to these facts we conclude that the ESB of the lateral hypothalamus given as post stimulation is sufficient to facilitate classical conditioning of the NM response. In this study also evoked potentials and multiple-unit recordings were obtained from hippocampus (CA1, CA3 and dentate gyrus). We are working on this data.

33.05 VOLUMES OF FRONTAL LOBE SUBREGIONS IN PATIENTS WITH SCHIZOPHRENIA IN RELATION TO COGNITIVE FUNCTION AND CLINICAL SYMPTOMATOLOGY. W.F.C. Baaré*, H.E. Hulshoff Pol, R. Hijman, K. van Reenen, M.A. Viergever, W. Mali, R.S. Kahn. Depts of Psychiatry, and Radiology, University Hospital Utrecht, Heidelberg 100, 3584 CX Utrecht, the Netherlands

Data from behavioral and functional imaging studies suggest that the frontal lobes are implicated in schizophrenia. Studies examining frontal lobe morphology have been few. Furthermore, most of these studies only measured total frontal lobe volume (33 % of the total brain volume). While abnormalities in frontal brain volume have been reported, the findings are inconsistent, as are the results from studies examining the relationship between frontal lobe morphology, symptoms and cognitive function. These inconsistent findings may be due to the fact that some subregions of the frontal lobe are involved while others are not.

MR imaging was performed on a 0.5 T Philips Gyroscan. Coronal T1-weighted gradient-echo 3D MRI scans (1.2 mm slices, TR =30 ms, TE=13 ms, 256 mm FOV) were obtained from fifteen male patients with schizophrenia and fifteen age, sex, handedness, and parental education matched healthy controls. Three-dimensional volume reconstruction of the brain enabled the identification of surface landmarks necessary for the demarcation of different frontal brain regions. Accurate volume measurements were obtained for the medial and dorsolateral prefrontal and orbitofrontal subregions. Symptoms were evaluated through the Positive and Negative Syndrome Scale (PANSS). Tests assessing frontal lobe function included the Tower of London Test and Subjective Ordering Tasks.

The results in patients with schizophrenia versus healthy controls will be discussed.

33.06 INFLUENCE OF SEPTAL NORADRENERGIC AND CHOLINERGIC SYSTEMS ON SPATIAL LEARNING AND MEMORY.

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In order to hightlight the role of noradrenergic (NA) afferents to the septal region in spatial working memory performance, C57BL/6 mice were infused bilaterally intraseptally with 500 ng/0.2 µl of a selective α1-adrenoceptor antagonist, the BE2254. The consequences of this reversible treatment were evaluated on spatial working memory performance expressed through the acquisition of a delayed non-matching to place (DNMTP) rule achieved in a eight-arm radial maze. In these conditions the results suggest that septal NA activation is not essential for the expression of spatial working memory per se but seems rather necessary to process new features of the environmental context. The possibility that septo-hippocampal cholinergic activity participate at this information processing function was further investigated after infusion of 2.5 µg/0.2 µl of scopolamine into the medial septal area before the habituation session. In this case, scopolamine induced a substantial improvement of time spent for visiting the eight arms. The next day, when mice were required to learn the DNMTP rule, they showed an improvement of their performances by comparison with saline group, which was not observed when animals were tested in a different spatial environment. This unexpected improvement was interpreted as an indication of a paradoxical better knowledge of the environmental context due to the lengthening of the habituation session duration. Altogether these results and recent electrophysiological data (BELOTTI et al., 1995) suggest that NA activation which takes place on early stage of this spatial learning situation, facilitates the treatment of stimuli associated with the experimental context through the modulation of septo-hippocampal loop activity.

33.07 **INTRACEREBROVENTRICULAR INJECTIONS OF THE PROTEINASE INHIBITOR LEUPEPTIN AND THE LYSOSOMOTROPIC AGENT CHLOROQUINE DIFFERENTLY AFFECT THE BEHAVIOR OF RATS.**

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Intracerebroventricular (icv.) infusions of leupeptin and chloroquine produce similar, Alzheimer-like neuropathologic changes in rat brain (interruption of lysosomal protein degradation, inhibition of calpains, accumulation of lipofuscin-containing dense bodies; generation of amyloidogenic fragments of amyloid precursor protein, accumulation of neurofibrillary tangles etc.). Leupeptin has been shown to impair the memory of rats in the radial maze but not in the passive avoidance test. Behavioral effects of chloroquine have yet not been studied. We investigated the behavior of rats after multiple icv. injections of leupeptin, chloroquine and a combination of both, in different behavioral situations (passive avoidance, balancing on a platform and open field). Additionally, a group of animals received diazepam to exclude anxiety reactions during the platform test. The intracerebral distribution of chloroquine after icv. infusion was estimated by using the histochemical acid phosphatase reaction as a lysosomal marker. No differences occurred between saline controls and treated animals in the passive avoidance behavior. Chloroquine significantly impaired the balancing ability of the animals in the platform test, whereas in the open field situation leupeptin-treated rats showed a significantly different behavior compared to the NaCl controls. The same holds true for the rearing behavior. Our results demonstrate that leupeptin and chloroquine may alter the behavior of rats, but not in the same way.

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33.08 INFLUENCE OF IMMOBILIZATION AND COLD EXPOSURE ON ADRENAL CATECHOLAMINE LEVEL IN FED AND FASTED RATS.

Beszczyńska B., Wasilewska E., Święcka E., Bargiel Z.

It is well known that the activities of catecholamines-synthesizing enzymes in adrenal medulla can be influenced by environmental stimulation, such as cold exposure, repeated and acute immobilization (IM). It seems that the 24h fasted rats show the greater resistance to immobilization stress than the fed ones. The aim of our experiments was to estimate whether short fasting, cold exposure and acute IM can influence catecholamine level in adrenal medulla and the rate of adrenaline (A) and noradrenaline (NA) synthesis in this gland.

Fasting did not change the content of A in adrenal medulla but increased the level of NA ($p<0.05$). In fed rats exposed to cold and acute IM simultaneously the level of A was unchanged but the content of NA significantly increased ($p<0.001$). In fasted rats in the same stress conditions the level of A increased and the content of NA decreased in comparison to control animals.

33.09 INACTIVATION OF HIGHER GUSTATORY CENTERS DISRUPTS KETAMINE INDUCED BLOCKADE OF LATENT INHIBITION AND OF EXTINCTION OF CONDITIONED TASTE AVERSION.

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The effect of NMDA antagonist ketamine (KET) and blockade of gustatory cortex (GC), amygdala (AM) and parabrachial nucleus (PBN) on latent inhibition (LI) and extinction (EXT) of conditioned taste aversion (CTA) were studied in anesthetized and non-anesthetized rats. I.p. injections of KET (50 mg/kg) applied after each of 3 saccharin preexposures disrupted LI. This effect was not due to aversive properties of KET, because 3 saccharin-KET pairings did not produce CTA. The KET induced blockade of LI was impaired by tetrodotoxin (TTX, 10 ng/ul) inactivation of GC or AM after each saccharin preexposure. TTX inactivation of GC, AM or PBN did not eliminate LI in non-anesthetized animals. Similar results were obtained in CTA EXT experiments. KET anesthesia elicited after each of the 3 saccharin EXT sessions prevented EXT of CTA to saccharin and this effect was disrupted by TTX inactivation of PBN. In non-anesthetized rats, TTX blockade of GC or AM prevented EXT neither before nor after the saccharin EXT session. These results indicate that functional blockade of the main CTA centers interferes neither with LI nor with EXT of CTA, i.e. with appetitive gustatory learning. Disruption of KET-induced blockade of LI and EXT by TTX blockade of GC, AM or PBN suggests that these structures modulate the mediation of KET effect. It is proposed that formation of aversively and appetitively labelled long term gustatory memories proceeds in separate brain circuits.

33.10 ELECTROCONVULSIVE SHOCK REVEALS RAPID CONSOLIDATION OF SPATIAL WORKING MEMORY IN THE WATER MAZE TASK.

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Electroconvulsive Shock (ECS) in humans typically causes retrograde amnesia (RA) for immediately preceding events. The consolidation theory predicts that the ECS disrupted gradual strengthening of the memory trace and thus caused a permanent loss of information. In the present study we investigated the amnesic effect of ECS in 10 rats trained on the working memory version of the water task. ECS (50 mA, 50 Hz, 1.5 s) applied immediately after a single trial in a new location produced tonic clonic seizures in all rats. A 2h interval was imposed between the ECS and the 2nd trial because previous findings showed that the anterograde amnesia and the retrieval impairment induced by ECS lasted less than 2h. Under control conditions escape latencies were about 20s in the first trial and dropped off 50% on the second trial, 2 h later. Retrograde amnesia would be manifested if the second trial latency reaches the level of the first trial. Results indicated that ECS applied 30s after the first trial had no amnesic effects because the escape latencies decreased between the first and second trial (t1: 21.5 s, t2: 11.4 s), similarly to control rats (t1: 21.1 s, t2: 9.2 s). It is concluded that the rats retained the spatial information acquired 30 s prior to the ECS. Fast consolidation of the memory traces is discussed in the context of the possible neural mechanisms involved. Supported by JSMF 92-57.

33.11 DEVELOPMENT OF ACUTE GASTRIC LESIONS IN INDIVIDUAL- AND GROUP-STRESSED RATS. Miroljub Popović[1], Dubravko Bokonjić[2]*, Silva Dobrić[2], Nenad Ugrešić[3], Julius Ivanuš[4] and Ljubiša Rakić[4]. [1]Immunology Research Centre, [2]Med. Dept., Military Technical Institute, [3]Faculty of Pharmacy and [4]Center for Multidisciplinary Study. Belgrade, FR Yugoslavia.

It has been established that cold restraint model could be useful for a study of influence of social behavior on the stress adaptation mechanisms. The aim of the present study was to determined the effect of group size on cold restraint-induced gastric lesions. Therefore, the 24 hr fasted male Wistar rats, weighing 300-320 g were put into individual or group restraint boxes (composed of two, three, six or nine single boxes). and than exposed 2 hr to the cold (4°C). The rats were sacrificed and gastric mucosa was examined for the lesions. The results showed that single stressed animals had significantly higher ulcer index than those stressed together (three, six and nine rats/group). Absence of significant differences between single and paired stressed rats, implyes that three is the lowest number of animals per group required for studying social influence on behavioral and adaptive processess.

33.12 EFFECTS OF THE mGLU RECEPTOR ANTAGONIST MCPG ON FEAR CONDITIONING LEARNING IN RATS.

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The involvement of the glutamate receptors and in particular the N-methyl-D-aspartate (NMDA) receptors subclass is critical in learning and memory formation. Recently, the metabotropic glutamate (mGlu) receptors also have been found to affect learning processes, such as the induction of long-term potentiation, a synaptic mechanism for information storage, and the performance of spatial learning in rats. Furthermore, the mGlu receptors mutant mice lacking of receptor subtype 1 presented deficits in motor coordination and in another form of learning, the context-dependent fear conditioning task. In the present study we have examined the effects of the mGlu receptor antagonist (+)-α-methyl-4-carboxylphenylglycine (MCPG) in the acquisition of conditioned fear responses to a cue (a tone paired with a footshock) and to context (background stimuli continuously present in the experimental chamber in which the tone-shock pairings occurred). The animals (n = 20) received 2 shocks each day for 2 consecutive days. From day 3 to 5 no shock was delivered and time spent freezing by the animal was recorded during the 6 min session. MCPG (0.0208 mg/ 5µl), injected into the lateral ventricle of rats previously implanted with a cannula, disrupted the performance in the conditioning of fear responses to the context, but not to the cue. A group of animals tested in a different apparatus to measure simple spontaneous activity, showed no differences between MCPG and vehicle-injected rats. Our findings suggest that blockade of the mGlu receptors produces impairment in context-specific associative learning, without causing deficits in motor activities.

33.13 IS THE CHOLINERGIC SYSTEM INVOLVED IN ADJUSTING A BALANCE BETWEEN FOCUSED AND SELECTIVE ATTENTION? C. BRANDNER*, P. LAVENEX, M. GAFNER, & F. SCHENK, Institut de Physiologie, CH-1005 Lausanne.

Spatial navigation is obviously affected by the presence of a local cue associated with the goal. But it is not clear whether and how this cue affects spatial representation. If it acts only as an attractor, it might impair learning based on the integration of distal redundant visuospatial cues. But it might also help organising efficient approach and escape behaviour and thus facilitate the acquisition of an optimal representation of the whole experimental context, or cognitive map.

We have thus trained rats in solid ground homing and water escape tasks with or without a local cue marking the position of the goal. In both tasks, the effect of this cue during training was assessed during probe trials with no proximal cue and no escape possibility. In addition, we have compared the performance of two different strains of hooded rats, rapid learners (Long Evans) and slow learners (PVG).

On the homing board, the presence of a salient object near the escape hole did not affect spatial memory in adults of both strains. But it reduced the expression of a spatial bias toward the correct position in immature rats. In contrast, the presence of an olfactory cue during training greatly improved spatial memory of the escape location in the slow learners only. In the Morris maze, the presence of a cue hanging above the escape platform had little effect on memory in both strains. However, it improved spatial memory in PVG rats with a perinatal choline supplementation and it had an overshadowing effect in Long Evans rats with a medial septum lesion.

Thus the presence of a local cue requires an optimal balance between selective attention to the cue and a more diversive attention to distant environmental cues. This balance appears to be strongly affected by changes in cholinergic efficacy.

33.14 **LEFT HEMINEGLECT IN A VISUALLY SIMULATED ENVIRONMENT: REPRESENTATION OF GOAL-ORIENTED MOVEMENTS**

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This paper presents a case report of a patient who exhibited a left hemineglect both in real space and in a virtual visual space in which a subject could simulating its own displacement by mean of a joystick. Such a device was used to address the issue of the representational processes involved in heminglect. Is hemineglect the result of a bias of spatial attention or does it stem from problems in the motor representation of goal-oriented movements?

The left hemineglect patient and a control subject were tested on two different tasks: (1) a reaching task in which they had to reach successive targets, and (2) a routing task in which they had to route between several obstacles. While the control subject performed equally well on both tasks, the patient exhibited different error patterns, depending on the intention of the movement to be made. These results suggest that distinct representational processes are involved in these two experimental situations. The nature of the involved representational processes, spatial attention or motor intention, is discussed in regards to current interpretations of the behavioral disorders associated with the hemineglect syndrome.

33.15 THE ROLE OF MEDIAL SEPTUM IN ACQUISITION, CONSOLIDATION AND RETRIEVAL OF RAT'S PASSIVE AVOIDANCE RESPONSE. C. Ambrogi Lorenzini, E. Baldi, C. Bucherelli* and G. Tassoni. Dipartimento di Scienze Fisiologiche, Università degli Studi di Firenze, Firenze, Italia

The importance of the medial septum (MS) in the phases of the memorization process has been investigated in male Wistar rats aged 60 days by means of the reversible Tetrodotoxin (TTX) blockade technique. A 10 mm-long stainless-steel guide-cannula was stereotaxically implanted 2 mm above the MS. The rats underwent a one-trial passive avoidance training session in the light-dark box apparatus. TTX (5 ng in 0.5 ul of saline solution) was administered to three groups of rats, respectively 50 min before the acquisition trial, immediately after the acquisition trial, and 50 min before the retrieval test. Rats retrieval was tested 48 hours after the acquisition trial. The results show that the pre-acquisition TTX blockade causes a dramatic impairment of the passive avoidance response, as shown by the very short step-through latency during retrieval testing. On the contrary, the post-acquisition blockade had no effect as shown by the absence of significant differences in step-through duration of these rats and of the control ones, to which saline had been administered in the same site. Finally, the pre-retrieval MS inactivation also causes a significant passive avoidance impairment, although less severe than that caused by the pre-acquisition TTX administration. These data define the differential involvement of the MS in the diverse phases of passive avoidance memorization in the rat.

33.16 **SEX DIFFERENCES ON DRL SCHEDULES DEPEND ON THE PRESENCE OF POSTNATAL DIHYDROTESTOSTERONE IN THE FEMALE.**

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It has been well demonstrated that female rats make fewer unreinforced lever pressing responses than males on schedules which maintain low rates of responding (differential reinforcement of low rate responding, DRL). Although sex differences in DRL-performance have been extensively investigated, there is no conclusive evidence about the role of sex steroids on this gender difference. Recently, we have demonstrated that postnatal dihydrotestosterone (DHT) organizes the female's reproductive behavior patterns. Therefore, in the present work we have studied the role of postnatal DHT in causing female performance under a DRL 15 sec. schedule (lever presses were reinforced if at least 15 sec had elapsed since the last press). Four groups of rats were used: a) females treated with 0.05 mg of cyproterone acetate (CA) between the postnatal days 6 to 11 (P6-11) and 1 mg of CA during the P12-20 period (CA group); b) females injected with the vehicle (sesame oil) over the period P6-20 (VEH group) and untreated males and females (UT groups). Sex differences were found, with UT or VEH females showing a higher response efficiency than UT males trough the course of acquisition. CA postnatal treatment of the female impaired female performance to the levels shown by males.

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33.17 ENKEPHALIN-DEGRADING AMINOPEPTIDASE ACTIVITIES AFTER LIDOCAINE ADMINISTRATION IN THE RAT BRAIN.

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Lidocaine is a local anesthetic widely used not only for minor surgical procedures, but also as antiarrhytmic agent. Since high dose of these local anesthetic can cause convulsions, it has been assumed that it can affect the CNS. However, although the electrophysiological properties of lidocaine and the molecular mechanisms by which this drug exert its action on the neuron are well documented, little is known concerning possible changes in the levels of neuromodulators in the CNS under the action of local anesthetics. This being the case, in this communication we present the levels of the three aminopeptidase activities involved in the degradation of enkephalins (soluble, M and MII) after lidocaine administration in several areas of the rat brain (frontal, parietal and occipital cortices, striatum, thalamus, hypothalamus, hippocampus, olphactory bulbus and pituitary gland). Aminopeptidase activities were fluorimetrically measured using Tyr-2-naphthylamide as susbstrate. Puromycin as inhibitor of MII activity was also used to determine aminopeptidase M activity. Lidocaine administration in a sub-convulsant dose significantly decreased soluble Tyr-aminopeptidase activity in the frontal cortex and the pituitary gland. Also decreases in the aminopeptidase M activity in the frontal cortex, the hippocampus and the thalamus were obtained. No changes in aminopeptidase MII activity were appreciated after the treatment. These data might suggest that enkephalinergic neuromodulatory system could be altered after local anesthetics administration.

33.18 EFFECTS OF 5-HT$_3$ ANTAGONISTS AND 5-HT$_4$ AGONISTS ON SCOPOLAMINE-INDUCED T-MAZE DEFICITS

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Following the work of Costall and colleagues with the prototypical 5-HT$_3$ antagonist ondansetron (Barnes *et al.*, 1990, Pharmacology, Biochemistry and Behavior, 35: 955), there has been increasing interest in the possible cognitive enhancing properties of 5-HT$_3$ antagonists. These molecules, however, may also interact with the 5-HT$_4$ receptor. Since 5-HT$_4$ stimulation can positively stimulate acetylcholine release in areas for cognition (Consolo *et al.*, 1994, NeuroReport, 5, 1230) this study examines the effect of 3 compounds with varying 5-HT$_3$ antagonist and 5-HT$_4$ agonist activity: ondansetron, ADR 932 and ADR 906 . The order of potency as 5-HT$_3$ antagonists in the guinea pig ileum (K_b microM) of the three compounds is ADR 932 (0.0039) > ondansetron (0.194) > ADR 906 (6.31), and as 5-HT$_4$ agonists in the rat tunica muscolaris (EC_{50} microM) is ADR 932 (0.0186) > ADR 906 (0.0789) > ondansetron (67.7). In the reinforced T-maze, scopolamine impairs performance significantly from an overall choice accuracy of 80% to 42%. Physostigmine restores this performance to 67%. ADR 932, ADR 906 and ondansetron were also able to improve choice accuracy in scopolamine-treated rats in this procedure. The percentage of improvement of these compounds compared to physostigmine was 82.4, 72.7 and 69%. These results support the suggestion of a role for 5-HT$_3$ antagonist activity in memory as well as a role for 5-HT$_4$ (Ghelardini *et al.*, Abstract presented at the 3rd IUPHAR satellite meeting on 5-HT, Chicago, 1994).

33.19 ALCOHOLISM AND MAJOR DEPRESSION : SIMILAR CONCENTRATIONS OF BASIC PROTEINS AND UBIQUITIN IN DOPAMINERGIC NEURONS OF THE SUBSTANTIA NIGRA (SN).

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We investigated the SN in postmortem tissue from human brains of alcoholics in search of alterations in the dopaminergic neurons, which in the primates project to the frontal cortex. These neurons appear to be sensitive to the effects of alcohol (Pellegrino and Druse, 1992) and are implicated in the networks associated with memory dysfunction. Many studies have demonstrated common biological changes and clinical features in depression and alcoholism. Our previous findings in the dopamine neurons (DA) of the SN from patients with major depression showed unusual increases in nuclear and cytoplasmic RNA, atypical highly basic proteins, as well as an intense ubiquitin (UBQ) immunoreactivity. Formalin-fixed paraffin-embedded tissues from 7 chronic alcoholic patients and 10 control subjects were used in this study. Histochemical methods for the demonstration of basic proteins and immunocytochemical method for the localization of UBQ were applied. The results showed that DA neurons of alcoholic patients display irregular, diffuse and granular concentrations of basic proteins in their perikaryon and dendrites. Also, the nucleolar basic protein in an increased concentration was displaced in the nucleoplasm. Most important, UBQ immunoreactivity was present in the cytoplasm of the DA neurons which contained the altered proteins. The above findings demonstrate aberrant protein synthesis, under the influence of alcohol, which implies altered genomic expression. The presence of UBQ, one of the stress proteins, supports the sressor effect of alcohol. DA neurons of depressed patients also show UBQ and similar atypical concentrations of basic proteins which are known to inhibit the responce of neurons to electrical stimulations (MacIlwain, 1963). Our combined findings demonstrate that the SN is a primary site of dysfunction affecting the cortex and causing, as a result, the cognitive and memory impairments which characterize major depression and alcoholism.

33.20 PRETREATMENT WITH 5-HT$_{1A}$ RECEPTOR AGONIST FLESINOXAN PREVENTS STRESS-INDUCED c-FOS IMMUNOREACTIVITY IN THE PVN

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Flesinoxan (Fles) acts as a full 5-HT$_{1A}$ receptor agonist and shows anxiolytic properties in a variety of animal models. Stressful events are known to activate the hypothalamic-pituitary-adrenal (HPA) axis: c-Fos activation in the paraventricular nucleus of the hypothalamus (PVN) and finally adrenal corticosterone (CRT) release. However, 5-HT$_{1A}$ agonists, among which Fles enhance also plasma CRT levels. Pretreatment with Fles prevents the Fles-induced CRT response, whereas the anxiolytic effects on behavior remain. In the current experiments male Wistar rats (Harlan-CPB, Zeist, The Netherlands), used to handling, received an injection of Fles (3 mg/kg s.c.) or vehicle (V: saline) at day 1. At day 2 all animals received a second injection of Fles or V, followed by the shock-probe burying (SPB) paradigm 30 min. later. One hour after the injection (30 min. after the start of SPB) the animals were decapitated and brains were fixated in paraformaldehyde (4%). This procedure included 4 groups: VV, VF, FV, FF, which we studied for immunoreactivity of c-Fos (c-Fos ir) in the brain. The animals who had received Fles at day 2 (VF) showed more c-Fos ir neurons in the PVN, as compared to vehicle (VV) treated rats. Apparently, Fles effects on c-Fos are superimposed on the stress-induced c-Fos ir. However, in Fles pretreated animals (FV and FF) the activation of c-Fos in the PVN is prevented, revealing the following order: VF > VV > FV = FF. 5-HT$_{1A}$ receptors are not present in the PVN, hence other brain areas are involved in the desensitization of the activation of the HPA-axis. Nevertheless, stress and flesinoxan induced c-Fos in the PVN are mediated by the same mechanism.

33.21 MISMATCH NEGATIVITY TO SPEECH STIMULI IN APHASICS

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In the present study we investigated to what extent left temporal lesion affects the automatic comparison of simple speech stimuli by analyzing the mismatch negativity component (MMN) of event-related brain potentials in aphasic patients. The stimulus material included both speech (vowel and consonant-vowel [CV]) and non-speech (tone bursts) sounds. The different stimulus types were given in separate stimulus blocks in a passive oddball paradigm. The vowels and CVs were digitized natural speech stimuli. The deviant vowels an CVs contrasted with the standard vowels and CVs in one phonological feature. The MMN to pure tones showed normal characteristics. While the vowel-evoked MMN showed only slight abnormalities and it could be recorded over the intact hemisphere in all patients studied, no CV-evoked MMN could be observed in several cases. Intact MMN could be elicited by CVs if the patients were able to differentiate in behavioral tests. The MMN to CVs was especially vulnerable in Wernicke's aphasics if the deviating feature was the place of articulation. Our findings lead us to the conclusion that an intact mismatch process does not form a sufficient condition for higher level speech processing. However, a comparatively preserved semantic system can compensate the impaired phoneme perception as long as the speech analysis has not to be based on phonemic feature analysis.

33.22 RECALL OF SPATIAL INFORMATION DIFFERENTIALLY AFFECTS THE ACTIVITY OF METABOTROPIC GLUTAMATE RECEPTORS IN HIPPOCAMPUS AND PREFRONTAL CORTEX OF RATS.

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Activity of metabotropic glutamate receptors was assessed in the hippocampus and prefrontal cortex of rats which had been trained for eight days in the Morris water maze to learn an allocentric spatial task. Measurements conducted 24 hours following the last training session revealed no differences in ACPD((1S, 3R)-1-amino-cyclopentane-1,3-dicarboxylic acid))-stimulated formation of inositol phosphates, either in hippocampus or in prefrontal cortex. However, a diminished activity of metabotropic glutamate receptors was found in the hippocampus of animals retrained after an 11 day interval. This decrease was absent in the prefrontal cortex, which indicates a differential involvement of metabotropic glutamate receptors in hippocampus and prefrontal cortex in the processing and retrieval of allocentric spatial information.

33.23 PRELIMBIC CORTEX IN RATS IS RATHER INVOLVED IN WORKING MEMORY PROCESSES THAN IN RESPONSE SELECTION.

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Medial prefrontal cortex (mPFC) has often been proposed to be involved in working memory (WM) processes, i.e. in the capacity to maintain actively a prior information in order to give an adequate response.

We have recently obtained a performance deficit in a spatial delayed alternation task with selective lesions restricted to a part of the mPFC, the prelimbic cortex (PLC). This effect can be due either to a WM deficit or to a deficit in response selection. To clarify this point, it was decided to investigate the effects of selective PLC lesions in two conditional tasks, both involving a response selection but differing in the use of WM. In the first conditional task, rats were required to associate a particular response (going left or right in a Y-maze) on the basis of a discriminative stimulus (slow flashing light vs rapid flashing light) that was delivered at the time of choice. In this task, involving a response selection but no WM component, PLC lesioned rats performed similarly as normal rats. In the other conditional task, rats placed in an operant chamber received either a light or a tone stimulus at the end of which a lever was inserted in the chamber. A lever pressing following a light stimulus was followed by a food reinforcer whereas a lever pressing following a tone stimulus led to an electrical footshock. In this training situation, there was a WM component since the response selection ever occurred in the absence of the discriminative stimulus. With a 0 s. delay, PLC lesioned rats acquired the task as rapidly as normal rats. However, when the delay between the discriminative stimulus and the response increased (to 10s. and 20s.), performance of PLC lesioned rats was largely disrupted as compared as the one of control rats. From these two experiments, it appears that PLC is more involved in WM processes than in response selection.

33.24 HEMISPHERIC LATERALIZATION IN BABOONS (PAPIO PAPIO) IN THE PROCESSING OF VISUAL STIMULI PRESENTED AT VARIOUS PRESENTATION DURATIONS.

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Using a video conditional matching-to-sample task in a divided field format, we examined the effects of stimulus exposure duration on hemispheric specialization in 6 baboons (Papio papio). In this study, after eye fixation on a fixation point, compound visual stimuli (e.g., a large circle comprising 3 smaller circles) were displayed in either the left of right visual field. By way of joystick manipulation, baboons had then to provide a conditional response depending on the category to which the sample stimulus belonged. In original training, 120 stimuli from two different categories were used. In testing, novel stimuli from the same two categories were presented, and we varied the exposure duration of the sample stimulus. For both 40 and 80 ms of sample presentation time, response times were found to be shorter, and accuracy greater, when the sample was displayed in the left visual field (i.e., right hemisphere), compared to right visual field presentations. For 120 and 160 ms of exposure duration, there was an advantage in RT and scores for right visual field (left hemisphere) presentations. The results, which are consistent with the human literature (e.g., Sergent, Perception and Psychophysics, 1982), suggest that the right hemisphere in baboons is better than the left to efficiently process rapidly perceived visual forms.

33.25 DECOMPOSING THE EEG ALPHA BAND: DIFFERENTIAL EFFECTS IN SELECTED 1 HZ BANDS.

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It is well known and accepted that the alpha rhythm is not a unitary phenomenon. There are at least two functionally distinct frequency bands within that range, the lower and the upper alpha band. Studies in our laboratory have indicated that the upper alpha band is more related to stimulus specific processes, whereas the lower alpha band seems to reflect attentional processes (Klimesch W., Schimke H., Pfurtscheller G.; Brain Topography, 5 (3), 241; 1993). In these studies, the alpha peak was used as cut-off point between the lower and upper alpha band.

The purpose of the present study is to show whether a further decomposition of the alpha band in narrow 1 Hz bands is useful for a better understanding of the functional meaning of the EEG rhythms. EEG data were recorded during an incidental memory task for a sample of 10 subjects. In using a method proposed by Pfurtscheller (Pfurtscheller G., Aranibar A.; Electroencephalography and Clinical Neurophysiology, 42; 817, 1977), the amount of event-related desynchronization (ERD) was calculated within the lower and the upper alpha as well as within 6 different 1 Hz bands. These analyses were carried out separately for good and bad memory performers.

The results show that within the lower alpha, only the 1 Hz band immediately below the peak showed effects that were comparable with the broad lower band. Within the upper band, comparable effects were found for the 1 Hz band immediately above the peak as well as the 1 Hz band which lies 2 Hz above the peak. The 1 Hz band lying in between shows quite different results. Our findings support the view that within the alpha band, power changes, even in small frequency windows, can be related to different cognitive processes. Thus, studying 1 Hz bands will be helpful in determining frequency bands that are relevant for particular types of task demands.

33.26 DEVELOPMENT OF LOADING RESPONSES DURING THE PRECISION GRIP

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Fifty children (2-10 years) and adults grasped and lifted an object with precision grip. A sudden unpredicted increase in load force was induced by dropping a small disc on to a receptacle attached to the object. In adults this resulted in an increase of grip force after 60-80 ms. At two years of age the grip force response was small and occurred after a long delay. With increasing age response intensity increased and latencies decreased. Concurrent EMG responses in extrinsic and intrinsic hand muscles occurred 40-50 ms after impact in all subjects, while the younger children showed another response at 20 ms. When the subject dropped the disc themselves, strategy changed. Adults showed an anticipatory grip force increase, scaled to the disc's weight. Children showed an anticipatory weight scaling which, however, was inappropriately timed.

33.27 INTRACEREBRALLY RELEASED VASOPRESSIN: ITS SIGNIFICANCE ON BEHAVIORAL PERFORMANCE

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The neuropeptide arginine vasopressin (AVP) has been thought to play a pivotal role in various learning and memory processes. We now provide data by means of an olfactory-cued paradigm for short-term memory indicating that both the amount of intracerebrally released AVP and the locally available AVP binding sites correlate with the behavioral performance in adult male rats.

In the first series of experiments, microdialysis probes were implanted into the area of the supraoptic nucleus (SON) of the animals. Direct osmotic stimulation of this brain area and simultaneous monitoring of intranuclear release patterns via microdialysis and of behavioral performance revealed an improvement of juvenile recognition abilities, which is directly dependent upon the amount of endogenous AVP released within the SON ($p < 0.05$). In the second series of experiments, antisense oligodeoxynucleotide targeting the AVP V1 receptor mRNA was chronically infused into the septum of another group of animals via osmotic minipumps. Behavioral testing revealed that animals treated in this way showed impaired juvenile recognition abilities compared to controls (vehicle, scrambled sequence, sense). Moreover, subsequent receptor autoradiography demonstrated a significant reduction of septal AVP binding sites due to antisense treatment and, again, individual behavioral and cellular data are correlated ($p < 0.02$).

In summary, these findings provide convincing evidence that intracerebrally released AVP that acts via V1 receptors plays a important role in the acquisition and/or processing of olfactory cues in short-term memory processes in rats.

33.28 RELATION BETWEEN COPING STYLE AND LATERAL SEPTAL VASOPRESSIN IN WILD TYPE RATS.

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In a wild population of rats and mice an active and a passive coping style can be recognized based on intermale aggression and behavioural flexibility to environmental challenges. Animals classified to either one of the coping styles are further known to have different sets of behavioural and neuronal traits. Mice, genetically selected for differences in intermale aggression, also differ in the level of the neuropeptide vasopressin (VP) in the bed nucleus of the stria terminalis (BNST) and in the lateral septum (LS). Active coping mice show relatively low levels of VP in these areas, whereas passive coping mice have high levels of the peptide. Differing neonatal androgen levels (testosterone, T) are thought to induce this difference in VP. In this experiment, we tried to confirm the relationship between coping style and VP in a non selected strain of wild-type rats. Therefore, rats were tested in a resident-intruder test to estimate their degree of aggression. After that, lateral septal VP and plasma-T levels were measured (radioimmunoassays). A clear correlation was found between intermale aggression and levels of VP in the LS. No such correlation was found regarding plasma levels of T. Therefore, these results confirm the previously found relation in mice between lateral septal VP and coping style. An active coping rat possesses low levels of VP, whereas a passive coping animal has higher levels of lateral septal VP. Lack of a correlation between adult plasma T and coping style strengthens the idea that T induces differential VP levels only neonatally.

33.29 DISSOCIATION BETWEEN FORM RECOGNITION AND LOCALIZATION IN PATIENTS WITH VISUAL NEGLECT. A. Farné*, G. Zeloni, R. Aloi and E. Làdavas. Department of Psychology, Univ. of Bologna and Hospital "I Fraticini" INRCA, Firenze.

The aim of the present study was to assess whether Form Recognition (FR) and Localization (L) could be differently impaired in patients with visual neglect. For this reason, four boxes, arranged to form a square, were presented to the upper and lower quadrants of left (LVF) and right (RVF) visual fields. One, or two stimuli (a triangle and a circle) were presented in one or two different boxes. The patients were required to perform three tasks: 1) to identify the shape or shapes of the stimuli, 2) to point manually, and 3) to identify verbally the location where the stimuli had been presented. The results showed that, as a group, there were no significant differencies between the three experimental conditions. In contrast, two patients showed a double dissociation between Form Recognition and Localization. Form Recognition was normal in M.V., whereas the ability to localize visual stimuli in LVF was impaired, mainly when the task required her to point at the stimulus manually. D. P. showed the opposite result. He was particulary impaired in Form Recognition, whereas his performance in the Localization tasks (both manually and verbally) was unaffected by the lesion. Therefore we can conclude by saying that the mechanisms underlying Form Recognition and Localization can be independently impaired in neglect patients.

33.30 ENHANCED ACTIVITY AND REDUCED AGONISTIC BEHAVIOUR IN RATS HOUSED IN A STANDARDIZED ENRICHED ENVIRONMENT. Fermont, P.C.J.*; Spruijt, B.M.; Netto, W.J. Dept. of Comp. Physiol., University of Utrecht, P.O.Box 80086, 3508 TB Utrecht, The Netherlands.

In the last few decades much research has been done on the effects and necessity of enriched housing for caged animals. Most of these studies are concerned with the housing conditions of rodents. Although there is some consensus on the animals used (most of the time mice and rats) there is a lack of unity in the housing conditions described in the above-mentioned studies. This may possibly be one of the reasons of the contradiction in the reported results. Furthermore, the enriched housing conditions are often very unpractical in use: they consist of cages with large floor areas and are not easy to clean due to the nature of the enrichment.

The main purpose of animal experiments is to study the performance of animals in different tasks, such as skinner box, morris maze, open field, etc. Not many attention is paid to the behaviour of the animals in their home-environment, although this can provide the researcher with valuable information about the performance in other tasks and the relevance of home-cage conditions.

Aim of this study is to develop a 'standardized enrichment' for rats that is applicable in various laboratory settings and which provides for most of the ethological needs of the animals. From this point of view it is important that the animals are stimulated in active behaviour and have the possibility to avoid each other as a way of regulating agonistic behaviour.

In the present study an enriched (opportunity to hide, climb, gnaw and avoid conspecifics) type IV laboratory cage with a removable rim in order to increase the height of the cage was used. This increases the available volume and area for the animals. The use of this enriched environment resulted in enhanced activity and reduced agonistic behaviour in enriched cages as compared to the old, standard type IV cages. It is concluded that the developed enrichment may improve animal welfare and biological relevance of the animal models used in behavioural sciences.

33.31 INHIBITOR PEPTIDASES POTENTIATE THE EFFECTS OF NEUROTENSIN AND NEUROMEDIN N ON SELF-STIMULATION OF THE PREFRONTAL CORTEX.

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In previous studies we have shown that central administration of neurotensin (NT) and neuromedin N (NN) produced a selective decrease of self-stimulation of the medial prefrontal cortex of the rat. Biochemical studies showed that both neuropeptides are inactivated by different peptidases. Thiorphan and bestatin are specific inhibitor of the peptidases that inactivate NT and NN respectively. In the present study we investigated whether or not central administration of thiorphan and bestatin potentiate the effects of NT and NN on self-stimulation of the prefrontal cortex. Male Wistar rats were bilaterally implanted with monopolar electrodes and 23 ga guide cannulae in the medial prefrontal cortex. Microinjections of NT (10 nM), thiorphan (10 μg), NN (20 nM), bestatin (25 μg), NT+thiorphan and NN+bestatin, all in a volume of 1 μl, were performed in the medial prefrontal cortex. Microinjections of NT and NN decreased self-stimulation during the first 30 and 20 min postinjection respectively. Microinjections of thiorphan and bestatin produced no significant effects when injected alone. However, microinjections of the neuropeptide together with its specific peptidase inhibitor increased the inhibition of self-stimulation produced by the neuropeptides. This inhibition was found during the entire period of testing (40 min). These results show that thiorphan and bestatin potentiate the inhibition of self-stimulation produced by NT and NN respectively and indicate the involvement of peptidases in the inactivation of both neuropeptides when injected into the medial prefrontal cortex.

33.32 AUDITORY MEMORY EFFECTS ON THE INFERIOR COLLICULUS DEMONSTRATED WITH CYTOCHROME OXYDASE HISTOCHEMISTRY. M. Garrosa*[1] and F. Gonzalez-Lima[2]. [1]Depto. de Biología Celular, Facultad de Medicina, Universidad de Valladolid, 47005 Valladolid, Spain; and [2]Institute for Neuroscience, University of Texas at Austin, TX-78705, USA.

The objective was to determine whether differential conditioning of sounds would produce long-lasting alterations in neural metabolic capacity as measured by cytochrome oxidase histochemistry. A within-subject differential conditioning paradigm was used consisting in a low frequency tone (2-3 KHz) which was paired with water reward (CS^+) and a high frequency tone (40-41 KHz) which was unpaired (CS^-). Another group of rats received random presentations of the same sounds and rewards and a third group remained unstimulated. The results showed a significant increase in the ratio of cytochrome oxidase activity between the low and the high frequency bands (CS^+/CS^-) of the inferior colliculus in the conditioned group when compared with the randomly treated rats. Therefore the inferior colliculus showed a significant difference between CS^+ and CS^- effects as opposed to its purely sensory stimulation. The cytochrome oxidase activity of the unstimulated rats was significantly lower than that of the conditioned and randomly stimulated group, what indicates the existence of a training effect in the metabolic capacity of the auditory stimulated rats. Finally, the CS^- effect was comparable to the metabolic capacity showed by the unstimulated rats. Our findings suggest that the inferior colliculus could facilitate subsequent differential responses to the CS^+ versus CS^-, serving to differentiate auditory memories to sounds which signal reward (CS^+) vs. no reward (CS^-). It may be concluded then, that the inferior colliculus of conditioned rats contained a memory-based alteration in cytochrome oxidase activity, and that this metabolic alteration resided in the specific tonotopic maps representing the CS^+ and CS^- after conditioning.

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33.33 EFFECTS OF LESIONS OF DOPAMINERGIC MESO-HIPPOCAMPAL PATHWAYS ON MEMORY IN THE RAT. A. Gasbarri[1*], A. Sulli[1], R. Innocenzi[1], C. Pacitti[1] and J.D. Brioni[2]. [1]Department of Science and Biomedical Technology, Lab. of Human Physiology, University of L'Aquila, 67100 L'Aquila, Italy and [2]Neuroscience Research (D47W), Abbott Laboratories, Abbott Park, IL, 60064-3500.

The hippocampal formation (HF) has long been thought to play a role in learning and memory. Previous studies from our laboratory examined the organization of mesencephalic projections towards the HF in the rat. In order to evaluate the effects on learning and memory of retrograde selective lesions of mesencephalic dopaminergic neurons, following bilateral injection of 6-hydroxydopamine (6-OHDA) in dorsal and ventral subiculum and adjacent CA1 field of HF, young adult Sprague-Dawley rats were trained in: a) the classical inhibitory (passive) avoidance (IA), b) IA using a multiple-trial (training to criterion) and c) standard Morris water maze task (MWM), cued and spatial version. Concerning IA, retention was examined 1, 3, and 10 days after training. Concerning MWM task, 6-OHDA lesioned and sham-operated rats received 4 training trials on each of 4 days. After training sessions, the rats were tested during a 60s probe trial (free-swim trial) in which the platform is removed from the maze. During the free-swim we recorded: a) the time to cross the original platform position (latency); b) the time spent in the target quadrant; c) the number of crossings over the original platform position. After behavioral tests, the loss of mesencephalic dopaminergic neurons in the 6-OHDA lesioned rats, compared to sham-operated rats, was verified by tyrosine hydroxylase immunohistochemistry. Though the 6-OHDA lesioned rats were indistinguishable from sham-operated rats in performing the IA and cued version of MWM task, in the spatial version of MWM, lesioned rats, compared to controls, spent significantly less time ($P<0.01$) in the target quadrant. These results suggest that the rat's ability to acquire spatial learning and memory for place navigation in the MWM is likely dependent also on the integrity of meso-hippocampal dopaminergic connections.

33.34 IMPAIRMENT IN SPATIAL LEARNING CAUSED BY NEONATAL ADMINISTRATION OF EXCITOXINS. M.J. Gayoso, M.A. Martín, J.M. Fernández, M. Garrosa and C. Iñiguez Department of Cell Biology, School of Medicine, University of Valladolid, 47005 Valladolid, Spain.

Glutamate receptors play an important role in the differentiation of the central nervous system and also in the synaptic processes involved in learning. In this study, we analyzed the effects of neonatal administration of glutamate agonists on spatial learning. Male Wistar rats were subcutaneously injected with kainic acid (1mg/kg, four rats) or glutamic acid (4g/kg, five rats) on alternate days from postnatal days 2 to 10. Nine control rats were injected with saline solution. When two months old, the animals were submitted to the Morris water maze (two blocks of four trials/day). Differences in latencies were compared by two-way ANOVA. During the ten days acquisition phase the latencies of the kainic-treated group were similar to those of the control group whereas those of the glutamic-treated group were significantly ($p<0.001$) increased. Post-hoc tests showed significant differences ($p<0.05$) from the second day of training onwards. Retention was tested after ten days of rest. During the retention phase (ten days), only the glutamic-treated group showed higher latencies than the control group ($p<0.001$). The differences were significant ($p<0.05$) every day. These results indicate that neonatal administration of glutamic but not kainic acid significantly impairs the learning of spatial tasks.

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33.35 THE INTERFERENCE AT THE RIGHT-HAND HEMISPHERE LEVEL IN DYSLEXIC CHILDREN

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This paper presents the results of an examination of 35 dyslexic children (E-group) and 35 children without dyslexia (C-group), aged from 8-11, of normal intelligence (IQ), 25 of which being boys and 10 girls in each group. In the examination the Kinsbourn and the Harris tests have been utilized.

The results of the Kinsbourn test have shown that the left-hand in the C-group significantly falls behind in relation with the right-hand, which indicates the dominance of the left-hand hemisphere, as a contrast to the E-group where the situation is reverse on behalf of the left-hand, although the usable right-hand is dominant, thus indicationg the existance of a hemispherical interference in the dyslexic children. With regard to the right-hand, no difference has been established between the E and C groups, whereas in comparing the left-hand in the two groups, the difference is statistically highly significant (p=0.06, t=2.88).

33.36 BEHAVIOURAL EFFECTS OF α-MSH AND MCH INJECTION INTO THE RAT VENTROMEDIAL NUCLEUS AND PREOPTIC AREA.

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α-Melanocyte stimulating hormone (α-MSH) and melanin concentrating hormone (MCH) interact on melanophores (MCH is an α-MSH antagonist in teleost but acts as a weak agonist in the mammals). Both peptides are present in the rat hypothalamus where they may also interact. The behavioural effects of α-MSH and MCH were investigated in the ventromedial nucleus (VMN) and preoptic area (POA), two areas known to be concerned with behaviour and to posses α-MSH receptors. Ovariectomised + adrenalectomised female Wistar rats were oestrogen primed and injected (100ng in 0.5 μl) bilaterally with saline, α-MSH, MCH or MCH followed 30 min later by α-MSH, into the VMN (n=36) or POA (n=49). Locomotor and exploratory behaviour (hole board test), anxiety (elevated plus-maze), social activity, sexual preferences and sexual behaviour were investigated 30 min later. Injection of α-MSH into the VMN, resulted in a significant ($p<0.05$) increase in aggressive behaviour that was inhibited by prior administration of MCH. Injection of α-MSH and MCH both separately and in combination stimulated lordosis in both areas ($p<0.05$ at 30 min and 1 h, $p<0.001$ at 3 h in the VMN; $p<0.01$ at 1 h, $p<0.001$ at 2 h, $p<0.01$ at 3 h in the POA). Injection of α-MSH into the POA resulted in reduced exploration ($p<0.05$) that was prevented by prior injection of MCH. Both α-MSH and MCH injection into the POA, resulted in a similar reduction ($p<0.01$) in the time spent in the open arms of the plus-maze (increased anxiety), that was prevented by MCH pretreatment. From this study we can conclude that α-MSH and MCH both stimulate sexual receptivity, but MCH appears to antagonise other behavioural effects of α-MSH, which suggests a partial agonistic relationship between α-MSH and MCH in the hypothalamic areas studied.

33.37 VEPs STUDY OF MATERIAL SPECIFIC DIFFERENCES IN INTERHEMISPHERIC TRANSMISSION TIME.

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The study investigated directional differences in interhemispheric transmission of information *to* and *from* the hemisphere specialized in its processing, using the VEPs method. Twenty four subjects were presented with two types of stimuli, words and gratings, for which in our previous electrophysiological studies left- and right-hemispheric predominance was found. The stimuli were exposed for 30 ms in random order in the left or right visual field. VEPs were recorded with electrodes located over the left and right occipital lobes at O1 and O2 according to the 10/20 system and referenced to linked ear lobes. Two VEPs components, N170 and P300, were analyzed. N170 had larger amplitudes and shorter latencies when recorded from the directly stimulated hemisphere (i.e., contralateral to the field of stimulus presentation) than when recorded from the hemisphere stimulated via corpus callosum (i.e., ipsilateral to the field of stimulus presentation). Interhemispheric transmission time (IHTT) was estimated by the difference in latency between the contralateral and ipsilateral responses. IHTTs in two directions - from the left hemisphere to the right and from the right hemisphere to the left were compared. In the case of words, shorter IHTTs were observed when the information was transferred from the right hemisphere to the left, whereas in the case of gratings IHTTs were shorter when the information was transferred from the left hemisphere to the right. The results showed, thus, that interhemispheric transmission time was shorter when the information was transferred *from* the hemisphere non-specialized for its processing *to* the specialized one than in the opposite direction. The results suggest the existence of a physiological mechanism that ensures fast transmission of information to that hemisphere which is more efficient in its processing.

33.38 DECISION PROCESSES AND ANTICIPATION IN A RADIAL MAZE TASK.

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A first experiment in a radial maze with various tilted arms (0°-60°) pointed out that the presence of tilts influences the organisation of the rat's foraging behaviour. Although rats had no problems in climbing in the most tilted arms, they organised their foraging sequences according to the effort cost of each bait and visited the highest arms last. Rats could be seen as reluctant to the effort of climbing on the most tilted arms, mainly visiting these arms only when the easier arms were no longer baited. Nevertheless, they developed efficient foraging sequences.

In a second experiment, we tested whether rats could plan a foraging sequence according to this effort cost when the information about the amount of effort necessary to reach the source was not available at the choice point. Rats would have thus to memorise the position of the most demanding food sources and to organise their behaviour accordingly. We designed an 8-arm radial maze with a climbing tower at the distal end of each arm and the food bait located on top. The towers were either low, medium, or high. Although rats were able to climb the towers easily, they were often observed to retreat from a high one without having reached the food reinforcement. These incomplete visits and the rats' persistent reluctance to climb in the higher towers seemed to considerably disturb the foraging sequences, inducing frequent revisits of the lower towers as well. After 15 trials, rats were still unable to develop correct visit sequences and showed no memory of the spatial distribution of the arms with high towers. In contrast, in a similar experimental design with more or less palatable food instead of the more or less high towers, rats rapidly developed optimal sequences, memorising the position of the arms baited with palatable food and visiting them first. The palatability of different arm baits was therefore easier to remember than the amount of effort necessary to reach similar baits.

These differences in planning optimal foraging sequences will be related to difficulties in anticipating effort and/or to interferences due to early retreat from the highest towers.

33.39 CHRONIC TREATMENT WITH FLESINOXAN, A 5-HT_{1A} AGONIST: EFFECTS ON CORTICOSTERONE AND DEFENSIVE BURYING.

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Serotonin (5-$HT)_{1A}$ agonists have anxiolytic and antidepressant effects. Apart from these behavioural effects, 5-HT_{1A} agonists also enhance corticosterone secretion when given acutely. In humans, 5-HT_{1A} agonists have a delayed onset of action. Changes in sensitivity of endocrine systems following chronic treatment may be involved in this delayed onset. We studied whether chronic treatment with flesinoxan in rats results in an altered anxiety state and changes the corticosterone response to stress.

Canulated (jugularis vene) rats received 1 mg/kg flesinoxan once daily for 7 days via an intragastric canula. On day 1, flesinoxan slightly enhanced plasma corticosterone levels under basal conditions. On day 8, rats were placed in the defensive burying situation. No drug was given on this day. Basal corticosterone levels did not differ between groups. The overall effect on plasma corticosterone (area under the curve) induced by shock-probe exposure was similar in flesinoxan and control rats. However, the time course of this response differed significantly. Chronically flesinoxan-treated rats showed a delayed increase in plasma corticosterone levels. Chronic flesinoxan treatment did not result in anxiolytic effects in the shock-probe test, in contrast to acute flesinoxan treatment.

In conclusion, chronic treatment with 5-HT_{1A} agonists seems to alter the time course of the stress-induced corticosterone response. However, 7 days pretreatment does not result in a changed anxiety state measured 1 day later.

33.40 **BEHAVIOURAL EFFECTS OF CHOLECYSTOKININ ANALOGUES JMV236, JMV179 AND JMV320**

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The in vivo effects of the cholecystokinin (CCK) analogues JMV236 (Boc-Tyr(SO_3)-Nle-Gly-Trp-Nle-Asp-Phe-NH_2), a potent CCK agonist, JMV179 (Boc-Tyr(SO_3H)-Nle-Gly-DTrp-Nle-Asp-2-Phenylethylester), a CCK antagonist, of JMV320 (a cyclic CCK peptide analogue), a highly selective CCK-B receptor ligand, and of endogenous CCK-4 on exploratory activity and memory in rats were studied. JMV236 dose-dependently decreased the horizontal (significant effect at doses of 12.5 and 50 μg/kg) and vertical (significant effect at a dose of 50 μg/kg) activity. JMV179 dose-dependently decreased only the vertical activity (significant effect at a dose of 50 μg/kg). JMV320 and CCK-4 did not modulate exploratory activity in open field test but decreased it in elevated plus-maze. JMV236 facilitated short-term memory in passive avoidance situation but only tended to increase the mean latency of passive avoidance response upon retention testing after 7 days. JMV179 tended to increase the latency of the passive avoidance response upon retention testing after 24 hours but not after 7 days. JMV320 (1 and 10 μg/kg) decreased active avoidance responses 24 hours after training while CCK-4 (50 μg/kg) impaired passive avoidance responses 3 hours after training. The behavioural effects of JMV320 resemble the effects of CCK-4 and suggest that in vivo JMV320 acts as a CCK-B receptor agonist. JMV236 and JMV320, more stable enzyme-resistant CCK agonists, and JMV179, a full CCK receptor antagonist, migh prove useful for elucidating the role of CCK in cognition.

33.41 RETRIEVAL ENHANCEMENT DUE TO **PRIOR CUING** IN RATS IS SELECTIVELY BLOCKED BY NALOXONE.

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Retention performance can be improved by prior cuing consisting in an exposure to some training events, delivered shortly before a retention test. We have already demonstrated that rats, partially trained in a brightness discrimination avoidance task in a Y-maze, exhibit an improvement of their retention performance - after a one-day Training-to-Test-Interval (TTI), following a pretest exposure to the discriminative stimulus (DS: a light) and - after a 21-day TTI following a pretest exposure to the experimental context (2.5 min exposure delivered 5 min before the retention test).

Previous studies of our own on changes of cerebral metabolic activities resulting from an exposure to the DS after a 1-day TTI provided evidence for a possible involvement of the endorphin system which was further supported by some data of the literature (Izquierdo, 1989). To investigate a possible involvement of the endorphine system in the facilitative effect of prior cuing, rats injected with saline and with Naloxone (0,8 mg/kg, ip, 11.5 min before testing) were compared during testing following -no prior cuing -control prior cuing (exposure to a neutral cue) or - effective prior cuing (exposure to the DS or to the experimental context). After a one-day TTI, the enhancement of the retention performance resulting from a pretest exposure to the DS is selectively blocked by Naloxone. Effects of Naloxone on the retention enhancement resulting from a prior exposure to the experimental context after 21 days are in progress. Effects of Bêta-endorphine delivered shortly before the retention test will also be studied.

Implications of opiod systems involvement in the retrieval processes promoted by retrieval cues will be discussed.

34. Poster Session: Development and plasticity II

34.01 BDNF AND NT-3 EXERT DIFFERENTIAL AND OVERLAPPING EFFECTS ON GAP-43 AND Tα1-TUBULIN EXPRESSION IN AXOTOMIZED CORTICOSPINAL NEURONS OF THE RAT.

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In the peripheral nervous system, successful regeneration is correlated with increased expression of regeneration associated genes (RAG), e.g. GAP-43 and Tα1-tubulin. In contrast, the expression of these genes is decreased in corticospinal neurons (CSN) after axotomy (Giehl et al., 1993, Soc. Neurosci. Abstr. 283.9). CSN, retrogradely labelled with Fast Blue, were axotomized at the internal capsule and the neurotrophins BDNF or NT-3 were applied intracortically via an osmotic minipump for 7 days. As shown with *in situ* hybridization, both BDNF and NT-3 increase Tα1-tubulin expression in axotomized CSN which is consitent with the expression of trkB and trkC receptors in these neurons. However, only BDNF but not NT-3 increases GAP-43 expression. Thus, BDNF and NT-3 have overlapping and differential effects on RAG expression in axotomized CSN.

34.02 TARGET SELECTION AND FINE-TUNING IN THE DEVELOPING CORTICOSPINAL TRACT IN THE RAT: SYNAPSE ELIMINATION

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In our research program on the development of the Corticospinal tract (CST) in the rat, we previously found a correlation between the postnatal differentiation of cervical motoneurons (MNs) implicated in the innervation of distal forepaw muscles (Curfs et al. 1993, Development 117: 535-541) and the outgrowth of CST collaterals into the cervical spinal gray (Curfs et al. 1994, Dev. Brain Res. 78: 182-190). After excessive motoneuron dendritic field formation and CST overgrowth up to postnatal day 10 (P10), the system then is fine-tuned by selective MN dendrite as well as CST collateral elimination.

Using anterograde HRP labelling of the CST in conjunction with retrograde CTB-HRP labelling of the cervical MNs involved in the control of distal forepaw flexion, we were now able to electronmicroscopically demonstrate a postnatal decline of the number of direct cortico-motoneuronal contacts.

In order to reveal the role of the cervical interneurons (INs) in the formation of the CST projection, kainic acid was unilaterally injected into the sensorimotor cortex of postnatal rats. A similar regressive pattern was found in the number and the dispersion of contralateral cervical INs expressing the immediate early gene *c-fos* during maturation.

In conclusion it seems reasonable to assume that the cervical interneurons and the flexor motoneurons act in concert in the target selection and fine-tuning of the developing corticospinal tract. Secondly, the mechanism of synapse elimination also operates in the development of central fiber systems.

34.03 THE α4 ISOFORM OF THE NICOTINIC ACETYLCHOLINE RECEPTOR IN THE ONTOGENY OF THE RAT HIPPOCAMPUS.

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The involvement of nicotinic cholinergic transmission in hippocampal signal transduction has heightened the interest in the role of nicotinic acetylcholine receptors (nAChR). By contrast to the adult rat brain, little is known on the development of nAChRs in the hippocampus.

Using a digoxigenin-labeled riboprobe, the expression of the mRNA for the α4 subunit was studied in the developing rat cerebral cortex by means of in situ hybridization between embryonic day 20 [E20] and postnatal day 60 [P60]. Hybrids were detected by applying an alkaline phosphatase-coupled digoxigenin-antibody, followed by incubation with BCIP/NBT.

At E20, strongly labeled CA pyramidal cells were observed. A signal was also present in the prospective granular layer of the dentate gyrus (DG). α4 mRNA-expressing cells migrating from the ventricular zone to the CA region were detected. At birth, in particular cells of the suprapyramidal blade of the DG were strongly labeled. The same held true for the CA pyramidal neurons. At P7, the number of labeled neurons in the DG appeared to decrease, while the pyramidal cells and a number of interneurons in the CA region were positive. At that stage of development, the mRNA distribution closely resembled that seen in adult rats.

In conclusion, expression of α4 mRNA in the DG, but not in the CA region, appears transiently increased during development. In the whole hippocampal formation, occurence of α4 transcripts precedes the ingrowth of cholinergic fibers. Further studies will have to be devoted to the elucidation of this developmental asynchrony.

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34.04 EXPRESSION OF BRAIN NGF AND NGF-RECEPTOR mRNA IN RELATION TO MAZE PERFORMANCE DEFICITS IN AGED RATS.

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Recent findings indicate that growth factor-related mechanisms are altered in the course of brain aging and that deficits in associative functioning seen with senescence may be based in part on a decreased sensitivity to and/or availability of neurotrophic factors. In the present study expression of mRNA for NGF and its receptors, $p140^{trk}$ (trkA) and $p75^{LNGFR}$ (LNGFR), was examined in different brain regions of adult (3-month-old) and aged (26-28-month-old) rats using quantitative in situ hybridization. Prior to hybridization histochemistry behaviorally impaired and severely impaired animals were selected form the group of old rats on the basis of their performance in the Morris water maze. Inspection of the hippocampus (CA3, dentate gyrus) revealed no age- or performance related changes in NGF mRNA. The expression of trkA mRNA was decreased in the basal forebrain (medial septum, diagonal band, striatum) of impaired as well as severely impaired aged rats, whereas a significant increase in LNGFR mRNA was found in the basal forebrain of the impaired rats compared to both severely impaired rats and adult controls. These findings suggest that age-related deficits in learning and memory functions are associated with a decrease in the expression of trkA mRNA in the basal forebrain. The increase in LNGFR mRNA expression observed for impaired, but not severely impaired aged rats, may reflect a restorative and/or compensatory mechanism that serves to improve function in the aged rat brain. Furthermore, the present study did not reveal age-related differences in hippocampal NGF mRNA, suggesting that alterations of post transcriptional processes might account for the reported decrease of hippocampal NGF levels in the aged rat brain.

34.05 Expression of Krox-20 and c-Jun by nerve fiber lesion in the rat: induction by ATF-2 and link to the UV response.

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The second messengers are still unknown which induce the regeneration-associated genes following axotomy. Since the c-Jun transcription factor is specificly expressed in axotomized neurons, we studied the c-Jun induction *in vivo* and *in vitro*. It is our hypothesis that axotomy and cellular damage by UV irradiation share common signal transduction mechanisms including activation of the constitutive ATF-2 transcription factor. (1) ATF-2 is pre-existing in axotomized neurons. Binding of ATF-2 to the *c-jun* promotor is increased in nuclear extracts from axotomized substantia nigra neurons following transection of the medial forebrain bundle as revealed by gelshift-supershift. (2) UV irradiation induced c-Jun in cultures of adult dorsal root ganglion neurons and (3) evoked phosphorylation of CREB in glial cells but not neurons, resembling the phosphoCREB pattern following axotomy *in vivo*. Krox-20 triggers the maturation of Schwann cells with subsequent myelination of peripheral nerve fibers. (4) Krox-20 shows a specific temporo-spatial expression pattern following nerve transection which is modified by neurotrophic factors.

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34.06 GENE DELIVERY WITH ADENOVIRAL-VECTORS IN MOTONEURONS AND SCHWANN CELLS.

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Recombinant adenoviral vectors can infect a wide variety of cell types including postmitotic cells in the nervous system. This enables us to use adenoviral vectors as genetic tools to directly introduce and express genes in neurons and glia cells. The objective of our current work is to devise *in vivo* gene transfer protocols for regeneration-related genes. As a first step necessary to achieve this, two adenoviral vectors were generated: Ad-CMV-LacZ, a vector containing a cytomegalovirus promotor (CMV) and the LacZ reporter gene, and Ad-CMV-B-50, an adenoviral vector containing an expression cassette for the growth-associated protein B-50/GAP-43. In a first set of experiments slow infusion (0.1 µl/min) of 1 µl of a viral vector (Ad-CMV-LacZ) solution close to or in the facial nucleus containing a total of 10^7 defective viral particles resulted in ß-galactosidase expression in the majority of motorneurons and their satellite cells. The presence of the marker gene product ß-galactosidase in numerous facial nerve axons clearly indicates that adenoviral vectors can serve to express a foreign protein in motorneurons that is subsequently transported distally to act at a peripheral nerve lesion site. In a second set of experiments 1 µl infusions of Ad-CMV-LacZ directly into the sciatic nerve resulted in the local ß-gal expression in numerous peripheral nerve Schwann cells. Current experiments focus on the overexpression of B-50/GAP-43 in injured motoneurons to examine a putative beneficial effect of this growth-associated protein on axonal sprouting and target muscle reinnervation.

34.07 EXPRESSION OF RECOMBINANT TRKB AS A FUSION WITH MALTOSE BINDING PROTEIN

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TrkB is a member of the tyrosine kinase receptor family and binds to the neurotrophins BDNF and NT-4 with high affinity. The extracellular domain of human TrkB has been inserted into the pMAL-c2 vector (New England Biolabs) downstream from the *mal*E gene encoding for maltose binding protein. The result is a MBP-fusion protein under the control of the strong P_{tac} promotor. *E. coli* (TG2) cells are induced with IPTG at mid log phase. The resulting pellet is freeze thawed and sonicated, then treated with DNAse I. The inclusion bodies are loaded onto a discontinous sucrose gradient and ultracentrifuged at 107K for 2 hours. They partition at the 53/67% interface. The fusion protein is purified on DEAE sepharose by dissolving the inclusion bodies in 6M urea and collecting the major peak eluting at 500mM NaCl. This purified fusion protein is refolded by dialysing against 10mM tris buffer at pH 8.0 for 24hrs. Refolding is confirmed by CD spectra showing α-helix and β-beta sheet secondary structure. The fusion protein is diluted to approximately 1mg/ml and incubated at room temperature for 24hrs with 1% Factor X_a. The extent of digestion is checked by PAGE, the 90kDa fusion protein separates into 42kDa maltose binding protein and 48kDa TrkB bands. The fusion mixture is separated by ion exchange chromatography (Resource S). The refolded human TrkB is being produced for co-crystallization with BDNF. This will enable the rational drug design for the treatment of neurodegeneration.

34.08 EXPRESSION OF B-50/GAP-43 IN ADULT OLFACTORY NEURONS IN TRANSGENIC MICE RESULTS IN MORPHOLOGICAL CHANGES IN THEIR PROJECTIONS IN THE OLFACTORY BULB.

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To study the function of B-50/GAP-43 *in-vivo*, we created transgenic mice, that express B-50/GAP-43 in the adult olfactory system. Using the olfactory marker protein (OMP) promoter B-50/GAP-43 expression was directed to mature olfactory neurons, which do not normally express B-50/GAP-43. Mice bearing the OMP-B-50/GAP-43 transgene exhibited B-50/GAP-43 immunoreactivity in cell bodies, dendrites and axons of numerous mature neurons throughout the olfactory epithelium. This pattern of transgene expression is consistent with the action of the OMP promoter.We find that B-50/GAP-43 expression in mature olfactory neurons results in the formation of numerous hypertrophic OMP-positive primary olfactory axons with enlarged nerve endings. Confocal laser scanning microscopy revealed that the mature olfactory axons often terminated in dilated grape-like structures which were preferentially located on the rim of the glomeruli. Double labelling with anti-tyrosine hydroxylase (TH) antibodies demonstrated that some OMP-positive olfactory neurons exhibit ectopic projections, between the TH-positive juxtaglomerular cells or associated with extra glomerular blood vessels. These phenomena were never observed in wild type litter mates and could be confirmed by Golgi staining of individual olfactory axon terminals. These data demonstrate that continued expression of B-50/GAP-43 in adult primary olfactory neurons *in-vivo* has a direct effect on the morphology and projection territory of their preterminal axons and supports a role of this growth-associated protein in nerve fiber formation.

34.09 COMPLETE REGENERATION AFTER PARTIAL ABLATION OF THE DENTATE AREA IN THE LIZARD GEKKO GECKO

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The dentate area of the lizard *Gekko gecko* is divided in two parts. The rostral part receives multisensory input from the dorsolateral thalamic nucleus, the caudal part receives an olfactory input from the lateral cortex. In a previous study we suggested that this bipartitioning of the dentate area is related to the fact that these lizards can walk on the ground, vertical walls as well as upside down on the ceiling. In order to test this hypothesis, we removed the rostral, thalamic, part of this area in a number of animals. After this surgical intervention the animals were trained in a maze to study the changes in spatial orientation related behavior. After this training period the animals were deeply anaesthetized and transcardially perfused. The brains were dissected from the skull to asses the place and the size of the lesion. To our surprise it appeared that in animals that survived for one year or more, the area dentata was completely regenerated. In order to find out wether this regenerated part of the cortex had the same connections as the original, untreated part, we consequently studied in a new series of experiments the connections of the regenerated cortex with biotinylated dextran amine. It was found that the regenerated cortex had the same connections as the ablated cortex. Also the laminar organization of the afferent connections appeared the same. It thus seems that the dentate area of the lizard *Gekko gecko* has a very strong regenerative capacity. Because the laminar organization of the afferent fibers is exactly the same as in the original cortex it is concluded that the plasticity in the dentate area is controled by the original genetic properties of the dentate area.

34.10 HIBERNATION MODIFIES SENSITIVITY TO VARIOUS NEUROMODULATORS IN THE HAMSTER HIPPOCAMPUS.

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The hippocampus seems to play an important role during entrance into and arousal from hibernation. In order to reveal hibernation-related modifications in the action of neuromodulators, we investigated the effects of serotonin (5-HT), histamine (HA), adenosine (AD), dopamine (DA), norepinephrine (NE), and carbachol (CCh) on stimulus-induced population spikes in hippocampal slices prepared from warm-acclimated (WH) as well as from hibernating Turkish hamsters (HH). Slices were studied at 37°C and 22°C in an interface type chamber continuously perfused with artificial cerebro-spinal fluid oxygenated with 95% O_2/5% CO_2. Neuromodulators were bath-applied for 15 min (CCh for 3 min). Field potentials evoked by stimulation of Schaffer collaterals/commissural fibers at 30 s intervals were extracellularly recorded in stratum pyramidale of area CA1.

Hibernation-related changes of the neuromodulatory action were found for HA, AD, NE, and 5-HT. HA (50 µM) increased the population spike amplitude. It was more effective in HH slices than in WH slices. In contrast, AD (50-100 µM) depressed the population spike amplitude. The effect of AD was weaker in HH slices as compared to WH slices. NE (20 µM), applied at 22°C, induced a long-lasting potentiation in HH slices which was not present in WH slices. 5-HT (20-100 µM) induced an initial depression and subsequent facilitation at 22°C, the facilitation being stronger in WH than in HH slices.

The hibernation-related decrease of the exciting effect of 5-HT could contribute to the depression of brain activity during entrance into hibernation. In contrast, the loss of sensitivity for AD as well as the increase of sensitivity for NE and HA seem to be suitable to facilitate hippocampal activity at low temperatures during arousal.

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34.11 *IN VIVO* CHARACTERIZATION OF CALCIUM CHANNELS INVOLVED IN THE BASAL AND K^+-EVOKED RELEASE OF GABA. EFFECTS OF AGING.

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Neurotransmitter release from synaptic vesicles to the extracellular space is triggered by the influx of Ca^{2+} into the presynapsis through voltage-dependent Ca^{2+} channels (VDCC). However, the type of Ca^{2+} channels involved, as well as the release conditions (basal or evoked) vary according to the neurotransmitter studied. GABA has been proposed as the most abundant neurotransmitter in the cerebral cortex, an area particularly affected by aging processes.

We used microdialysis to analyze the effects of age on the basal and 100 mM K^+-evoked release of GABA in the frontal cortex of the awake, freely moving rat. The effects of ω-conotoxin GVIA (ω-CTX) and aminoglycosides (neomycin and kanamycin) as VDCC blockers, and tetrodotoxin (TTX) as a Na^+ channel blocker, were determined in two groups of rats aged 3 and 24 months. The GABA content of the dialysates was determined as OPA-derivative by HPLC with fluorescence detection.

TTX, ω-CTX (an N-type specific VDCC blocker) and kanamycin had no effects on the basal release of GABA in young or aging rats. However, neomycin potently enhanced the basal GABA efflux in both age groups. The K^+-evoked release was higher in young than in aged animals. ω-CTX or kanamycin did not affect the evoked release in either age groups. However, this release was completely abolished by TTX. Furthermore, neomycin enhanced K^+-evoked GABA levels in both age groups, but to a lesser extent than when neomycin was perfused alone.

We conclude that K^+-evoked GABA release is diminished in the aging frontal cortex, probably as a consequence of loss of the functional capacity of the neurons. N-type VDCC do not mediate the *in vivo* evoked GABA release in either age groups. Finally, neomycin, but not kanamycin, enhances the basal and K^+-evoked release of GABA with the same potency in young and aged rats, probably acting through a Ca^{2+}-independent mechanism. (Supported by DGICYT 90-0146 and Junta de Andalucía).

34.12 THE EFFECT OF BLOCKING OF NMDA RECEPTORS UPON THE PLASTIC CHANGES IN THE BARREL FIELD IN ADULT MICE.

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NMDA receptors play an important role in plastic changes in CNS. We investigated the effect of blocking of NMDA receptor in the somatosensory cortex by implantation of slow-release polymer (Elvax) containing 50mM APV on plastic changes of cortical representation of a row of vibrissae induced by classical conditioning. The plastic changes were mapped with 2-DG method one and 24 hours after the last training session, when CS (whisker stroking) was paired with UCS (tail shock). Elvax released a small amount of APV which blocked 20% of NMDA receptor in the barrel field. In intact mice seven days after implantation of Elvax-APV metabolic labelling of intensity of 2DG uptake was unchanged as compared to the control hemisphere. In experimental animals the first training began 24 hours after implantation of Elvax-APV in vicinity of the barrel field. Three 10 min.daily session of CS+UCS pairing were given. In animals without Elvax-APV implant the training produces enlargement of cortical representation of the "trained" row on the order of 20-40%. In animals with Elvax-APV implants no changes in the dimension of cortical map of this row were observed. These result support the involvement of NMDA receptor in changes of cortical body maps.

34.13 APPEARANCE AND DISTRIBUTION OF NADPHd/NOS I-POSITIVE SUBPLATE NEURONS IN THE HUMAN FETAL NEOCORTEX. M. Judaš*, N. Šestan and I. Kostović, Section of Neuroanatomy, Croatian Institute for Brain Research, Šalata 3b, 41000 Zagreb, CROATIA

We analyzed appearance and distribution of NADPHd/NOS I-positive subplate neurons (NNSNs) within the developing cortex of 22 human fetuses ranging in age from 12 to 37 weeks of gestation (WG). In frozen sections of 4% paraformaldehyde-fixed brains, the first NNSNs appear at 15/16 WG in the ventral portion of the mid-lateral part of the fetal telencephalic wall. Between 16. and 24. WG, both the number and the intensity of staining of NNSNs significantly increase. Furthermore, during this period, the pattern of distribution of Golgi-like NNSNs was characterized by both developmental gradients and superimposed regional differences, as follows: (a) from the site of their initial appearance, NNSNs "spread" in dorsomedial, frontal and caudal direction; (b) however, they remain the most numerous in the middle part of the fetal hemisphere, less numerous in frontal and the least numerous in occipital lobe in all examined stages (i.e., during both 16-24 WG and 24-37 WG period); (c) within the cortical anlage overlying the diencephalon and basal ganglia, they are always more numerous in ventrolateral ("opercular") and medial ("cingular") than in dorsolateral cortex; and (d) there was a developmental lag in the appearance of NNSNs below the primary visual cortex - they were very scanty during 16-24 WG period and their number increases significantly only after 24 WG. In fact, no significant changes in the number or distribution of NNSNs were noted between 24. and 37. WG, except that they become more numerous below the primary visual cortex. In conclusion, NADPHd/NOS I-positive subplate neurons appear and distribute throughout the subplate zone during the developmental period which closely corresponds to the "waiting" period of thalamocortical axons (16-24 WG). However, their number or distribution displayed no conspicious changes during the remaining late fetal period, except in the primary visual cortex. *Supported by Ministry of Science of the Republic of Croatia.*

34.14 CASE-CONTROL AND NEURO-IMAGING STUDY IN PERSONS WITH SCHIZOPHRENIA AFTER PRENATAL EXPOSURE TO THE DUTCH FAMINE IN 1945. J.S. Kalkman*[1], H.W. Hoek[1], E.S. Susser[2], H.E. Hulshoff Pol[1], R.S. Kahn[1]. [1] University Hospital Utrecht, Department of Psychiatry, Heidelberglaan 100, HPnr A.01.126, 3584 CX GA Utrecht, The Netherlands. [2]Columbia University, New York.

The proposed study will take advantage of a unique opportunity to investigate the association between prenatal exposure to the Dutch famine in 1945 and the risk of schizophrenia. It has been shown that among persons born in the six largest cities of western Holland in November and December 1945 (conceived at the height of the famine in March/April 1945) the risk of schizophrenia was increased twofold. In order to clarify the causal relationships that underlie the observed association, the individuals who developed schizophrenia after famine exposure will be traced and studied.
Twenty famine exposed cases of schizophrenia will be compared with two separate control groups. The first control group will comprise 40 matched persons without schizophrenia who were born in the famine region in November and December 1945. The second control group will comprise 40 matched persons with schizophrenia who were born in the famine region in November and December of previous and subsequent years. Groups will be compared on nutritional intake of the mothers at the time of famine, brain structure and function (MRI and neuropsychological tests), current physical condition, family history of psychiatric illness, potential genetic markers, and obstetric complications.

34.15 POSSIBLE EVOLUTION OF BRAIN GANGLIOSIDES SIGNAL ROLE

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Current data on gangliosides - sialoacid-containing complex glycolipids - show that gangliosides due to their physico-chemical properties and specific distribution are able to serve as specific informational molecules in different evolutionary distant organisms, demonstrating a variety of CNS signalling mechanisms (membrane domains and clusters formation; binging to specific ganglioside-recognizing membrane proteins (GRMP); gangliosides concentration/colocalization with GRMP in local cellular areas and formation of gangliosides-containing membrane "probes" for cellular recognition; stimuli-dependent cellular transport of gangliosides (the model of cellular "semaphore" signalling system of informational molecules delivery ?); Ca++ - binding and Ca++ - dependent ganglioside modulation of synaptic activity and mediators release; specific binding of some neuronal mediators, hormones and hormone-like proteins (role of gangliosides as pro-receptory molecules?); alteration of the activity of key membrane proteins; gangliosides transmembrane transmission in synaptic regions and transcellular signal molecules exchange; induction of antiganglioside AB-genesis and specific long-term AB-effects on neuronal membranes). These mechanisms have different degree of molecular complexity and are likely to be the object of gangliosides signal properties natural evolution. The study summarizes data on signal properties of gangliosides in animals of different groups in terms of their evolutionary complication and the development of specific ganglioside-recognizing systems.

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34.16 ANIMAL MODEL OF SCHIZOPHRENIA: COMPARATIVE ANALYSIS OF AMPHETAMINE, PHENCYCLIDINE AND HALOPERIDOL INDUCED CHANGES IN GAP-43 GENE EXPRESSION. S.Kanazir*, S.Vukosavić, R.Veskov, S.Ruždijić, Lj.Rakić
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Growth associated protein (GAP-43) is a specific phosphoprotein involved in neurite outgrowth and synaptogenesis and it can be used as a selective marker for processes underlying synaptic reorganization within CNS. In this study we attempted to investigate possible changes in GAP-43 gene expression in rat brain after chronic treatment with psychostimulant drugs, known to produce psychosis-like symptoms in experimental animals. Adult rats were treated for 7 days with amphetamine (AMPH), phencyclidine (PCP) and haloperidol (HAL) in doses of 5mg/kg/day, on 12h intervals. Brain sections (12μm) were used for *in situ* hybridization with ^{35}S labeled riboprobe for GAP-43. Quantification of hybridization signals were performed using the PhosphorImager and software package Image Quant. *In situ* hybridization revealed significant changes of GAP-43 mRNA expression in AMPH treated animals in fronto-parietal cortex (73% over the control value), CA3 (40%) and CA1 (38%) regions and entorhinal cortex (71%), while no changes were detected in dentate gyrus and thalamus. Similar changes were induced with PCP in fronto-parietal cortex (50%), CA3 (20%) and CA1 (25%) regions and in thalamus (23%), unlike in enthorinal cortex, where the increase in GAP-43 was 95%. In HAL-treated animals changes of GAP-43 mRNA expression were significant, but less than 20% in all investigated regions.

In conclusion, chronic administration of both, AMPH and PCP, although affecting different neurotransmitter systems, induced changes of GAP-43 mRNA expression. The observed differences in spatial pattern of GAP-43 expression in these two treatments could indicate that specific regions undergo synaptic remodeling in pathogenesis of schizophrenia in an animal model.

34.17 NEURITE OUTGROWTH FROM CULTURED ADULT MOUSE SUPERIOR CERVICAL GANGLIA

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The excised superior cervical ganglia (SCG) of embryonic or neonatal rats and mice are extensively used for studies of neurite outgrowth and neurotransmitter/ neuropeptide plasticity . In contrast, neurite outgrowth from adult ganglia is usually poor. The purpose of this study was to try to establish conditions which promoted neurite outgrowth from cultured SCG from adult animals. SCG were removed from adult male NMR 1 mice and mounted in Matrigel in plastic tissue culture dishes. Serum-free RPMI 1640 medium ± NGF was then added to the preparations. The cultures were maintained in either 5 % CO_2 in air (LO) or 5 % CO_2 in 95 % O_2 (HO) at 37 oC. Neurite outgrowth was sparse in LO but improved in HO. The addition of NGF dramatically increased the number of neurites both in LO and HO. However, the mean neurite length was shorter in the NGF exposed cultures. Immunostaining for galanin showed no or few positive cell bodies in freshly excised ganglia. The number of galanin positive cell bodies increased in all cultured preparations although to a different extent. These cultures could be valuable models for studies of regeneration and neurotransmitter/neuropeptide plasticity.

34.18 BDNF PROMOTES THE SURVIVAL OF ADULT RAT SPINAL MOTONEURONS AFTER VENTRAL ROOT AVULSION.

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It has previously been shown that neurotrophic factors may rescue developing motoneurons from naturally occurring cell death. In the present study, the effects of brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) on the cell survival and nitric oxide synthase (NOS) expression were investigated in adult rat spinal motoneurons following ventral root avulsion.

Medial gastrocnemius (MG) motoneurons were retrogradelly prelabeled with Fast Blue (FB). Following unilateral L5 ventral root avulsion, BDNF (10 µg/24 hrs), CNTF (12 µg/24 hrs) or vehicle (PBS) was infused into the lumbar subarachnoidal space by means of an osmotic pump. After 4 weeks of continuous treatment, the number of FB-labeled MG motoneurons was counted and the NOS expression of the injured L5 motoneurons studied histochemically.

In vehicle-treated rats, about 80% of the MG motoneurons had died and disappeared at 4 weeks after the axonal lesion. Treatment with BDNF, but not with CNTF, reduced the cell loss and 50-60% of the MG motoneurons then remained after 4 weeks. BDNF, but not CNTF or vehicle, also completely down-regulated the NOS expression induced by the avulsion.The BDNF effect remained for at least 2 weeks after cessation of the treatment. Thus, long-term application of BDNF may protect adult spinal motoneurons from axotomy-induced degeneration and cell death.

We thank Regeneron Pharmaceuticals, Inc. for supplying us with BDNF and CNTF.

34.19 GLUCOCORTICOID RECEPTOR GENE EXPRESSION IN RAT BRAIN AND PITUITARY DURING EMBRYOGENESIS.

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The early ontogenetic pattern of glucocorticoid receptor (GR) gene expression was studied in the rat brain beginning from embryonic day 13. Using a [^{35}S]-labelled GR mRNA probe for *in situ* hybridization, we detected GR mRNA in E13 Rathke's pouch, choroid plexus and the neuroepithelium lining the ventricles. GR gene expression was further extended to the neuroepithelium of the telencephalon, diencephalon and myelencephalon by embryonic days 15 and 17. The integrity of the mRNA transcripts revealed by *in situ* hybridization was assessed by Northern blot analysis of total RNA from embryonic brain and pituitary. A major ~7 kb transcript was detected throughout embryonic development. A 94 kDa receptor-protein was shown by immunoblotting analysis to be expressed in brain and pituitary extracts already by day E13. Based on our results, we postulate a regulatory role for glucocorticoids, through their functional receptors, in the embryonic rat brain.

34.20 Abstract withdrawn

34.21 SELECTIVE LESION OF RAT FOREBRAIN CHOLINERGIC NEURONS BY 192 IgG-SAPORIN REDUCES BASAL AND KINDLING-INDUCED BDNF mRNA LEVELS THROUGH DIFFERENTIAL REGULATION OF EXON SPECIFIC PROMOTERS.

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Brain-derived neurotrophic factor (BDNF), promotes the survival of different types of neural cells during ontogeny and *in vitro* but its role in the mature brain is poorly understood. The basal forebrain cholinergic system has been implicated in regulation of BDNF gene expression as well as in the development of kindling. However, until now, lesions of this system have either been incomplete or lacked the selectivity required for determining the functional significance of the cholinergic system *in vivo*. Immunotoxin 192 IgG-saporin destroys basal forebrain cholinergic neurons expressing the p75 NGF receptor, leading to almost complete, selective cholinergic denervation of neocortex and hippocampus. 192 IgG-saporin also reduces basal and kindling-induced expression of BDNF mRNA in several brain areas, particularly in the hippocampus, and accelerates kindling development. Here we demonstrate, using *in situ* hybridization, that changes of BDNF mRNA expression in dentate gyrus of lesioned animals are due to reduction of basal and kindling-induced mRNA levels for exon I and exon III (26% and 42%, and 48% and 34%, respectively) in the BDNF gene, while exon II and exon IV mRNA expression is not altered. We conclude that the basal forebrain cholinergic system controls BDNF gene expression via differential regulation of exon specific promoters.

34.22 NEUROGENESIS IN THE DENTATE GYRUS OF THE ADULT RAT CEASES DURING AGING.

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Postnatal neurogenesis in the hippocampus of rodents is well preserved throughout adulthood. Neural precursor cells, that reside at the border between the hilus and granule cell layer (GCL) of the dentate gyrus, go through cell division, migrate from the subgranular zone into the GCL and differentiate into granule cells. Neurogenesis has been observed in rats of up to 1 year of age.

In the present study dentate gyrus neurogenesis was analyzed in 6 month old (adult) and 24 month old (aged) Fischer rats using bromodeoxyuridine (BrdU) to label cells undergoing mitosis. In aged rats, 1 day after BrdU labeling, cell proliferation in the GCL and subgranular zone was reduced to 25%. This decreased proliferation in the dentate gyrus was not due to a general decrease in metabolic activity since proliferation of glia cells in the hilus and proliferation of neural precursor cells in the subependymal zone of the lateral ventricle were not decreased. Six weeks after BrdU labeling immunohistochemical co-labeling of BrdU with neuronal markers like NeuN and Calbindin were only detected in adult, but not aged rats. Moreover, immunostaining for polysialylated NCAM, a cell adhesion molecule that is involved in differentiation and migration of developing neurons, was found only in the GCL of adult rats. These data suggest that neurogenesis of granule cells in the hippocampus is age dependent.

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34.23 SPACE/TIME EXPRESSION PATTERN OF GLIAL MARKERS IN THE OPTIC NERVE OF *Tinca tinca* AFTER LESION.

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After lesion the axons of the ganglion cells of the retina of teleosts are capable of restoring the visual function. In this process the glial cells which respond to the lesion with changes that make possible the effective regeneration, intervene.

In this work, using as a model the tench submitted to crushing of the optic nerve, we analyze the space/time sequence of modifications of the expression of neuroglial (Vimentin, S-100 and GFAP) and microglial (poly-N-acetyl lactosamine) markers.

Vimentin and S-100 have similar patterns of modifications of expression, with a period after the lesion in which the labelling disappears from the zone of the lesion and increases at its edges. For Vimentin the progressive recovery of the labelling in the zone of the lesion and the normalization of the surrounding immunoreactivity are completed some 200 days after the injury. In the case of S-100 the recovery of a pattern comparable with the normal is somewhat earlier. With the antibody used the modification of the expression of GFAP is chronologically comparable with the former ones and is limited to the appearance of immunoreactivity tangles at the edges of the lesion which are intensified initially but decrease in density and intensity until normal conditions are approximated.

The modifications of the expression of the microglial marker is early and affects both the distribution and the morphology of the microglia. The lesion zone and its edges are the most affected. The recovery of the normal pattern is more rapid than in the cases of the neuroglial markers.

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34.24 **GABA$_A$-RECEPTOR ACTIVATION CAUSES ELEVATION OF [CA^{2+}]$_i$ IN IMMATURE RAT HIPPOCAMPAL CELLS.**

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GABA$_A$ currents are depolarizing in neonatal rat hippocampal pyramidal cells (Y. BEN-ARI et al., J. Physiol., 416: 303-325, 1989), presumably because of a different [Cl$^-$]$_i$ homeostasis. In order to test whether in the immature hippocampus exogenous or synaptic GABA$_A$ stimulation leads to an increase in [Ca^{2+}]$_i$ through voltage gated calcium channels and whether neonatal interneurons share the immature "depolarizing GABA" feature with pyramidal cells, [Ca^{2+}]$_i$ changes were recorded from immature (P$_{2-5}$) or mature (P$_{12-13}$) hippocampal slices using a confocal laser scanning microscope. Visually selected cells from the CA$_3$ region of hippocampus were loaded extracellularly by pulse pressure application of the cell permeant Ca^{2+} sensitive fluorescent dye Fluo-3AM (3.3 µM, 5-10min).

Brief pressure application of isoguvacine (GABA$_A$ agonist) or electrical stimulation of afferents, in combination with pharmacological agents (GABA$_A$ or glutamatergic antagonists: bicuculline or APV+CNQX respectively), showed that immature but not mature pyramidal cells and interneurons responded to GABA$_A$ stimulation by an increase in [Ca^{2+}]$_i$. The response to isoguvacine was sensitive to the voltage gated Ca^{2+} channel blocker D600. Clamping immature cells at their resting potentials (whole-cell with Fluo-3 in the pipette solution, E$_{Cl}$=-10mV) prevented the GABA$_A$-mediated increase of [Ca^{2+}]$_i$, showing its dependence on depolarization.

We could demonstrate, without interfering with [Cl$^-$]$_i$, that GABA$_A$ causes a Ca^{2+} influx through voltage gated calcium channels in immature (P$_{2-5}$) interneurons and pyramidal cells. This fact may underlie the trophic role of GABA in development of the hippocampus.

34.25 TRANSIENT NEURONAL STRUCTURE CONNECTING GANGLIONIC EMINENCE WITH DORSOMEDIAL THALAMIC NUCLEUS IN THE DEVELOPING HUMAN BRAIN. K. Letinić* and I. Kostović. Croatian Brain Research Institute, School of Medicine, University of Zagreb, Croatia.

Some cells of the telencephalic origin migrate to the pulvinar thalamic nucleus via a transient structure, named corpus gangliothalamicum (Rakic and Sidman, Z. Anat. Entwickl.- Gesch. 129:53,1969). The aim of the present study was to determine whether telencephalic matrix (ganglionic eminence) contributes to another thalamic nucleus, dorsomedial nucleus, which is intimately connected with the prefrontal granular cortex. We analysed 52 postmortem human brains ranging in age from 10.5-40 weeks of gestation (w.g.), using Nissl and Golgi methods (Rio Del Hortega modified by Stensaas and Golgi-rapid). Nissl sections revealed the presence of thin elongated stripe of cells, underneath the dorsal surface of thalamus, reminiscent of corpus gangliothalamicum, extending from the area of the ganglionic eminence towards the dorsomedial thalamic nucleus, and present exclusively in fetuses from 15 to 34 weeks of gestation. Golgi analysis in the same period discloses population of simple, immature looking bipolar elongated cells, with longer axis of their somata oriented mostly parallel to the pial surface, occupying the dorsalmost thalamic area from ganglionic eminence to the dorsomedial nucleus. Such distribution was in contrast to apparent lateral to medial gradient of neuronal maturation. We conclude that some neurons migrate from ganglionic eminence into the anlage of dorsomedial thalamic nucleus through the transient corpus gangliothalamicum, during the period from fourth to eighth month of gestation. Neurons of telencephalic origin could contribute to the expansion of this "association" nucleus in humans, particularly of its dorsolaterally situated parvicellular portion, characterized by distinct areal distribution of its projections in primate prefrontal cortex (Giguere and Goldman-Rakic, J. Comp. Neurol. 277:195,1988), thus possibly subserving specific functions. *Supp. Ministry of Science, Republic of Croatia.*

34.26 A GOLGI STUDY OF THE PROJECTION NEURONS OF THE LIZARD MEDIAL CORTEX

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In the lizard medial cortex (lizard "fascia dentata") the neuronal somata of its principal or projection neurons appear densely packed forming a conspicuous cell layer. This cell layer (granule layer) appears flanked by two almost cell free plexiform layers (outer or "molecular layer" and inner plexiforms) where dendritic trees and axonal arbours articulate and synapse.

Due to the particular properties of the lizard medial cortex (postnatal neurogenesis, continuous growth, neuronal regeneration, etc.) a careful assessment of the classification of the lizard medial cortex granule neurons has been done using a sample of 830 well-impregnated granule neurons taken from 60 successful Golgi impregnated brains of the lizard Podarcis hispanica (from perinatal, young and adult specimens). After camera lucida drawings of each neuron it was classified according its dendritic tree morphology, spine density and axonal arbour. Five main types were clearly identified: 1) heavily spiny superficial, 2) very spiny bitufted, 3) spiny bitufted, 4) sparsely spiny bitufted and 5) multipolar superficial. Moreover, soma shape and location differences give rise to presumably 15 subtypes. The most abundant dendritic tree archetype: the bitufted ("bipenachado", "double bouquet") appears consistent (determined by?) with the trilaminar cytoarchitectural pattern. Spiny types appear more frequent in perinatal-young specimens indicating that late recruited neurons of the medial cortex are likely sparsely spinous.

34.27 **Morphological and physiological features of synaptic connections between layer V pyramidal neurons.** *[1]H. Markram, [2]J. Lübke*, [1]B. Sakmann and [2]M. Frotscher, [1]Max-Planck-Institute for Medical Research, Jahnstr. 29, D-62110 Heidelberg and [2]Institute of Anatomy, University of Freiburg, P.O. Box 111, D-79001 Freiburg, FRG.*

A general feature of the neocortex is that neurons are arranged in functional vertical columns. The neural circuitry that subserves the function of these neocortical columns is poorly understood. We have therefore investigated anatomical and physiological features of a potential synaptic pathway between layer V pyramidal neurons within a column. Whole-cell patch clamp recordings were obtained from 106 synaptically coupled pairs of layer V pyramidal neurons in slices of rat somatosensory cortex using infrared differential interference contrast videomicroscopy. Of the 106 synaptically connected pairs, 72 (68%) were unidirectionally coupled, the remaining 34 (32%) were reciprocally connnected. The experimental probability of obtaining synaptic connections was as high as 1:1 in some preparations (mean 1:2.9) for unidirectional coupling and as high as 1:2 (mean 1:4.2) for reciprocal coupling. Fourty neurons were intracellularly labeled with biocytin, processed and analyzed at the light- and electron microscopic level. Synaptic responses varied from 50 µV to more than 6 mV. The number of synaptic contacts made on one neuron ranged from 2 to 9 (mean ± S.D. 3.24 ± 1.71) for both uni- and bidirectionally coupled neurons. Axo-spinous and axo-dendritic synaptic contacts were distributed onto proximal and distal parts of basal dendrites, the main apical trunk, oblique and terminal tuft dendrites. Most synapses (64%) were found on basal dendrites. Our findings clearly demonstrate that layer V pyramidal neurons within a neocortical column are extensively uni- and bidirectionally coupled and that the synaptic connections are distributed over the whole dendritic tree. *Supported by the Von-Helmholtz-Foundation of the BMFT.*

34.28 CD15 POSITIVE RADIAL GLIAL FIBERS DEFINE PROSOMERIC BOUNDARIES THE MOUSE DEVELOPING FOREBRAIN

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The carbohydrate epitope 3(α)-fucosyl-N-acetyl-lactosamin or CD15 is expressed by cells of the hematopoetic and (neuro)ectodermal system. The significance of CD15-expression in the brain is unknown, although it has been implicated in cell-adhesion mechanisms. Using the monoclonal antibody (MAB) produced against the human histiocytic cell line (U-937 1) we have investigated CD15 expression in the brain of postimplantated mouse embryos.

Immunoreactivity (IR) is first detected at around embryonic day 7 (E7), labeling the whole neuroectodermal layer. After closure of the neural tube at E9, the expression is abruptly reduced, and can no longer be detected in the CNS until midgestation time. Beginning at late E11, CD15 becomes re-expressed. It is first found accumulated at facing areas of the ventricular and pial surfaces, which later become interconnected by radially oriented processes. About three days later (E14), these can be clearly ascribed to as radial glial fibers, spanning throughout the wall of the CNS. Their spatial distribution along the ventricular surface of the forebrain is confined and marks regional fields, identical to those described as neuromeric boundaries within the prosencephalon. Between E17 and the end of the embryonic period the transformation of radial glial cells into regular astrocytes is followed by the changing CD15 expression pattern. Western blots from CNS samples obtained between E14 and birth shows a single band of CD15 glycosylated protein with an approximate molecular weigth of 24kD.The basic organization of the mammalian forebrain can thus for the first time be correlated with the location and orientation of radial glial fibers which are responsible for the translocation of neuroblasts to their settling regions.

34.29 THE DISTRIBUTION OF DENDRITES IN THE BARREL CORTEX IN MICE AFTER AN UNILATERAL PARTIAL LESION OF VIBRISSAL FOLLICLES.

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The barrel field is an area of the somatosensory cortex in rodents where granular cells form unique groups in layer IV (barrels) which show one-to-one correspondence to individual whiskers on the contralateral face. Neonatal lesions of vibrissae result in profound changes of cytoarchitectonics of the barrels. The distribution of dendrites has been examined in the barrel field after unilateral ablation of vibrissae sparing row C. Mice were lesioned on the day of birth and sucrificed after 8 weeks. Tangential brain sections through the layer IV were subjected to immunohistochemistry with a monoclonal antibody to MAP-2, a cytoskeletal protein specific to dendrites. The density of stained cross-sections of single dendrites and clusters of dendrites, in terms of number per area, increased in the center of barrels and decreased in walls of the barrel row C representing the spared vibrissae row in the denervated hemisphere, as compared to the control hemisphere. A possible explanation would be that dendrites from the denervated areas bend to enter the remaining barrels. If this were the case it would be desired to establish whether these dendrites originate from the layer V or from the superficial layers. It is still intriguing why the number of dendrites in the barrel walls of the spared row C declines. It might be suggested that there is an incresed tendency for dendrites entering the barrel walls to form clusters and hence the density of stained objects becomes lower comparing to the control state.

34.30 POSTNATAL NEUROGENESIS IN THE OLFACTORY BULBS OF TURTLES: MIGRATION OF NEUROBLASTS FROM DISTANT PROLIFERATIVE CENTERS.

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Previous studies have shown that several regions in the brains of lizards undergo postnatal neurogenesis, even persisting during adult life. However, evidence of neurogenesis after birth in other reptilian groups is scarce.

We used BrdU-immunocytochemistry to document the occurence of postnatal neurogenesis in the telencephalon of turtles. For this purpose, 16 young red-eared turtles (*Trachemys scripta*, Emydidae) were injected with the thymidine analogue 5'-Bromodeoxyuridine (BrdU) and allowed to survive for periods ranging from 7 to 180 days.

Our results indicate that cells in the walls (ependyma) of the telencephalic ventricles proliferate postnatally. Shortly after the BrdU treatment (7 days) most of the labelled cells were found in the ventricular ependyma, particularly in the dorsal and ventral germinal zones (sulci). Other ependymal zones, such as those adjacent to the olfactory bulbs and cerebral cortex displayed very few labelled cells. With long survival times (90 and 180 days) many labelled cells resembling neurons were found in several telencephalic regions, most of them in the olfactory bulbs. These labelled cells were indistinguishable from surrounding neurons and are thus presumed to be of neuronal phenotype.

The intense postnatal neurogenesis observed in the olfactory bulbs contrasts with the extremely scarce proliferative activity observed in the ependyma adjacent to this region. On the other hand, incorporation of new neurons into telencephalic regions adjacent to proliferative sites is scarce. This evidence suggest that, as has been recently described for adult neurogenesis in the rodent olfactory bulbs, neurons incorporated postnatally into the olfactory bulbs of turtles could come from the proliferative ventricular sites migrating paralel to the brain surface.

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34.31 EFFECTS OF LOW IODINE INTAKE VERSUS GOITROGEN INDUCED HYPOTHYROIDISM ON MYELINATION PROCESS ON THE RAT BRAIN.

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To make this study a group of 15 dams was fed with a Low Iodine Diet (LID) with a content of 0.04 ± 0.02 μg. Iodine/g. of food three months before mating. A second group of 15 rats was supplied Mercaptometilimidazol (MMI) in the drinking water, at a dilution of 0.02%. A third group, serving as controls (C), received the normal diet. Three offsprings of each of these three groups of rats were taken at random when they were 10 days old. They were perfused and the region of their brains containing the striatum, at the level of the anterior commissure, was cut in 50 μm. thick sections and inmunocytochemically processed using Myelin Basic Protein (MBP) as primary antibody. The superficial density of MBP marked processes were measured according to the procedure described by Weibel[1], in the dorsolateral (DL), ventrolateral (VL), dorsomedial (DM) and ventromedial (VM) regions of the striatum. The values of the superficial density$X1000 \pm$S.E.M. obtained in these four regions were respectively: 111.67 ± 17.98; 62.33 ± 6.49; 38.67 ± 23.45; 8.33 ± 6.01 in C animals; 44 ± 6.03; 36.00 ± 2.65; 40.00 ± 19.00; 8.33 ± 4.26 in MMI treated animals and 67.83 ± 11.40; 30.83 ± 11.06; 33.00 ± 17.09; 10.00 ± 7.44 in LID animals. The two-way ANOVA applied to these data, showed that both treatments affect the development of myelin in the medial, but not in the lateral region of the striatum, suggesting that LID and MMI affect the interconnection between the cortex and subcortical structures. Given the ages of the animals studied, to know if this result can be interpreted as a delay in the development, or a permanent effect, further studies, now in progress, are necessary.

1)Weibel E.R. Stereological Methods. Vol 1. p. 109. Academic Press. London. 1979.

34.32 NEUROTROPHIN-3 FUNCTION IN GENETICALLY-ALTERED MICE: EFFECT OF NT-3 GENE DOSAGE AND TISSUE-SPECIFIC EXPRESSION

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A frequent problem of knock-out experiments is lethality. This is true for Neurotrophin-3 nullmutant mice most of which die before postnatal day 2. The few survivors can live for 16 days and have body weights of only 20-40% of wildtypes. One way around this situation is the analysis of heterozygous (+/-) animals which cannot be distinguished from wildtype littermates by simple observation. These +/- mutants have a very specific defect of skin sensory innervation: they lack most (up to 80%) of slowly adapting type I units and correspondingly most of the Merkel cells in touch domes of hairy skin. Another population of skin afferents (D-hairs) is less affected (about 50% loss). Compared to the known 50% loss of proprioceptive neurons and muscle spindles these data demonstrate, first, the limited availability of NT-3 and, second, the differential susceptibility of various parts of the sensory system towards NT-3 gene dosage reduction. An alternative way to study NT-3 function in adult mice is by crossing with NT-3 overexpressing transgenics. We have generated such mice expressing high levels of NT-3 mRNA in DRG sensory neurons and spinal motoneurons. Mice -/- for the endogenous NT-3 locus and +/+ for the transgene are viable into adulthood. Parvalbumin-immunoreactive neurons in lumbar DRGs and a parvalbumin-immunoreactive projection to ventral horn motoneurons reappear. Our preliminary conclusion is that neuronal expression of NT-3 is sufficient to allow establishment of proprioceptive neurons and their central branches. Development of spindles and their sensory and motor-innervation is under investigation. Using different overexpressor lines varying in qualitative or quantitative aspects of NT-3 expression we hope to be able to evaluate the significance of endogenous NT-3 expression patterns.

34.33 THE LONGEVITY GENE PRODUCT OF *DROSOPHILA MELANOGASTER* PROMOTES SURVIVAL OF MESENCEPHALIC DOPAMINERGIC NEURONS IN CULTURE.

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We have recently shown that adult life span in inbred strains of *Drosophila melanogaster (Dm)* has been found to be controlled by a few major genes (Hereditas 111:207,1989; Hereditas 117:251, 1992). Life-prolonging effect of the 77 kDa protein, ju-myo protein (JP), which is the product of the gene on autosomal locus JmA on adult *Dm* and mice was revealed when JP was supplied in food or drinking water. However, knowledge of its precise phygiological role in development and maintenance of the nervous system neurons is still unclear. Here we show that JP can exert neurotrophic activities on postmitotic dopaminergic neurons isolated from midbrain of embryonic day 14-15 (E14-15) rat fetuses: it enhances survival of tyrosine hydroxylase immunoreactive neurons isolated from midbrain by approxymately 2-fold over control group. JP did not increase the density of astrocytes nor expression of glial fibrillary acidic protein (GFAP) in the neuron cultures. Our work provides the basis for defining at the molecular level the phygiological role of JP and for exploring its potential utility as an alternative approach to the treatment of Parkinson's disease and for studying mechanisms of aging.

34.34 CALCIUM-BINDING PROTEINS IN THE DEVELOPING HUMAN NERVOUS SYSTEM. A. Milošević*, C. Verney and N. Zečević Institute for Biological Research, 29. Novembra 142, 11000 Beograd, Serbia, INSERM U-106, Hopital de la Salpetriere, 47, Bld. de l'Hopital, 75651 Paris, France

Calcium-binding proteins (CaBPs) are large group of molecules that have the ability to bind Ca^{2+}-ion, that is involved in numerous functions during development of the central nervous system (CNS), such as mitosis of nerve cell progenitors, cell division and movement, process of outgrowth, cell death. As CaBPs appear rather early during development of CNS it was interesting to study the immunoreactivity (ir) of three CaBPs: calbindin D28-k (CB), calretinin (CR) and parvalbumin (PV) in human embryos of 4 to 8 gestational weeks (gw). Human material was obtain from legal abortions with the approval of the Ethical Committee. At 4 gw we detected different subpopulations of CB-ir and CR-ir cells and fibers in the marginal zone (MZ) of the neural tube. No PV-ir could be detected at this age. At 6 gw large bundles of CB-ir fibers that were spread throughout CNS, from medulla oblongata to the rostral forebrain, while CB-ir cells were organized in the groups that were the most prominent in the pons and mesencephalic tegmentum. Rare CB-ir cells were found in the MZ of the rostral telencephalic wall. CR-ir cells and fibers were observed in all areas of developing CNS, but are more prominent in the medulla oblongata and the pons. Numerous CR-ir cells were observed in the telencephalon. PV-ir cells and fibers were detected only in the spinal cord and remain restricted to this area until the end of examined period. At 8 gw CB-ir and CR-ir increased in the telencephalic wall. CB-ir cells and fibers formed fine network in the subplate (SP) and MZ, while CR-ir cells and fibers were formed the dense network in the SP, cortical plate and MZ.

In conclusion, CB, CR and PV appear very early during development of the human CNS, labeling different subpopulations of developing neurons. CB and CR appeared at 4 gw-old human embryo, while PV appear at 6 gw. CB and CR expressed early in the cells of the telencephalic wall. Because of its early appearance in human CNS, CaBPs have probably the special role in its development.

34.35 EXPRESSION OF THE NICOTINIC ACETYLCHOLINE RECEPTOR α4-1 SUBUNIT mRNA DURING THE ONTOGENESIS OF THE RAT OLFACTORY BULB.
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Nicotinic acetylcholine receptors (nAChR) are involved in several different ways in signal transduction in the mammalian telencephalon. With the availability of isoform specific nucleic acid probes and sensitive non-isotopic detection systems, nAChRs can be studied on mRNA level in individual neurons. This is of particular interest for the ontogeny of the central nAChR system.

The expression of the α4-1 nAChR subunit was investigated during the development of the olfactory bulb, starting from embryonic day 14 (E14) to postnatal day 120 (P120). In situ hybridizations were performed on three individuals per age using a digoxigenin-labeled riboprobe and an alkaline phosphatase-based detection system.

At day E14 a signal for α4-1 mRNA was observed in the region of the developing olfactory bulb. At E20 the strongest signal was observed in the mitral cell layer (MCL) and the olfactory bulb neuroepithelium. During further development of the MCL towards a thin, loosely packed cell layer, the number of labeled neurons decreased. Prenatally, some neurons of the external plexiform layer (EPL) also showed a strong expression of the α4-1 mRNA which markedly decreased in adult stages. In the internal plexiform layer, α4-1 mRNA expressing neurons were only found until P7. Between P7 and P14, a clustering of strongly labeled cells occured in the granular layer which lateron showed a decrease of signal intensity. The glomerular layer, clearly distinguishable at day P2, also showed developmental changes in the expression pattern. The initially high number of labeled periglomerular cells decreased continously towards later stages of development. These findings fit in with α4-1 mRNA expression changes observed during ontogeny in other parts of the telencephalon.

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34.36 TRANSIENT CHANGES OF THE CORTICAL ACTIVITY IN THE RAT BARREL CORTEX DURING CONDITIONING.
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In order to reveal the dynamics of the conditioning stream flowing through the rat barrel cortex we recorded the EEG and potentials evoked (EPs) by single vibrissa stimulation (CS) before and after pairing it with aversive reinforcement (US). Immediately with the first US the EPs amplitudes recorded on conditioned side of the cortex grow in relation to the control ones, evoked by stimulation of symmetrical vibrissa on the other side of the snout. Simultaneously, we observed an increase of the EEG spectral power in the 0 - 10 Hz band with an especially prominent enhancement of 10 Hz peak. Both these signs of enhanced activity cease on the second (or third) day of conditioning, suggesting habituation of the sensory signals at the barrel cortex level.
We propose that the observed effects are due to modulatory influences from the brain stem centers.

34.37 DIFFERENTIAL EVOLUTION OF THE ELECTROPHYSIOLOGICAL CHARACTERISTICS OF THE NMDA RECEPTOR DEPENDS ON CULTURE CONDITIONS.
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The NMDA receptor is involved in the development of cerebellar granular cells *in situ*. This receptor is an heterogenous oligomer made from distinct NR1, NR2A-D and the expression of each subunit has been shown to be regulated during development. The aim of this study was to investigate, using the patch-clamp technique, the evolution of the characteristics of the NMDA receptor on different types of primary cultures of mice cerebellar granule cells.

In a first type of culture, the entire cerebellum was dissociated and cells plated in either high (30 mM) or low (5 mM) KCl culture medium. In high KCl condition, the NMDA receptor density increased progressively during development, changing from -39.8 ± 3.5 pA/pF (n=25) at DIV6 to -94.2 ± 5.1 pA/pF at DIV11 (n=20). The application of 10 µM ifenprodil, the preferential antagonist for the NR1-NR2B oligomer, inhibited NMDA responses in granule cells with a blockade stronger at DIV5 than at DIV10 suggesting that the NR2B subtype is prevailing during the first days of *in vitro* differentiation. In low KCl condition, the evolution of the NMDA receptor density was accelerated when compared to high KCl, reaching the value of -67.8 ± 9 pA/pF (n=15) at DIV6, but the cells did not survived longer than 8 days. The addition of 100 ng/ml BDNF in the culture medium, in both low and high KCl, resulted both in a faster morphological differentiation and a 30 to 50 % increase of the current density. In a second type of culture where granule neurons were collected directly from the external granular layer, the NMDA receptor followed a different evolution: the NMDA current density increased until DIV7 and remained constant after.

These results show a clear dependence of NMDA receptor expression on the culture conditions, with a facilitating effect of BDNF and a protecting action of high KCl. A study of the NMDA receptor subtype distribution is now investigated as well as the putative modulatory effect of other trophic factors.

34.38 SOMATOSTATIN-IMMUNOREACTIVE INTERNEURONS IN THE LESION-REGENERATION OF THE LIZARD CEREBRAL CORTEX.
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The lizard medial cortex (a zone homologous to the mammalian fascia dentata) shows postnatal neurogenesis and is able to regenerate after being lesioned with an intraperitoneal injection of the neurotoxin 3-acetyl pyridine (3AP). The lesion mainly affects the projection neurons of the medial cortex leaving many interneurons unaffected. Many of these resistant cells express somatostatin (SST) immunoreactivity.

In order to detect the role of these interneurons during the lesion-regeneration process, we have studied the evolution of thr SST-immunoreactive neurons in a longitudinal series of 3AP lesioned lizards, i.e., sacrificed at different times after the injection of the neurotoxin.

There is a significant increase of SST immunoreactivity (number of somatostatin immunoreactive cells per hemisphere) in the animals sacrificed 1 day after the 3AP injection. The increase in SST immunoreactivity correlates with the onset of massive proliferation ("reactive neurogenesis") in the subjacent ependyma wich has been detected using Proliferating Cell Nuclear Antigen (PCNA) immunocytochemistry and pulses of DNA markers (5'bromodeoxyuridine, tritiated thymidine). Threafter, when the "reactive neurogenesis" period is finished, SST immunoreactive cells return to normal or even lower levels.

These facts suggest an hippotetical participation of the SST immunoreactive neurons in the lesion-regeneration process of the lizard medial cortex.

34.39 DEVELOPMENT OF GABAERGIC TRANSMISSION IN THE IMMATURE RAT HIPPOCAMPAL CA1 AREA
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GABAergic transmission was studied in P6-36 rats using current-clamp techniques in 500µm slices [alveus (Alv.) or stratum radiatum (SR) stimulation under CNQX (20µM) and APV (50µM)]. In P6-8 cells, Alv. and SR evoked ipsp, had reversal potentials (E_{ipsp}) depolarized respective to Vm; this showed a hyperpolarizing trend in the course of maturation. The maturation of ipsp, evoked by Alv. and SR stimulation had different time courses, Alv. evoked ipsp, being more premature. $GABA_B$ dependent ipsp, were not observed before P12. From P15 on, the mean E_{ipsp} values (Alv. and SR evoked) were similar to those found in the adult. The present results may reflect developmental modifications in the integration of the synaptic potentials by the soma and in the anionic distribution between the soma and the dendritic tree. Application of furosemide showed that the Na-Cl cotransport is not the only mechanism participating in putative soma-dendritic anionic gradients. Justa-somatic GABA ionophoresis evoked a poliphasic (hyperpolarizing-depolarizing) bicuculine-sensitive response in older cells; this was simply depolarizing in P8-13. SR GABA ionophoresis evoked a single (depolarizing) response at all ages. These responses were not Na dependent.

34.40 GRAFT OF HUMAN FETAL TISSUE DEVELOPMENT IN BRAIN OF IMMUNOSUPRESSED RATS.
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Previously we have showed the possibility of survival of human fetal nervous tissue in mammalian brain. The purpose of this experiment was to study histogenesis of xenograft human forebrain in brain immunosuppressed rats. Solid pieces of forebrain from aborted human fetuse brains were transplanted into brain of rats received daily injections of Cyclosporine A (Sandoz, 20 mg/kg P.O.). Light microscopic study demonstrated mitotically divided cells in neuroepithelial plate reorganised into "rosettes" during 2 - 6 week's postgrafting. Number of these cells decreased progressively. Period of proliferation is much longer than in grafts without immunosupression. Differentiated neuroblasts and immature synapses were seen at 2 months postgrafting under electron microscopic study. Results demonstrate the influence of immune reaction on histogenesis of human forebrain grafts.

34.41 IS B-50/GAP-43 IMMUNOREACTIVITY IN THE HIPPOCAMPAL NEUROPIL AFFECTED BY DIFFERENTIAL REARING OF RATS?

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Rearing in an enriched environment of rats is known to affect learning and the synaptic architecture of certain brain areas. B-50/GAP-43 is considered to be a marker for synaptic neuroplasticity. The effect of differential rearing of rats on the distribution of B-50 immunoreactivity (BIR) was studied in the hippocampus. Following weaning, Wistar rats were housed for 3 months under standard social conditions (C) or under enriched conditions (EC). The EC group scored significantly better in performance of the Morris maze task than the C group. 12 animals with a gradient in learning performance were selected for immunocytochemical analysis. The optical density (OD) of BIR was quantified for the str. radiatum (SR), str. lacunosum moleculare, stratum moleculare, 2/3 extern (Mex) and 1/3 intern (Min) by an Image Analysing System. The relative length (RL) of the hippocampal neuropil layers was also measured. With the used procedure, the minimal sensitivity to group differences was 12% for the OD and 5% for the length. The differential housing did not result in a significant difference in RL nor in OD of the neuropil layers between the groups. A rank correlation test demonstrated that the better learning performers had a significantly ($p=0.03$) lower OD (BIR) of SR than the slower learners. In contrast, a trend ($p=0.07$) in the opposite direction was observed for Min. Our study demonstrates that it is relevant to distinguish separately functional sublayers in the hippocampus in order to discover an effect of altered learning. Apparently, a lasting difference in living conditions has structural consequences in the rat hippocampus as revealed by B-50 immunocytochemistry.

34.42 Postnatal development of the expression of the proenkephalin gene in rat neocortex and in slice cultures of rat neocortex.

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In the present study, we have investigated the postnatal development of the expression of the proenkephalin (PEnk) gene in vivo and in slice cultures of rat cerebral cortex. PEnk mRNA was visualized by non radioactive in situ hybridization in cultures and in brain sections of corresponding age.

In the cortex of newborn rats (P0) only a few scattered cells contained PEnk mRNA. At day P7, positive cells were mainly close to the pial surface, while at day P13, they were arranged in two bands (layers II, III and V). This pattern did not differ from that in adult rats. Slices of rat cerebral cortex, brought into culture on day P0 or P8, were maintained for 3 to 13 days. In slices prepared at day P0, the PEnk positive neurons increased in number with the duration of culture period. They were first located in deep cortical layers and later also found in superficial layers. However, after 13 days in vitro these cultures showed a distribution of PEnk mRNA containing cells which was similar to that of 13 day old rats. This pattern was also observed, when slices were obtained from P8 rats and cultured for 5 days.

The data show that neocortical neurons express the PEnk gene also in slice cultures. The development of the expression can differ from that in vivo depending on the time point at which the slices are brought into culture. However, 2 weeks after birth the positive cells are arranged in a manner similar to in vivo.

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35. Poster Session: Motor systems, sensory motor integration II

35.01 Abstract withdrawn

35.02 RELATIONSHIPS OF THE BASAL AMYGDALOID COMPLEX WITH THE COMPARTMENTAL ORGANIZATION OF THE NUCLEUS ACCUMBENS IN RATS.

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The nucleus accumbens (Acb) and the basal amygdaloid nucleus have been implicated in stimulus-reward/punishment associations (e.g. Everitt et al., 1991). Direct, topographically organized projections from the amygdala to the Acb have been described, but their precise relationships with immunohistochemical and cellular compartments of the Acb remain unclear. The present study uses small injections of anterograde tracers (PHA-L and BDA) in the amygdala, in combination with calbindin-immunohistochemistry in the Acb to reveal striatal compartments. The results show that the caudal basal and accessory basal amygdaloid nuclei project topographically to cell rich areas in the shell of the Acb. In addition, the mid-rostrocaudal parts of the accessory basal nucleus projects to the matrix of the core of Acb, whereas the parvicellular and magnocellular components of the basal nucleus project to the patches in the medial and lateral core of the Acb, respectively. The present results indicate that different amygdaloid subnuclei reach distinct accumbal regions and compartments, in this way presumably affecting different Acb output channels. It is a future challenge to relate the presently revealed multiplicity of amygdalostriatal "channels" to the various functional behavioural aspects in which the amygdalostriatal system has been implicated.

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35.03 RETURN OF COORDINATED GAIT AND ELECTROPHYSIOLOGICAL SIGNAL AFTER EXPERIMENTAL SPINAL CORD INJURY ARE CORRELATED

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Spinal cord injury is an important cause of invalidity. Neuronal damage develops is a complex way and therpentic interventions are not very successfull as yet. In our laboratory, putative beneficial therapies in experimental spinal cord injury (weight drop method) are investigated in rats. The degree of disability is quantified in several ways; clinically, electrophysiologically and histologically.

Clinical function is assessed by a modified Tarlov Motor Score (TMS). Electrophysiological function is assessed by epidural recordings of motor evoked potentials after stimulation of the N.Ruber under hypnorm anaesthesia and neuromuscular block. In rodents, the rubro-spinal tract is an important efferent motor tract. Conduction through the rubro-spinal fibers is fast, resulting in a very specific and reproducible signal with low latency over the thoraco-lumbal spinal cord, the region of the segments controlling the leg. The signal acutely disappears after spinal cord lesion and partly returns following functional recovery of the animal. Eight weeks after injury, signal is visible once more in 6 out of 19 animals with TMS3 (weight bearing, uncoordinated gait), and more clearly so in 10 out of 10 animals with TMS4 (coordination between fore- and hindlimbs in gait) or TMS5 (no visible abnormalities).

These results indicate that restoration of function of the rubro-spinal tract is needed in order to regain coordinated gait. Experiments are planned to test chronically implanted electrodes for longitudinal assessment of spinal cord motor evoked potentials.

35.04 OPPOSITE SPINAL REFLEX RESPONSES OF γ-EFFERENTS TO CUTANEOUS AFFERENT STIMULATION IN THE CAT.

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In previous experiments, using premammillary decerebrated cats, we found that sural nerve stimulation (single shock, up to 20T) produced short latency spinal excitation of medial gastrocnemius static and dynamic γ-efferents. We have now examined the effects of cutaneous afferents in the medial plantar nerve on γ-efferents in the same nerve/preparation. Units were classified as static or dynamic indirectly, on the basis of their discharge characteristics. The responses of dynamic units consisted of short latency (15 ± 1.2ms; mean $\pm$ SD) spinal inhibition followed by weaker excitation. Static units showed two patterns of response. About half were excited at medium latency (39.9 ± 12.2ms) while the remainder showed mixed effects comprising short latency (18 ± 3.6ms) spinal inhibition followed by stronger excitation. Inhibitory and excitatory responses were generally present at 2T. The results suggest that low threshold cutaneous afferents from the sole of the foot are capable of influencing the discharges of static and dynamic fusimotor neurones. Further, the cutaneous responses of γ-efferents appear to vary according to both the source of the afferent input and the type of unit involved.

35.05 VIDEO SYSTEM FOR MEASURING 3D-EYE POSITION, BASED ON THE GEOMETRY OF THE EYE.
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Measurement of 3-dimensional eye position is essential for oculo-motor research, and a main technique of investigating the vestibular system. The most common method employed over the last few years has been the scleral search coils technique, despite problems such as coil slippage and the use of expensive contact lenses. Video-based systems have remained on the side-line, due to their high costs and their limited demonstrated accuracy.

Based on a geometrical model of the eye, we have developed a theoretical basis which allows accurate 3-dimensional eye position measurement over a large range of eye positions. The technique has been implemented in the *VTM* system("video-torsion measurement"), a previously developed video-system for measuring ocular torsion, which is based on an extended form of the polar cross correlation technique. The ideas and mathematics underlying the system are presented, and the validations are shown. We also present the results of simulations of possible sources of errors, eg. distortion of the image of the iris by the cornea, translation of the eye-ball, or an angle between the optical and the visual axis of the eye.

This new technique allows accurate measurement of 3-dimensional eye position, and enables us to represent the eye position in well established coordinate systems, eg. in rotation vectors or Fick Angles. As a practical example, we present a Listing's Plane recorded with the VTM-system.

35.06 DEFICITS OF CONDITIONED TASTE AVERSION AFTER PREFRONTAL MICROLESIONS IN THE RAT.
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The hypothalamus, amygdala and globus pallidus are essential in neural control of body weight and food and fluid intake behaviors. The prefrontal cortex (PFC) has mutual interconnections with these areas. Although much is known of PFC, its specific roles on regulation of feeding are poorly understood. In the present study, our aim was to characterize the feeding behavior of PFC lesioned animals. Kainic acid (KA; to damage intrinsic neurons) or 6-hydroxydopamine (6-OHDA; to destroy cathecolaminergic (CA) fibers and terminals) were microiontophoretically applied in the medio-dorsal PFC. Body weights, food and fluid intakes of both lesioned and control animals were daily measured. Effects of intracellular dehydration and water deprivation were also recorded. Open field (OF) activity and scores of orientation towards visual and somesthetic stimuli were pre- and postoperatively studied. To test possible changes of central taste information processing, the acquisition and retention of saccharine conditioned taste aversion (CTA) were also examined. There were no major changes in body weights and food and water consumptions among the groups. Water intakes after dehydration or deprivation schedules were increased in all animals. The 6-OHDA group showed higher OF activity scores than the others. Both the KA and 6-OHDA lesioned rats displayed deficits in the CTA acquisition and retention tests. Our present findings indicate that the PFC is a structure of great importance in memory storage and retrieval of learned taste information. Prefrontal CA mechanisms, in addition, appear to be essential in goal-directed, adaptive behavior of animals.

35.07 MODULATION OF RAT AND MARMOSET STRIATAL GLUTAMATE RELEASE BY ENADOLINE, A SELECTIVE KAPPA OPIOID AGONIST.
MP Hill*, NR Hughes & JM Brotchie. Division of Neuroscience, School of Biological Sciences, University of Manchester, Manchester, U.K.

Recent studies have implicated excessive glutamatergic neurotransmission throughout the basal ganglia as a cardinal feature mediating the pathophysiology of parkinsonism. It has been suggested that κ-opioid receptor agonists modulate glutamate release through pre-synaptic mechanisms and thus could be used in the treatment of Parkinson's disease. κ-Opioid receptors are densely distributed in regions of the basal ganglia known to be overactive in Parkinson's disease, namely the striatum and the output regions of the basal ganglia. Previously we have demonstrated anti-parkinsonian effects of the κ-opioid receptor agonist enadoline. In the present study we have investigated whether enadoline mediates glutamate transmission in the striatum. Glutamate release from rat or marmoset striatal synaptosomes was measured continuously using an enzyme-linked fluorimetric assay. 4-Aminopyridine (4-AP) was used to mimic physiological depolarisation of the terminals. In rat and marmoset synaptosomes glutamate release was inhibited in a concentration-dependent manner. Maximum inhibition was seen at 100μM enadoline. In the rat the IC_{50} was approximately 8.5μM whereas in the marmoset it was 2.4μM. The effect of enadoline was inhibited by the selective κ-opioid receptor antagonist nor-binaltorphimine. These data suggests that the anti-parkinsonian properties of enadoline may be mediated through reduction of striatal glutamate release.

35.08 MODULATION OF GLUTAMATE TRANSMISSION IN THE EXTERNAL GLOBUS PALLIDUS AND SUBSTANTIA NIGRA PARS RETICULATA BY ENADOLINE IN THE MARMOSET AND RAT
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It is now well established that the glutamate-utilising pathways from the subthalamic nucleus to substantia nigra pars reticulata (SNr) and globus pallidus are overactive in Parkinson's disease. Additionally, glutamate antagonists injected into the SNr have been shown to alleviate parkinsonian symptoms in the MPTP-treated marmoset model of Parkinson's disease. We have previously shown that the kappa selective opioid agonist Enadoline can successfully reverse akinesia in the reserpine treated rodent model, and the MPTP-treated marmoset model of Parkinson's disease. We therefore tested the hypothesis that Enadoline may act to reverse parkinsonism disease by modulating the release of glutamate in the SNr and external globus pallidus (GPe). For this purpose 400μm slices of GPe and SNr tissue were prepared from marmoset and rat brains and loaded with [^{3}H]-glutamate. The high K+-evoked release of [^{3}H]-glutamate was highly calcium-dependent (85% inhibition of release in Ca^{2+}-free conditions). In the marmoset Enadoline significantly reduced the K+ evoked release of [^{3}H]-glutamate in the SNr (28 ± 8% reduction as compared to vehicle) at a concentration of 300μM; in the GPe Enadoline produced a dose dependent reduction in the K^+-evoked [^{3}H]glutamate release, and significantly reduced the release of glutamate at the highest concentration used (48 ± 10% reduction at 300μM). In the rat Enadoline significantly reduced the release of [^{3}H] glutamate at a concentration of 200μM (70 ± 7% reduction); in the GPe Enadoline failed to inhibit the release of glutamate at the concentrations used. We conclude that the antiparkinsonian actions of Enadoline may be mediated via a reduction in the release of glutamate in the SNr of rodents and marmosets.

35.09 THE HOPPING RESPONSE AFTER HEMIDECORTICATION IN YOUNG AND ADULT RABBITS: ABSENCE OF NEURONAL REMODELLING.
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In adult rabbits, unilateral ablation of the sensory motor cortex permanently abolishes the lateral hopping reaction in the foreleg, contralateral to the lesion. However, such lesions before the 6th -7th week do not lead to impairment in this reaction. Theoretically, the remaining cortex might compensate for the unilateral ablation at early age. This possibility was tested in the rabbit by removing one hemisphere in the 3rd week of life. The hopping reaction was spared and at adult age the second hemisphere was ablated. The result was that the hopping reaction contralateral to the recent lesion could not be elicited anymore but the reaction contralateral to the early lesion remained present. This demonstrates that in rabbits not the motor cortex but another part of the CNS compensates for the early lesion. In the present study we investigated whether early ablation leads to neuronal remodelling in descending pathways projecting upon the spinal cord.

The left cortex was ablated in 4 rabbits at ages between the 14th and 21st day of life and in 4 adult rabbits. The hopping response was tested in all these animals. In addition, we studied 3 control rabbits. Descending pathways were studied by means of HRP, injected in the cervical spinal cord (in C5 - C7) at the right side. Results indicate in early and late lesioned animals as well as in control rabbits, bilateral projections from the red nuclei, from the vestibular nuclei and from several nuclei in the reticular formation. These data, along with data from the literature suggest behavioural sparing of lateral hopping is induced by remodelling of segmental circuitry after early lesioning.

35.10 TRAJECTORIES OF BINOCULAR REFIXATIONS IN THE HORIZONTAL VERSION-VERGENCE PLANE.
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Transient changes in vergence during saccades, commonly known as transient divergence, are generally thought to reflect plant properties. Upon studying trajectories of binocular refixations in the version-vergence plane, we observed substantial intra-subject variabilities in the amount of transient divergence exhibited. In order to deduce neural version and vergence control signals from these trajectories, it is necessary to isolate the transient divergence contribution. Our approach was to simulate, for different subjects, the dynamical properties of binocular refixations with various version and vergence components, using the saccade-vergence interaction model proposed by Zee et al. (J. Neurophysiol. 68:1624, 1992).

We recorded binocular horizontal gaze-shifts, to LED targets in the dark, using the scleral coil technique. Stimuli consisted of horizontal target shifts, of different amplitudes, and target-shifts in direction and depth. Subjects were observed to have differing amounts of transient divergence for a given horizontal shift of the binocular fixation point. We also found that subjects, with large or small degrees of transient divergence during horizontal saccades, exhibited version-vergence trajectories that were similarly affected.

Our simulations, for different subjects, suggest that intra-subject variability is related to idiosyncratic differences in the dynamic properties of the lateral and medial rectus muscles, causing adduction to lag abduction. By relatively small adjustments of only a few model parameters, different oculomotor signatures reflected in adducting and abducting main sequences, saccadic and vergence velocity profiles and trajectories in oculomotor space can be closely matched.

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35.11 CHOLINERGIC MOSSY FIBRES INNERVATE GRANULE CELLS AND UNIPOLAR BRUSH CELLS IN THE RAT CEREBELLUM. Dick Jaarsma[1], Constantino Cozzari[2], and Enrico Mugnaini[3]. *(1) Dept. Anatomy, Erasmus Univ., 3000DR Rotterdam, The Netherlands; (2) Inst. Cell Biol., CNR, 00137 Rome, Italy; (3) Lab. of Neuromorph., Univ. Connecticut, Storrs, USA.*

Choline acetyltransferase (ChAT)-positive mossy fibres are concentrated in the vestibulo-cerebellum, where they originate from the medial vestibular nucleus and the nucleus prepositus hypoglossi (Barmack et al., *J. Comp. Neurol.* 317:250). The vestibulo-cerebellum is also enriched in unipolar brush cells (UBCs), a small cerebellar cell type, that forms giant synapses with mossy fibres (Mugnaini et al., *Synapse* 16:284). In this study we explored by immuno-electron microscopy, whether ChAT-positive mossy fibres innervate UBCs. A monoclonal antibody to rat ChAT was utilized. As previously described, a high density of ChAT-immunoreactive mossy fibres occurred in the nodulus and the ventral uvula. Immunostained mossy fibre rosettes mostly contained high densities of round synaptic vesicles and mitochondria, but few large dense core vesicles. They formed asymmetric synaptic junctions with dendritic profiles of both granule cells and UBCs. The synaptic contacts between ChAT-immunoreactive mossy fibres and UBCs were very extensive, and did not differ from synapses of ChAT-negative mossy fibres with UBCs. Systematic ultrastructural analysis of large areas of the nodulus and ventral uvula revealed that a minority (10-20%) of ChAT-immunoreactive mossy fibre rosettes formed synapses with UBC profiles. ChAT-positive rosettes accounted for 10-30% of the rosettes forming synapses with UBCs. Thus the present data suggest that UBCs are innervated by a heterogeneous population of mossy fibres, and that some UBCs may respond to mossy fibre stimulation with cholinergic effects.

35.12 EVIDENCE FOR A PERIAQUEDUCTAL GRAY - NUCLEUS RETROAMBIGUUS - SPINAL CORD PATHWAY IN THE RAT.
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In the cat the nucleus retroambiguus (NRA) has been shown to receive strong projections from the periaqueductal gray (PAG) and to send fibers to distinct motoneuronal cell groups in brainstem and spinal cord. The NRA plays a role in the production of vocalization and possibly lordosis. The question arises whether such a PAG-NRA-spinal cord projection exists in the rat also.
WGA-HRP injections in various levels of the spinal cord indicated that the NRA sends its fibers mainly through the contralateral spinal cord. Further retrograde tracing experiments demonstrated that a distinct group of neurons in the lateral and ventral PAG project to the caudal medullary lateral tegmentum. Anterograde WGA-HRP tracing studies finally showed that neurons in the lateral PAG project specifically to the NRA and not to the lateral tegmentum in general, which seems the case for the neurons in the ventral PAG.
The results demonstrate that also in the rat a PAG-NRA-spinal cord projection exists, which might be of crucial importance for the study of the anatomical and physiological framework of vocalization and lordosis behavior in this animal.

35.13 REMEMBERED SACCADES IN SCHIZOPHRENIC PATIENTS: EVIDENCE AGAINST DEFICITS IN STORING VISUAL-SPATIAL INFORMATION.
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Major arguments for the involvement of prefrontal cortex and for spatial working memory deficits in schizophrenia are based on disturbances of eye movements in this disease. Deficits in oculomotor accuracy in response to unpredictable target jumps as well as abnormalities in spatial delayed-response tasks and in the antisaccade task have been observed. These findings have been interpreted to be due to the loss of representational processing. However, while much work has been done on the dependence of *primary* saccades on memory-related events, almost nothing is known about the occurrence of representation-based *correction mechanisms* in these tasks.

Here we report oculomotor recordings with a new optical technique, which allows the direct localization of the fovea on the visual scene. The experiment consisted of three oculomotor delayed-reponse tasks, i.e., two memory-guided response tasks and one visually guided control task. The goal was to make an eye movement to the position where a target was previously flashed. By computing the angular distance between the target location and the foveal position at the end of initial and following corrective saccades, the accuracy of primary and successive saccades was determined.

Our findings show that although schizophrenic patients were impaired in the accuracy of primary saccades to remembered targets, final eye positions show a similar distortion relative to normal controls. Contrary to previous studies suggesting deficits in storing visual-spatial representation due to prefrontal dysfunctions, we conclude that oculomotor deficits in schizophrenic disease can be characterized as a failure in the gating or suppression of information derived from *internal representation*. In addition, our observations are in line with the assumption that the prefrontal cortex is involved in the gating or suppression of information.

35.14 PERI- AND SUBMILISECOND PRECISION OF SPIKE TIMING IN VISUAL CORTICAL SPIKE TRAINS.
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Neuronal spike trains contain precisely replicating patterns whose presence cannot be accounted for by chance production. For instance, in a given window of time the cell might emit triplets of spikes the interspike intervals of which are replicated in other triplets in the same window, with a precision better than a given tolerance δ. In visual cortical spike trains and for δ smaller than $\approx$ 2 ms, the number of detected patterns is usually much higher than would be expected for a Poisson-like renewal process at the same average firing frequency. The ratio of the number NT2 of triplets of spikes present two times and the number ND3 of doublets present three times in the same window gives a frequency insensitive measure of this type of fine temporal organization (*Soc. for Neurosci. Abstr. 1994 #18.1*). By varying the tolerance δ with which such NT2/ND3 ratios are measured, the precision with which spikes are timed in the train of spikes was evaluated. Analysis of a large sample of spikes (N = 141,387) from single units recordings in the visual cortex of anaesthetized cats, stimulated by a sinusoidal drifting grating, showed that the calibration of spikes in most replicating patterns was in the range 0.4 to 1.4 ms.

This observation is at variance with the simplistic "integrate and fire" model of neurons and call for the search of the detailed mechanisms of production and detection of such precisely replicating patterns.

35.15 EXPRESSION OF α4-1 SUBUNIT mRNA OF NICOTINIC ACETYLCHOLINE RECEPTORS DURING ONTOGENESIS OF THE RAT CEREBELLUM.
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There are conflicting reports on cholinergic projections to the cerebellum and very little is known about the ontogenesis of nicotinic acetylcholine receptors (nAChR) in the cerebellum. The expression of the most widely distributed α-subunit of the neuronal nAChR, α4-1, has therefore been investigated on the mRNA level in the developing and in the adult rat cerebellum. Between embryonic day 14 (E14) and postnatal day 120 (P120=adult), α4-1 transcripts were visualized by non-radioactive in situ hybridization using a digoxigenin labeled riboprobe. -Already on E14, a strong signal for α4-1 mRNA was detectable in the neuroepithelium of the cerebellar premordium. On E20, a distinct label was found in the external germinal layer, in Purkinje cells still distributed in several cell rows and in the developing deep cerebellar nuclei. The external germinal layer remained positive both in its proliferating and in its premigratory zones until it had disappeared on P25. The granular layer, first distinguishable on P2, initially showed a strong staining which gradually decreased during development and almost completely disappeared between P25 and P120. Interneurons of the molecular layer were also intensely labeled during the period of their formation (P7-P25). Thereafter, staining diminished to moderate labeling intensity at adulthood. Label of Purkinje cells reflected their differentiation: on P7, only the apical cytoplasmic cone was stained, subsequently a perinuclear staining developed. Although staining intensity decreased from P25 to P120, a moderate label of Purkinje cells persisted in the adult cerebellum. In the deep cerebellar nuclei, signal intensity hardly changed during development, and α4-1 mRNA expression remained strong until adulthood. Our results support the assumption that Purkinje cells, interneurons of the molecular layer and deep cerebellar nuclei receive a cholinergic input; in addition, they indicate that there is a transient expression of α4-1 mRNA in developing granule cells.
Supported by the Deutsche Forschungsgemeinschaft (Schr 283/8-2)

35.16 PELVIC MUSCULAR REFLEX PRODUCED BY GENITAL STIMULATION IN FEMALE RABBIT. M. Martínez-Gómez*, M. Carro, R. Hudson, H. Distel, J. Manzo and P.Pacheco. Centro de Investigaciones Fisiológicas-UAT, México; Inst. Med. Psychol., Univ. of Munich, Germany; Instituto de Neuroetología-UV México; Inst. Invest. Biom.-UNAM, México.

An understandig of the function of the striated pelvic muscles is basic to an understanding of the processes accompanying copulation and parturition. In adult chinchilla-breed female rabbits, reflex EMGs of the constrictor vulvae and vestibuli, bulbospongiosus, ischiocavernosus, pubococcygeus, coccygeus and rectus abdominis muscles were recorded in response to stimulation of the clitoral sheath, vagina, cervices, perineal and perianal skin, and the flanks. Strong EMG activity was elicited by clitoral pressure and vaginal stimulation with a glass rod in all muscles except the rectus abdominis. Both kinds of stimulation resulted in prolonged afterdischarges. Stimulating the cervices produced a response only in rectus abdominis also with afterdischarges. Perineal or perianal skin stimulation resulted in EMG activity in constrictor vulvae and vestibuli, ischiocavernosus and pubococcygeus muscles. Through the direct electrical stimulation of the muscles it was possible to observe distinctive movements of the vagina, clitoral sheath, bladder, anal glands, tail and hind legs. These findings can contribute to explaining the functions of these structures when they are reflexively activated during reproductive activities. (Conacyt 3569-N MMG, FOMES-UAT 95 MMG)

35.17 MORPHOLOGY AND DISTRIBUTION OF MOTOR NEURONS OF THE GLOSSOPHARYNGEAL-VAGAL AND ACCESSORY NUCLEI IN THE FROG, RANA ESCULENTA

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The motoneurons of the glossopharyngeal (IX), vagal (X) and accessory (XI) cranial nerves form a ventrolateral column in the caudal part of the brainstem. With the aid of the cobalt labelling method we have investigated the central representation of the peripheral targets to find the musculo-viscerotopic organization within the nucleus. The position, the dendritic morphology, and the size of the perikarya of labelled motoneurons were taken into account in the establishment of the nuclear organization of the different components. In the rostral part of the nuclear complex the small cells are located dorsally laying in a groove formed by the ventrally located medium-sized cells. In the caudal portion of the nucleus a new type of cell, having a large perikaryon, appears. Dorsomedially to the continuous cell column 15-20 cells intermingle with the cells of the reticular formation that can be regarded as the primordial form of the dorsal nucleus of the vagus nerve (Xd) in mammals. Labelling of the branches of vagal nerve revealed that a musculo-viscerotopic organization exists within the IX-X-XI nuclear complex of the frog. The reconstruction of the dendritic tree revealed that the cardiac, gastric and pulmonary neurones have similar dendritic arborization pattern with a weak dorsomedial and a broom-like ventrolateral dendritic tree. The dendritic arborization of the Xd neurones occurs mainly within the gray matter. Most of the dendrites of laryngeal neurones are oriented in a dorsal direction, the cucullaris dendrites have a mediolateral orientation. On the basis of the morphology and peripheral targets of the neurones we can conclude that the cells of the IX-X-XI nuclear complex are organizied in a similar manner as described in the lizard and the rat.

35.18 DIPOL ANALYIS OF MOVEMENT-RELATED CORTICAL POTENTIALS IN PERSISTENT MIRROR MOVEMENTS

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Mirror movements (MM) are involuntary movements executed on one side of the body during voluntary movements of the contralateral homologous body parts which may abnormally persist into adulthood. In six subjects affected by persistent MM scalp-recorded movement-related cortical potentials during self-paced extensions of either the left, right or both middle fingers were analysed by spatio-temporal dipol models.

In contrast to normal subjects, which showed preponderance of generators in the sensorimotor cortex contralateral to the intended movement in the unilateral tasks, in the MM group fairly bilateral sources in both hemispheres during unilaterally intended movements were found.

We propose that these results reflect a bilateral activation of both primary motor areas, which compensate for abnormal ipsilateral corticospinal pathways in subjects with persistent MM.

35.19 EFFECTS OF SOMATOSENSORY CORTEX TETANIC STIMULATION ON MOTOR CORTICAL UNIT RESPONSES IN THE CAT.

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It is known that tetanic stimulation of the somatosensory area can induce long-term potentiation (LTP) of the EPSPs recorded from neurons in the superficial layers of the motor cortex. It has been suggested that the LTP in the cortico-cortical circuit is involved in motor learning and memory. In the present study the effects of somatosensory cortex tetanization on the evoked spike activity of motor cortical neurons were studied using extracellular recording method. The experiments were carried out on eight adult cats initially anesthetized with ketamine (15 mg/kg i.m.). Surgical procedures were carried out under inhalation anesthesia (100% oxygen supplemented with 1.5-2.5% halotane) and the recordings were performed under Nembutal (1.5-2 mg/kg/h i.v.) anesthesia. Extracellular spike activity was taken from the postcruciate motor cortical units (area 4γ), while intracortical microstimulation (ICMS: 25-40 μA, 200 μs, 1Hz, 3 pulses 4 ms interval) were delivered to the anterior bank of the ansate sulcus (area 2). Tetanic stimulation (100-200 Hz, 10-20 s) of the same area induced different response patterns in the motor cortical neurons. In four trials high frequency stimulation of the somatosensory cortex induced a long lasting potentiation, which persisted more than 60 min. On the contrary, in two trials a remarkable long-term depression (LTD) was detected after tetanization of the somatosensory cortex. All recordings were obtained from layers II and III except for one case of LTD observed in neurons located at the border between layer V and VI. These results show that the cortico-cortical input change the activity of a group of postsynaptic neurons in the motor cortex and support the existence of a clear neuronal plasticity at motor cortical level.

35.20 THE BALANCE BETWEEN STRIATAL OUTPUT ROUTES IS LESS DISTURBED BY RISPERIDONE THAN BY HALOPERIDOL.

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Numerous studies have shown that antipsychotic drugs exert a regulatory influence on the opioid peptides dynorphin and enkephalin. These two peptides can be used as markers for the two different output-routes of the striatum. It has been proposed that the balance between these output-routes is essential for normal basal ganglia function. Based on this idea, extrapyramidal side-effects (EPS) due to antipsychotic drug treatment may be related to a disturbed balance between the opioid peptides contained in the two pathways. We hypothesize in the present study that the balance between dynorphin and enkephalin is less disturbed after treatment with the atypical drug risperidone (D_2/5-HT_2 antagonist) compared to the typical drug haloperidol. This hypothesis was tested using quantitative *in situ* hybridisation for mRNA encoding preproenkephalin (ppenk) and prepreodynorphin (ppdyn) mRNA in the striatum of the rat. Our results indicate that both haloperidol and risperidone increase ppenk mRNA levels in dorsal and ventral striatum, however, haloperidol is far more potent (76% dorsal, 45% ventral) than risperidone (18% dorsal, 11% ventral). Ppdyn mRNA is slightly, but significantly increased by haloperidol in dorsal (6%) and ventral (7%) striatum, whereas it is not changed by risperidone with exception of a modest decrease (5%) in the shell region of the ventral striatum. In conclusion, the enkephalin/dynorphin mRNA ratio is less disturbed after risperidone than after haloperidol treatment in all striatal subregions measured. This agrees with the clinical profile of risperidone as an antipsychotic with a low EPS-inducing profile.

35.21 DEVELOPMENT OF RECIPROCAL INHIBITION IN NORMAL BABIES AND THOSE WITH SPASTIC CEREBRAL PALSY.

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Co-contraction of antagonist muscles is characteristic of spasticity and a feature of early postnatal motor development. Monosynaptic Group Ia projections from biceps brachii to motoneuronal pools throughout the brachial plexus, shown in the newborn baby, become restricted during the first two postnatal years (O'Sullivan et al. 1991;439:529-543). Heteronymous Group Ia excitatory projections between the antagonist muscle pair, biceps and triceps brachii, persist in children with spastic cerebral palsy (O'Sullivan et al., adjacent poster). The hypothesis was that spinal reciprocal inhibition is not functionally present at birth and fails to develop in subjects with spasticity due to perinatal brain damage (cerebral palsy).

A cross-sectional study was performed of 80 normal children aged 2 days to 4 years with a further 1 year longitudinal study of 37 healthy newborn babies and 21 at high risk for cerebral palsy, 4 of whom had developed spastic quadriparesis by 1 year. Electromechanical taps were applied to the tendon of triceps brachii when contracting, to elicit the phasic stretch reflex, and when relaxed, to study Group Ia heteronymous projections to biceps. Surface EMGs were recorded from biceps and triceps. In neonates of both studies, low threshold heteronymous excitatory projections from triceps to biceps were obtained at 0.6-0.9 times the threshold of the homonymous phasic stretch-reflex in triceps. In normal subjects the thresholds for these responses increased at a faster rate than those of the homonymous phasic stretch reflex but responses were still present in 80% of subjects at 9 months. All the high risk group showed persistence of low threshold heteronymous excitatory responses. In both studies reciprocal inhibition from triceps to biceps occurred in 25% of neonates and in all subjects by 9 months, including subjects at high risk for cerebral palsy and all 4 who actually developed cerebral palsy. In the normal babies the increasing threshold and disappearance of the heteronymous reflexes occurred independently of the establishment of reciprocal inhibition. In conclusion, the persistence of low threshold heteronymous Group Ia excitatory projections between antagonist muscles is not due to the failure of development of reciprocal inhibition.

35.22 3D INTERACTION OF SMOOTH PURSUIT AND VESTIBULO-OCULAR REFLEX (VOR) IN HUMANS.

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We examined the mechanisms of VOR cancellation – where a subject fixates a target that is moving with the head – by looking at eye position dependent velocity during VOR (*V*), pursuit (*P*) and combined VOR & pursuit (*VP*). Seven subjects were rotated sinusoidally (0.3 Hz, ± 20°) in darkness fixating an imagined target at 20° up, down, right or left (*V*) or while fixating a laser spot projected at the rotating sphere (at the same locations – *VP*). For pursuit, the subjects tracked a target oscillating (0.3 Hz, ± 20°) horizontally (elevation: center or 20° up and down), vertically (azimuth: center or 20° left and right) or "torsionally" (along a circle at 20° up, down, right or left). Angular positions of head and left eye were measured using 3D search coils. Eye velocities are represented as 3D angular velocity vectors.

P velocity vectors tilted half as far as the gaze line, that is smooth pursuit follows Listing's law: when the eye is rotated x° away from primary position, the velocity vector of the eye must lie in a plane that is tilted $x^\circ/2$ away from Listing's plane in the same direction. Velocity vectors during *V* tilted a quarter as far as the gaze line for yaw and pitch and in the same direction; during roll they tilted about as far but opposite the gaze line. In other words: the VOR follows a half-Listing's law strategy. Thus, the eye rotation axis tilted twice as far during horizontal and vertical *P* as compared to *V*. When passing from horizontal and vertical *V* to *VP*, the main eye velocity component was completely canceled. However, torsional modulation of eye velocity in eccentric gaze directions remained but changed its direction when the light went on. During roll, reduction in *VP* speed is smaller but, again, the velocity vector changes its sign when compared to *V*. The *VP* eye velocity vector in all cases lies close to the gaze direction allowing for foveal image stabilization.

A superposition model of *V* and *P* angular velocity vectors accounts for the main findings of 3D VOR cancellation: (1) reduction in speed; (2) change in direction; (3) *VP* velocity vector pointing along the gaze line.

35.23 THE EFFERENT PROJECTIONS OF THE INTESTITIAL NUCLEUS OF CAJAL IN THE SQUIRREL MONKEY.

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The efferent projections of the Nucleus Interstitialis of Cajal (NIC) have been studied in the squirrel monkey following bulk injections of biocytin and PHAL near functionally identified oculomotor related burst-tonic neurons of the NIC. Dense terminal fields were seen: a) contralaterally, in the NIC, the oculomotor nucleus and the trochlear nucleus, and b) ipsilaterally, in the Fields of Forell, the rostral interstitial nucleus of the medial longitudinal fasciculus, the oculomotor and trochlear nuclei, the gigantocellular reticular formation, and in the ventralmost portion of the anterior horn of the first two spinal cervical segments. Moderate or weak terminal fields were observed in the mediodorsal, centre medianum and inferior central thalamic nuclei, bilaterally, as well as the zona incerta, nuclei reticularis pontis oralis and caudalis, the superior and medial vestibular nuclei, the nuclei prepositus hypoglossi, abducens and hypoglossal, the gigantocellular and magnocellular reticular formation, the inferior olive as well as the pontine and medullary raphe, ipsilaterally (supported by PENED Grant 91ED433).

35.24 REFLEX REVERSAL IN DYNAMIC γ-EFFERENTS DURING LOCOMOTION IN THE CAT.

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In previous experiments, involving decerebrate cats in the resting state, single shock electrical stimulation of the medial plantar nerve (cutaneous) produced short latency inhibition, followed by weaker excitation, in the discharges of medial gastrocnemius dynamic γ-efferents. We have now examined the effect of stimulating this nerve (0.1ms width; 50,100/s for 100ms; 2,3,20T; 1/3s) during locomotion in the same preparation to determine whether the pattern of responses varies with behaviour. Units were classified as dynamic indirectly, on the basis of their discharge characteristics. Stimuli ≥2T either produced inhibition (9 units) or had no net effect (1 unit) on medial gastrocnemius dynamic γ-efferents in the resting state. During locomotion responses were phase dependent. Mean responses during EMG bursts were inhibitory while those between bursts were, generally, not statistically different from zero ($P>0.1$). However, for three units, excitation occurred between EMG bursts at some stimulus intensities (2T for 3 units; 20T for 1 unit). Thus while inhibition dominates the responses of dynamic γ-efferents during posture, excitation may be more evident during locomotion depending upon the phase of the step cycle. Such phase dependent reflex reversal may be of functional importance for the locomotor task.

35.26 A DIVERGING TOPOGRAPHIC PROJECTION OF THE D_2 AND C_2 CEREBELLAR BANDS TO THE DEEP NUCLEI. M. R. Pantò, F. Cicirata, R. Parenti and M.F. Serapide. Istituto di Fisiologia umana, Viale Andrea Doria ,6, 95125-Catania , Italy.

The topographic arrangement of the cerebellar corticonuclear projections has been described in terms of sharply segregated sagittal bands based on the afferences coming from the inferior olive (IO). Such a rigid topographic pattern does not agree with the integrative motor activities played by the cerebellum, so we planned to reinvestigate the organization of this pathway. 20 rats received iontophoretic injections of either wheat germ agglutinine horseradish peroxidase (WGA-HRP) or biotine dextrane amine (BDA) in the rostral or in the caudal part of the paraflocculus (Pf), which respectively are part of the D_2 and the C_2 band. The labelling was researched both in the IO and in the nucleus lateralis (NL). After injection in the rostral Pf, labelled body cells were found in the lateral part of the principal olive (D_2 region). From the Pf, there were observed fibres dividing into two roots respectively directed to the ventral and the dorsal part of the NL. The ventral one terminated in the parvocellular (slp, D_2 region) whereas the dorsal one terminated in the magnocellular region (D_1 region). After injections in the caudal Pf, labelled body cells were found in the main accessory olive (MAO, C_2 band) while labelled fibre terminals were observed in the interpositus nucleus (NIP, C_2 band), but also in the slp (D_2 band). The results show that the corticonuclear projections are not so sharply segregated in sagittal bands as they have been supposed up to now .

35.27 EYE MOVEMENTS DURING OPTIC FLOW STIMULATION IN MONKEYS. M. Pekel*, M. Lappe & K.-P. Hoffmann; Dept. Zoology & Neurobiology, Ruhr-University. 44780 Bochum, Germany

Optic flow (OF) is the movement pattern induced on the retina when an animal is moving through a 3D environment. This pattern depends not only on the movement trajectory of the animal but also on its eye movements. Although many experiments investigated the performance of heading detection from OF under specific, restricted conditions, little information is available about naturally occuring eye movements when OF stimuli (OFS) are applied.

We tested this in two macaque monkeys. The animals were seated in a primate chair with the head fixed and eye movements were measured with the search coil technique. OFS of 20 s duration consisted of random dots and were projected on a 90x90° flat screen 48cm in front of the animal. We separated the saccades from inter-saccade intervals (ISI) by a velocity level criterion. Since the motion of dots in an OFS is not uniform across the visual field, eye movements were analysed with respect to gaze direction. The direction of eye movements showed a good correlation with the local motion vectors of the OFS in the direction of gaze. Generally the monkeys mean X- and Y-eye positions were clustered in the inner 10 deg of the screen. For expansion (forward movement simulation) the gain was always lower than for contraction. For a full-field expanding stimulus the median gain amounted to 0.8 but it decreased for lower as well as upper half field stimulation to 0.45. The median ISI-duration also decreased from 440 to 330 ms. When we varied the horizontal position of the focus of expansion the horizontal mean eye position changed only little, but the gain increased for both monkeys. The results show that the different OFS lead to different eye movement patterns and stress the importance of considering eye movements in investigations involving OF.

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35.28 PLASTICITY OF STRIATAL NEURONS AND MONOAMINE NEURONS OF THE BASAL GANGLIA AFTER NEONATAL 6-OHDA LESIONS

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Intrastriatal unilateral injection of 6-OHDA (a neurotoxin selective for catecholamine neurons) was performed in 1day old rats and resulted in a retrograde degeneration of central DA neurons. Ipsilateral DA neurons located in the pars compacta of the subtantia nigra (SNc) were predominantly destroyed To a less extent, DA neurons of the ventral tegmental area (VTA) and of the retrorubral Field (RRF) were also lesioned.

In the lesioned striatum, when examined 2-4 months later , the levels of α subunit of Golf and of Gs were increased as measured by immunoblotting. This suggests that stimulatory G proteins located on striatal neurons are involved in the D1 receceptor supersensitivity following DA denervation.

Using biochemical and histochemical methods, a serotonin (5-HT) hyperinnervation could be revealed , at the adult stage, in the rostral part of the lesioned striatum. The levels of 5-HT in the rostral striatum were increased (+100%) after intrastriatal injections of high doses of 6-OHDA (12-20μg) which result in a very strong striatal DA depletion (90-95%). However, even after a moderate DA depletion (50%) obtained using a low dose of 6-OHDA (4μg), the tissue levels of 5-HT were increased (+50%).

Finally, a DA neoinnervation in the lesioned Subtantia Nigra was observed using TH-immunochemistry. In the pars reticulata of the SN, a network of thin beaded DA fibers had replaced the numerous dendritic processes normally present at this level. Preliminary results suggest that DA neurons implicated in this neoinnervation originated from ipsilateral VTA and RRF.

35.29 VESTIBULAR, PREPOSITUS HYPOGLOSSI AND CEREBELLAR PROJECTIONS TO THE SPINAL CORD. Batini, C., Buisseret-Delmas, C., Compoint, C. and Vota-Pinardi*, U. Laboratoire de Physiologie de la motricité, CNRS, Université Pierre et Marie Curie, Paris France and Istituto di Cibernetica, CNR, Napoli, Italy.

The vestibular, prepositus hypoglossi (PH) and cerebellar nuclei receive outputs from Purkinje cells (PC) of the cerebellar cortex to regulate somatomotor activity. We have investigated the localization of the neurones of these nuclei projecting to different levels of the spinal cord in the albino rat since the descriptions so far available are still incomplete. WGA-HRP was injected in the hindlimb (lumbar 1-3) the forelimb (cervical 6-8) and the neck (cervical 2-3) spinal levels and neurones containing the retrogradely transported tracer were identified in the vestibular, PH and cerebellar nuclei. The results showed the following: i) spinal projections from vestibular nuclei arose in the four principal nuclei; the great majority in the nucleus vestibularis descendens (NVD) (receiving PC axons from zone A and flocculus) and vestibularis lateralis (NVL) (receiving from zone B); only a few marked cells were present in the neighbouring parts of the nucleus vestibularis medialis (NVM) and vestibularis superior (NVS); the projections were bilateral from the four nuclei with an ipsilateral dominance from the NVL and NVS and a contralateral dominance from the NVM and NVD. ii) The PH (receiving from flocculus) sent fibres bilaterally with contralateral dominance mostly to the neck but also to the hindlimb and forelimb spinal levels. iii) From the cerebellar nuclei a negligible number of neurones sent fibres to the hindlimb and forelimb while an appreciable number innervated the neck spinal levels. This projection was essentially contralateral and arose in neurones localized in the anterior part of the nucleus medialis (receiving from zone A), in the nucleus interpositus (mostly the medial part receiving from zone C1), and to a much lesser extent from the NL (receiving from zone D1). In addition, many labeled neurones were found in the contralateral interstitial cell group localized in the interface between the NM and NI; this area is innervated by PC axons from zone X which receives input from the forelimb.

35.30 LOCALISATION OF NITRIC OXIDE SYNTHASE AND NADPH-DIAPHORASE IN ONUF'S NUCLEUS OF THE CAT AND HUMAN.

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The putative transmitter nitric oxide (NO) has been associated with pudendal nerves which innervate the external anal and urethral sphincters, but it is not known whether sphincteric motoneurones in Onuf's nucleus express NO. This has been examined immunocytochemically in sections of aldehyde-fixed cat sacral cord (S1-S2), and paraffin-embedded human cords obtained during routine autopsy, using a polyclonal antibody detecting the NO forming enzyme nitric oxide synthase (NOS) and antigen retrieval methods. To test whether NADPH-diaphorase (NADPHd) histochemistry detects NOS, as claimed, additional sections of cat sacral cord were stained for NADPHd prior to immunostaining for NOS. Sacral motoneurones in cat and the human showed similar results. On ommission of primary antibody or NADPH substrate, sections failed to stain. In the presence of antibody, 55-66% of cat sacral motoneurones were NOS-immunoreactive (66% in Onuf's nucleus). Remaining motoneurones showed negligible NOS reactivity. Most, but not all, human sacral motoneurones were NOS-immunoreactive, including those in Onuf's nucleus. Similarity between the overall proportions and sizes of sacral motoneurones reactive for NOS or NADPHd suggested possible co-localisation of these peptides, but the double staining experiment did not support this suggestion. Co-localisation of NADPHd and NOS occurred in only 61% of sphincteric motoneurones, 7% expressed neither peptide, 23% stained only for NADPHd and 9% stained solely for NOS. It is concluded that some sphincteric motoneurones in cat and the human utilise NO; that sacral motoneurones display phenotypic differences in their utilisation of NO, and that NADPHd histochemistry is an inadequate method for illuminating NOS containing sacral motoneurones.

35.31 THE LOCALIZATION OF LAST-ORDER PREMOTOR INTERNEURONS IN THE LUMBAR SPINAL CORD OF RATS. Z. Puskár* and M. Antal, Department of Anatomy, University Medical School of Debrecen, H-4012 Debrecen, Hungary

There is strong evidence that neural circuits underlying certain rhythmic motor behaviours are located in the spinal cord. Such local central pattern generators are thought to coordinate the activity of motoneurons through specific sets of premotor interneurons, some of which (last-order interneurons) establish monosynaptic contacts with motoneurons. In the experiments presented here we intended to identify and localise interneurons that can likely be regarded as last-order premotor interneurons. After small iontophoretic injections of neurobiotin and biotinylated dextran-amine into the lateral motor column (LMC) or adjacent white matter at L3-L6 segments, retrogradely labelled spinal interneurons were investigated in the lumbar spinal cord of rats. Following injections centred within the LMC, labelled interneurons were revealed in a 3-4 segment long compartment of the spinal gray matter ipsilateral to the injection site. With the exception of the very close vicinity of the injection site where stained perikarya were distributed throughout the entire extent of the ventral horn, labelled neurons were confined to a narrow horizontal layer of laminae V-VI and the dorsal regions of lamina VII. In cases the tracer was injected into the lateral white matter adjacent to the LMC, labelled perikarya were observed within the same location but in a substantially lower number. Following injections into the subpial region of the white matter, however, very few, if any, labelled perikarya were revealed. The results suggest that most of the premotor interneurons that may establish synaptic contacts with a specific set of motoneurons are distributed in a 3-4 segment long section of the spinal cord, and they are mostly confined to a narrow horizontal layer of the intermediate gray matter in rats. The findings also indicate that most of the last order interneurons may form synaptic appositions with somata and proximal dendrites of motoneurons, while distal dendrites may receive synaptic contacts from segmental interneurons only in a limited number.

35.32 FORCE CODING IN MOTOR CORTICAL NEURONAL POPULATIONS SCALES WITH THE FORCE RANGE.

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The goal of the present investigation was to uncover specific features of the neuronal correlates of grip force shown in motor and premotor cortex, and to search for some regional specialisation.

Several quantitative analyses were performed on 176 finger-related neurones which had been recorded in 2 monkeys trained to produce isometric grip force in a visuomotor step-tracking paradigm, and which showed significant linear correlation coefficients between their firing rate and total force. For single neurones as well as for the neuronal populations, indices of force sensitivity were calculated separately for the data acquired in the trials requiring 2 and 3 consecutive force steps, the latter reaching higher force. These indices yielded steeper slopes for the 2-step than for the 3-step trials, the differences between both being only significant for the population indices ($P < 0.01$), except for those obtained in a transitional premotor region (PMvc). These differences suggest some saturation at higher forces, as seen in a few cells. The linear model was thus compared to quadratic and logarithmic fits by computing mean residual errors (MSE). The population MSEs disclosed neither a clear preference for one of the models, nor differences between regions. An important new finding was the presence of significant differences in force sensitivity between the 2- and 3-step trials when the data obtained for the first and second force steps, overlapping in their force range, were compared.

Together these findings suggest that cell populations located in motor and premotor cortex can scale their firing rate as a function of the force required by the task, thus showing some kind of functional plasticity. Further, this investigation also shows that some force coding features can only be clearly demonstrated for the whole neuronal population and not for single neurones.

35.33 ORIGIN OF THE GLYCINERGIC AFFERENT PROJECTIONS TO THE TRIGEMINAL MOTOR NUCLEUS OF THE RAT. C. Rampon*, P-H. Luppi, C. Peyron, P. Fort, J-M. Petit and M. Jouvet. Département de Médecine Expérimentale, 8 avenue Rockefeller, 69373 LYON cedex 08, France.

It has been shown that glycine is responsible for the hyperpolarization of the trigeminal motoneurons during paradoxical sleep (PS) and therefore plays an essential role in the muscular atonia characteristic of this sleep state. Based on a number of experiments, it has been further proposed that the glycinergic neurons at the origin of this inhibition are localized in the alpha and ventral gigantocellular nuclei (Giα and GiV). To test this hypothesis, we determined with a double staining method the origin of the glycinergic innervation of the rat trigeminal motor nucleus (V). We combined the use of a retrograde tracer, the b subunit of the cholera toxin (CTb) with glycine immunohistochemistry. To obtain CTb injection sites limited to the motor V, we first made electrophysiological recordings of the motoneurons through the glass micropipette containing the tracer, which was then iontophoretically injected. One week later, the animals were perfused with a 4% glutaraldehyde and 0,5% paraformaldehyde fixative solution. Coronal sections were then realized, pretreated in a natrium borohydride solution and incubated in a rabbit antiserum to glycine. After CTb injections limited to the motor V, a large number of large-sized double-labeled cells was observed bilaterally in the parvocellular nucleus alpha (PCRtα) lateral to the descending branch of the facial nerve. A substantial number of small-sized double-labeled cells was also localized in the more caudal parvocellular nucleus (PCRt). Only a few medium-sized double-labeled neurons were found in the Giα and GiV. These results suggest that the neurons at the origin of the glycinergic innervation of the motor V responsible for the trigeminal motoneurons inhibition during PS might be localized in the PCRtα and/or the PCRt rather than in the GiV or Giα. To test this hypothesis, we will use a double immunostaining technique to detect c-fos and glycine in rats after pharmacological treatment inducing long PS periods.

35.34 IMMUNOREACTIVITY AND AMINO ACID UPTAKE OF COMMISSURAL FIBERS IN THE BRAINSTEM OF FROGS

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The bilateral vestibular and auditory nuclei are connected by commissural fibers. In part this commissural connection is inhibitory in mammals and uses glycine (auditory) and glycine or GABA (vestibular) as putative neurotransmitters. Compared to cat, most of the vestibular neurons in frog receive an excitatory, glutamatergic commissural input. Therefore, frogs have either only few inhibitory commissural fibers or the potency of these fibers is relatively weak. We therefore investigated the commissural system of frogs with different methods.

Immunocytochemistry was performed on serial semithin sections (0.5-1μm) of the brainstem (N=7) treated with antibodies against glycine (Gly), glutamate (Glu) or GABA. Many Gly immunoreactive (Gly-IR) fibers were present in the internal as well as in the external arcuate tract of the commissure. Glu-IR fibers were frequent in the internal arcuate tract but less numerous in the external arcuate tract. Some fibers in the internal arcuate tract colocalized Glu and Gly. GABA-IR fibers were rarely seen in the commissural tracts. A similar staining pattern was observed for the cell bodies in the vestibulo-acoustic area.

Autoradiography was performed on frozen sections (20μm) of the brainstem (N=11) after injection of tritiated Gly or GABA into the vestibulo-acoustic area. Gly, but not GABA, was taken up by terminals of commissural fibers and transported retrogradely to the cell bodies in the contralateral vestibular and dorsal (auditory) nuclei. About 5x more neurons were labelled in the vestibular than in the auditory nuclei.

Electrophysiological results from intact and lesioned in-vitro brainstems suggest that vestibular commissural fibers project through the internal arcuate tract.

35.35 DIFFERENTIAL EFFECT OF DOPAMINE LESION WITH AND WITHOUT L-DOPA THERAPY ON STRIATAL OUTPUT PATHWAYS IN THE COMMON MARMOSET

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In rat striatum dopamine depletion results in an increase in the activity of the indirect output pathway of the striatum, containing enkephalin, and a decrease in the acitivity of the direct output pathway, containing substance P. In primates, this effect has not been established. L-DOPA therapy, as utilised in Parkinson patients, is thought to restore the balance between both pathways, but this effect has only been poorly investigated. In the present study the effects of dopamine depletion with and without subsequent L-DOPA therapy on levels of tyrosine hydroxylase (TH), met-enkephalin (ENK) and substance P (SP) in the marmoset striatum has been investigated. Marmosets were unilaterally injected with 3 x 0.5 μl 6-OHDA (16 mg/ml) in the ascending dopaminergic bundle. Half of the animals received L-DOPA therapy. 6 weeks after the lesions all animals were perfused with 4% paraformaldehyde and the brains were processed for semiquantitative immunohistochemistry. Differences in optical density of immunoreactivity (IR) between lesioned side and unlesioned side were taken as a measure for changes in neuropeptide levels.

Injection of 6-OHDA resulted in a severe decrease in TH-IR and an increase in ENK-IR, while no effect was seen on levels of SP. The increase in ENK was proportional to basal levels without subregional differences. The subsequent treatment with L-DOPA did not change the increased levels of ENK, but increased the levels of SP as compared to the non-lesioned control side as well as compared to the untreated group.

The present findings suggest, that dopamine depletion mainly affects the indirect output pathway containing enkephalin and that subsequent L-DOPA therapy mainly affects the direct pathway, containing substance P.

35.36 MORPHOLOGY OF CORTICOTHALAMIC TERMINALS ORIGINATING FROM THE HAND REPRESENTATIONS OF THE PRIMARY (M1) AND THE SUPPLEMENTARY (SMA) MOTOR CORTICAL AREAS IN MONKEYS.

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Two, morphologically distinct, types of corticothalamic terminals have been described in the motor, somatosensory and auditory systems of rodents and cats. It consisted of a main projection formed by small endings and a minor projection terminating with giant endings. The goal of the present study was to establish whether the same duality is present in the corticothalamic projection from primary and non-primary motor cortical areas in subhuman primates. The hand representations of M1 (n=2) or the SMA (n=3) were defined electrophysiologically in five macaque monkeys by intracortical microstimulation. The anterograde tracer Biotinylated Dextran Amine (BDA) was then injected in the hand representation in order to label the corticothalamic projection. The projection originating from M1 terminates mainly in the thalamic nucleus VPLo with small endings. In addition, restricted zones within the same terminal fields in VPLo showed the presence of giant endings mixed with the small ones. The main projection originating from the SMA terminates in the thalamic nucleus VLo with small endings, while giant endings were found in the thalamic nucleus MD, mixed with small endings. Along the rostrocaudal axis, the giant endings were distributed in a restricted zone of about 3 mm, going from AP 8 to 11 mm, both for projections coming from M1 and the SMA. We conclude that the dual morphology of corticothalamic endings, previously found in rodents and cats, is present in the motor system of subhuman primates for both primary and non-primary motor cortical areas. We suggest that the giant endings from M1, located in the main thalamic nucleus, serve a feedback projection, whereas the SMA giant endings in MD may well serve a feedforward projection towards areas in the prefrontal cortex.

35.37 OLIVARY PROJECTION TO THE CEREBELLAR NUCLEI IN THE RAT.

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The climbing fiber collateral projection to the cerebellar nuclei was studied in 75 male Wistar rats in which PHA-L or BDA was injected into the inferior olive. After 6-8 days, the rats were fixed, brains embedded in gelatin and cut at 40μm. Sections were incubated with standard immuno- or ABC histochemistry.

Projections from the medial accessory olive (MAO) were found to the medial cerebellar (MCN) and posterior interposed nucleus (PIN). Group A of MAO mainly connects to rostrolateral parts of the MCN, group B to its rostromedial part, group C to the dorsolateral protuberance. Central MAO regions project to the interstitial cell groups. Rostral MAO projects to the PIN proper; the rostralmost tip of the MAO projects laterally in the PIN. Group ß is connected to the caudomedial MCN and to ventral parts of the central and rostrolateral MCN.

The dorsal accessory olive (DAO) is connected with the anterior interposed nucleus (AIN) and the lateral vestibular nucleus (LVN). The dorsal fold of DAO specifically projects to the LVN. The caudolateral half of DAO proper projects to medial AIN, whereas its rostromedial part is connected to the lateral AIN.

The principal olive (PO) is connected to the lateral cerebellar nucleus (LCN). Its dorsal lamella projects dorsolaterally to the LCN, while the ventral lamella lines up with more ventromedial areas in the LCN. Moreover, an inverse rostrocaudal topography is noted. Injections of the ventrolateral outgrowth result in a dense patch of labeling in a specific area of the ventromedial LCN. The dorsomedial group of the ventral PO lamella projects to the dorsolateral hump. The dorsal cap was the only olivary area that did not show a nuclear projection.

It is concluded that the organization of the olivo-nuclear projection is basically reciprocal to the nucleo-olivary projection. These data strengthen the concept of the modular organization of the cerebellum.

35.38 METABOLIC ACTIVITY PATTERN IN THE MOTOR AND SOMATOSENSORY CORTEX OF MONKEYS PERFORMING A VISUALLY GUIDED ARM REACHING TASK

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The metabolic activity in the precentral primary motor (MI) and the postcentral primary somatosensory (SI) cortex, in monkeys (Macaca fascicularis) performing a visually guided arm reaching and key pressing task, was mapped by the 2-[^{14}C]deoxyglucose method. Three 20 μ thick adjacent horizontal brain sections every 140 μ, along the entire dorsoventral extent of the cortical areas lying between the posterior crown of the arcuate and the anterior crown of the intraparietal sulci, were used to reconstruct MI and SI in two dimensions on the sagittal plane. The data arrays resulting from image segmentation of the anteroposterior activity pattern in each horizontal section were aligned on the fundus of the central sulcus. The metabolic mapping of the control inactive monkey demonstrated homogeneous activity all around the central sulcus, bilaterally, whereas that of the unimanually performing monkeys displayed two different global spatiointensive patterns. The first pattern, contralateral to the moving forelimb, had a fish-bone shape. It was characterized by several discrete regions of increased activity, which were distributed in a mirror image fashion around the fundus of the central sulcus and extended beyond its anterior and posterior crowns. The activated regions corresponded to the lower body, forelimb, and mouth areas of previously reported precentral motor and poscentral somatosensory maps of body representation. The second activity pattern, ipsilateral to the moving forelimb, demonstrated precentral and postcentral activated regions corresponding only to the lower body and mouth areas. This is the first time that the quantitative activity pattern around the central sulcus has been reconstructed in monkeys performing a reaching task. (Supported by HCM Grant ERBCHRXCT 930266).

36. Poster Session: Other systems I

36.01 SUBSTANCE P RECEPTOR IS EXPRESSED BY A HETEROGENEOUS POPULATION OF INTERNEURONS IN THE HIPPOCAMPUS

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A specific antibody against Substance P receptor (SPR) has been reported to label GABAergic interneurons in the cerebral cortex of the rat (Kaneko et al.,'94; Nakaya et al.'94). In the present study we aimed to identify the types of SPR-immunoreactive neurons in the hippocampus according to their content of neurochemical markers, which are known to label interneuron populations with distinct input-output characteristics. In the dentate gyrus a dense meshwork of SPR-immunoreactive dendrites covered the hilus, whereas the CA3 region contained large numbers of spiny and aspiny interneurons scattered in all layers. Spiny neurons of the hilus and the CA3 region colocalized somatostatin, 25% of the aspiny neurons contained calretinin, and in the CA3 region another 25% cholecystokinin (25%). In CA1 most of the SPR-containing cell bodies were in the pyramidal layer and at the border of str. radiatum and lacunosum-moleculare. Of these 40% contained calretinin, and 35% colocalized CCK. In addition, a small number of SPR-positive neurons were immunoreactive for somatostatin, or showed NADPH diaphorase activity. Only 2-3% of the SPR-positive cells contained parvalbumin or calbindin. All SPR-containing cells were immuno-reactive for GABA, except those in the hilar region, where GABAergic cells with long projections are found. Based upon the known termination pattern of the colocalized markers, we conclude that SPR-positive interneurons participate in various inhibitory processes including feed-back dendritic inhibition in the entorhinal termination zone (somatostatin-containing cells), perisomatic inhibition (CCK-containing cells) and innervation of other interneurons (calretinin-containing cells).

36.02 STRUCTURAL ORGANIZATION OF AVIAN HIPPOCAMPUS. EM AND IMMUNOLOGICAL OBSERVATIONS.

Alpár, Alan and Teréz, Tömböl

Recently, in a comparative Golgi study, the structure of the hippocampus was described. It consists of three major layers: the suprapyramidal along the dorso-medial telencephalic surface; pyramidal in the middle of the area, and subpyramidal or paraventricular. On the basis of these data the EM structure of the three layers were studied. In the suprapyramidal layer, below the myelinated fibers, densely arranged synaptic area was found both with axo-spiny and axo-dendritic synapses. The axo-dendritic synapses were both symmetrical and asymmetrical. In the pyramidal layer a great number of perikarya and apical dendritic shafts were present. Most synapses were axo-spiny, but also axo-dendritic and axo-somatic ones were found. In the subpyramidal layer's neuropil axo-spiny synapses were more often observed than axo-dendritic ones. The large, highly dense dendritic multiangular neurons were located in this layer. In the EM GABA immunostained preparations GABA positive INs were found: perikarya, dendrites and the terminals of the GABA-ergic interneurons.

36.03 DIFFERENTIAL EFFECTS OF TTX INACTIVATION OF MEDIAL SEPTUM AND HIPPOCAMPUS ON RAT'S FOOTSHOCK-MOTIVATED BEHAVIOR. C. Ambrogi Lorenzini*, E. Baldi, C. Bucherelli and G. Tassoni. Dipartimento di Scienze Fisiologiche, Università degli Studi di Firenze, Firenze, Italia

Male Wistar rats (aged 60 days) were implanted with stainless steel guide-cannulae either 2 mm above the medial septum or the hippocampus. Tetrodotoxin was injected 50 min before the administration of an escapable electrical footshock in the light-dark box apparatus at the following dosages: 5 ng in 0.5 ul (medial septum), 10 ng in 1 ul (hippocampus bilaterally). Step-through latency was measured before the footshock and exit latency was measured after the footshock had been delivered in the dark chamber. Locomotion, explorative behavior and general reactivity were assessed. The results show that before the footshock in all groups (medial septum, hippocampus, controls) locomotion was good, as was explorative behavior (short step-through latencies from the light to the dark chamber, absence of freezing). During footshock administration, escape behavior was the same in the three groups of rats (no significant differences in exit latency), but there were significant differences in the response to environment and to the experimenter's manipulations. The medial septum group exhibited a very marked increase in aggressiveness, while there were almost no differences between hippocampus and control groups. Therefore it appears that the medial septum and the hippocampus, both components of the limbic system, play diverse roles in the extrinsecation of footshock-motivated behaviors.

36.04 THE MEDULLARY INTERFACE: A NEW DIRECT PATHWAY TO THE SUPERIOR CERVICAL GANGLION AND RELATIONSHIP WITH THE MIDLINE THALAMUS

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In order to investigate the eventual occurrence of monosynaptic input from the brain to sympathetic neurons, fluorescent tracers (fluorogold, FG, or fast blue, FB) were injected in the superior cervical ganglion (SCG) of rats. Retrogradely labeled cells were consistently detected in the ventral medullary tegmentum, in the lateral paragigantocellular and retroambigual regions. The relationships between the medullary neurons projecting to the SCG and *i)* the parasympathetic cells in the same areas, or *ii)* medullary-thalamic neurons, were investigated with multiple tracing. To this purpose combined injections of FG and FB, or FB and diamidino yellow, were made in the SCG and either the vagal nerve or the midline thalamus. In both these experimental sets differently labeled cell populations (whose chemical characterization is in progress) were intermingled in the medullary tegmentum; a minor proportion of double labeled neurons was also found. These results point out a previously undetected pathway from the lower brainstem to the SCG. In addition, the present data indicate that sympathetic, parasympathetic and thalamic-projecting neurons form a mosaic subserving central-autonomic interactions in the ventral medulla. The expression of immediate early genes in the brain following sympathetic perturbations is now being examined.

36.05 THE INFLUENCE OF CHOLECYSTOKININ (CCK8-S) AND ITS ANTAGONISTS ON POWER SPEKTRA OF HIPPOCAMPAL UNIT DISCHARGES IN THE THETA- AND DELTA- FREQUENCY RANGE.

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The elucidation of the function of cholecystokinin (CCK) and cholecystokinin receptors in the hippocampus was the aim auf various investigations. Mainly excitatory actions of CCK were found by examinations of single units and small groups of neurons. Inhibitory effects have been also reported, however. Furthermore, CCK seems not only to change the rate of discharges, but olso their rhythmicity. Zhang (Neuropeptides (1993)25:73-76) supposed that a low cerebral content or a poor release of CCK accounts for a high susceptibility to epileptiform seizures. The various effects of CCK were often blocked by the CCK-B antagonist and rarely reduced by the CCK-A antagonist.

Recently we have studied the rhythms of hippocampal unit discharges using autocorrelation functions. Unit activity was recorded extracellularly during control conditions and during iontophoretical administration of CCK in albino rats anesthetized with urethane. Now we used power spectra to characterize the rhythmic properties of hippocampal single cell discharges. The power spectrum is the result of the Fourier transformation of the autocorrelogramm and investigates the time series in the frequency range. In result of the transformation individual frequency components can be determined: frequency and amount of the power peaks.

Of 31 hippocampal neurons analysed 23 had a peak of the power spectrum in the delta range, and 18 neurons had a peak in the theta range. During administration of CCK8-S the theta-peak disappeared in 14 neurons, was unchanged in 4 neurons and appeared in 0 neurons, whereas the frequency of the delta peak did not change in 15 neurons; the amount of the peak increased in 6 neurons and decreased in 7 neurons. Additionally we analysed the power spectra for sequences of baseline activity during the effect of the CCK-B receptor antagonist PD 135 and the CCK-A receptor antagonist KL 1001, applied alone and in coadministration with CCK8-S (all substances: 0.25 mM, pH 7.8). Supported by the BMFT.

36.06 TWO STAGE LEARNING IN A COMPUTER MODEL OF THE HIPPOCAMPAL FORMATION.

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Supported by amnesia studies the hippocampus has early been considered as being relevant for memory trace formation and consolidation. Based on detailed experiments with rats G.Buzsáki[1,2] suggested a two stage model for the physiological mechanisms that may underlie these learning processes within the hippocampal formation: 1.) During theta-associated exploratory behavior, sparse representations of the environmental situation are transiently stored in subsets of CA3 pyramidal cells. This is done by weak heterosynaptic potentiation induced by fast firing granule cells in the dentate gyrus. 2.) During consummatory behavior, immobility and slow wave sleep, CA3 cells are subcortically disinhibited and discharge in strong arythmical bursts (sharp waves, SPW), which start at the most recently excited cells (burst initiators) and spread to less excitable cells via CA3 recurrent collaterals. These population bursts might be well suited to induce long lasting synaptic potentiation (LTP).

We present computer simulations based on the above ideas.[3] Our model consists of 4 areas of artificial spiking neurons which are modulated in activity by inhibitory interneurons. The areas correspond to the enthorhinal cortex (EC), dentate gyrus (DG), CA3 and CA1 regions of the hippocampal formation and are coupled in feedforward manner. The rich collateral connectivity of CA3 cells is taken into account in form of an associative feedback matrix in the modelled CA3 area. A Hebbian-type nonlinear correlation rule is chosen to mimic synaptic plasticity and LTP. Subcortical control signals (theta and inhibition) are applied globally to DG and the CA3-field.

The network reproduces many properties also found in experiments. During theta-controlled phases (stage 1) with random input patterns at EC, the DG area shows relative fast firing phase-locked to the theta-rhythm. Due to the feedback-interaction of DG cells with inhibitory interneurons we also find superimposed HF-oscillations which may be interpreted as gamma-range oscillations. The DG activation evokes only sparse firing in CA3 (spatial as well as temporal), which in turn leads to only moderate and stochastic firing of a few CA1 cells and restricted learning rates in CA3. On the other side, when theta and EC input are missing (stage 2), there is no activation in DG. Transient subcortical disinhibition easily induces strong population bursts in CA3, and these in turn high rates in their CA1 target cells. Due to a different mechanism as for the gamma oscillations CA1-activity again organizes into HF-oscillations ('ripple'). Learning is strongly enhanced during 'sharp waves', but the simulations show that assemblies in CA3 have the tendency to merge if there is only synaptic potentiation in the theta phase. Some type of transient 'cell-potentiation' can resolve this problem.

Lit. [1] Buzsáki et al. (1989). Neuroscience 31, 551-570. [2] Buzsáki et al. (1994). Temporal Coding in the Brain, pp145-172. [3] Bibbig et al. (in preparation).

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36.07 DISTRIBUTION AND MORPHOLOGY OF SEROTONERGIC AXONS IN THE HIPPOCAMPAL FORMATION OF THE NEW ZEALAND WHITE RABBIT.

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Serotonergic axons were demonstrated in frontal sections of the rabbit hippocampal formation by an indirect immunohistochemical technique, using a primary monoclonal rat antibody (MAB 352 Kingo Diagnostika) against serotonin, and a secondary biotinylated anti-rat Ig, visualised by the avidin-peroxidase technique.

The hippocampal formation was innervated by 3 morphologically different types of serotonergic axons. Hilus fasciae dentatae, stratum moleculare hippocampi and the outer half of stratum moleculare fasciae dentatae were amply supplied with thin axons which had large spherical varicosities, and thin axons with small fusiform or granular varicosities, whereas thick, non-varicose axons often were seen in the fimbria. These axons are probably stem-axons for one of the above-mentioned thin fibers. The distribution of the serotonergic axons was specific and most pronounced in area dentata, where hilus and the outer half of stratum moleculare were strongly innervated. Furthermore, stratum moleculare hippocampi received a considerable serotonergic innervation. This innervation pattern was present throughout the entire hippocampal formation, but there were great septo-temporal differences in the intensity of the serotonergic innervation. The ventral/temporal part of the hippocampal formation was thus heavily innervated by serotonergic fibers, whereas the dorsal/septal part only received a more moderate innervation.

These results strongly suggest, that the serotonergic system, through its specific innervation of the hippocampal formation in the termination zone of the perforant path and the hilus, is in a unique position to modulate the internal circuitry of the hippocampal formation, while the difference in innervation intensity suggests a dissimilarity in function between the ventral and dorsal part of the hippocampal formation.

This study was supported by grants from Aarhus University Research Foundation, and the Novo Nordisk Foundation, and Etatsraad C.G. Filtenborg og Hustru Marie Filtenborgs studielegat.

36.08 ANALYSIS OF PROTEIN SYNTHESIS INHIBITOR MODELATING OF LEARNING AT THE HIPPOCAMPAL NEURONS.

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Elementary form of learning manifests as a habituation or as a sensitization. In our study we recorded and analysed the development of habituation in neurons of the hippocampus under conditions of indifferent light stimuli, with special reference to the influence of protein synthesis (cycloheximid CH) to the development of habituation. The investigation was carried out on the rabbits.

The applications of light stimulations changed activity of 67% neurons. Repeated ofstimulations resulted in developing of habituation at 45% registered neurons. During the microiontophoretic applications of CH the activity to light stimuli changed at 58% neurons. The habituation waspresent at 26% neurons.

The obtained results showed that protein synthesis inhibitor CH impede the development of habituation. So that CH had an effect on learning.

36.09 TRIGEMINOCEREBELLAR PROJECTION TO THE PARAMEDIAN LOBULE WITH EMPHASIS TO THE CLIMBING FIBRE ZONES: A RETROGRADE TRACING STUDY IN THE RABBIT.

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Projection of the trigeminal sensory nuclei (TSN) onto the cerebellar paramedian lobule (PML) was investigated by the retrograde horseradish (HRP, WGA-HRP) and fluorescent (FB, DY) tracing method in the rabbit. Following injections of the tracers into the various regions of different sublobules of PML, the retrograde labelling pattern in TSN was analyzed, in relation to the climbing fibre zones identified by retrograde labelling in the inferior olive (Neurosci. Res., 7, 173, 1989). The results indicate that the projection is bilateral with a clear ipsilateral preponderance. The major projections originate from the dorsolateral and ventromedial regions of the principal trigeminal nucleus (Vp) and from the rostral two-thirds of the subnucleus interpolaris (Vi). Afferents from the subnucleus oralis (Vo) are moderate and arise mainly from its caudal one-third. Projections from both the mesencephalic trigeminal nucleus and the subnucleus caudalis to PML seem to be absent. Differences in distribution patterns of labelled neurones indicate a topical relationship between subdivisions of TSN and sublobules of PML. Hovewer, no clear-cut correspondence could be found between subdivision of TSN and climbing fibre zones in PML. Zone C_1 is supplied exclusively by fibres from Vi. Zone C_2, at least in sublobule *e*, and zones D_1 and D_2 receive afferents from all subdivision of TSN. No neurones of TSN appeared to project to zone C_3. The study provides new detailed data on the trigeminocerebellar system in the rabbit.

36.10 INDUCTION OF C-FOS AND BDNF mRNA IN THE RAT MEDIAL ENTORHINAL CORTEX BY MK-801.

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Phencyclidine and related drugs, such as MK-801 and ketamine are antagonists of the NMDA type glutamate receptors and protect neurons against brain insults, such as ischemia. However, they produce psychotomimetic side effects in humans, which has limited their clinical use. These same drugs have been reported to paradoxically produce neurotoxic effects and induce expression of c-fos and HSP70 in certain limbic structures, most notably in the posterior cingulate and retrosplenial cortices. We have previously reported that mRNA for brain-derived neurotrophic factor (BDNF) is strongly increased in these same brain areas after MK-801 administration.

We now report that MK-801 increases c-Fos and BDNF mRNA also in the entorhinal cortex. This increased expression is observed only in the dorsal part of the medial entorhinal cortex and is confined to layer III. A very prominent induction of c-Fos and BDNF mRNA is observed in the majority of neurons in this cell layer. The induction of c-Fos begins unusually slowly and is remarkably long-lasting: c-Fos is hardly detectable 1 h after injection, clearly increased at 3 h, peaks between 6 and 8 h and is still elevated 24 h after MK-801 administration. The induction of BDNF mRNA follows similar time course.

Neurons in the layer III of the medial entorhinal cortex project to the CA1 and CA3 area of the hippocampus and to the subiculum and are thought to be important in the normal information processing in and through the hippocampus. Disturbances in the function of these neurons might be expected to produce cognitive dysfunctions. The paradoxical effects produced by phencyclidine-like drugs in the medial entorhinal cortex might therefore be related to the psychotomimetic symptoms produced by these drugs.

36.11 ZINC-CONTAINING AFFERENT INNERVATION OF THE CENTRAL AMYGDALOID COMPLEX: A RETROGRADE TRACING STUDY IN THE RAT

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The aim of the present study was to identify the specific neurons giving origin to zinc-containing afferent projections to the central amygdaloid complex in the rat. This was done by use of a newer tracing method for selective labeling of zinc-containing neurons (Howell and Frederickson, Brain Res. 1990, 515: 277-286; Christensen et al., J. Histochem. Cytochem. 1992, 40: 575-579). The method involves local intracerebral injection of selenium ions (Se^{--}), which form zinc-selenide complexes that are transported retrogradely to the somata of the zinc-containing neurons and can be visualized using autometallography.

The infralimbic and dorsal peduncular cortices give origin to very light zinc-containing projections to the central nucleus whereas the agranular insular cortex and the perirhinal cortex contain a moderate number of heavily labeled neuron somata consistent with a projection to the central nucleus. All labeled neurons were situated within layers II-III. Within the piriform cortex only a few sparsely labeled zinc-containing neurons, situated within layers IIa-b, project to the central nucleus. Intrinsically, the central nucleus receives zinc-containing projections from the basolateral nucleus; rostralmost the labeling is only found within the lateral part whereas the nucleus at more caudal levels is filled with heavily labeled neuron somata. Within the corticomedial part of the amygdaloid complex the posterolateral cortical nucleus and the amygdalopiriform transition give origin to rather heavy zinc-containing projections to the central amygdaloid nucleus.

In conclusion, the present findings of zinc-containing intramygdaloid projections are in accordance with the findings of Christensen and Geneser (Anat. Embryol. 1995, 191: 227-237). The projection from the posterolateral nucleus is wellknown whereas the projections from the basolateral nucleus and the amygdalopiriform transition have not previously been described.

36.12 EFFECTS OF PRENATAL EXPOSURE TO ETHANOL ON HIPPOCAMPAL NEUROANATOMY AND LEARNING IN THREE INBRED MOUSE STRAINS.

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Children suffering from fetal alcohol syndrome show some symptoms indicative of possible hippocampal damage (A.P. Streissguth, H.M. Barr, P.D. Sampson, F.L. Bookstein and B.L. Darby, Neurotoxicol. Teratol. 11:461, 1989). However, these symptoms show large interindividual variations, perhaps indicating differential susceptibility to the effects of prenatal exposure to ethanol. Experiments with rats have shown a hypertrophy of the intra- and infrapyramidal mossy fibers (IIPMF) after *in utero* exposition to ethanol (J.R. West, C.A. Hodges, and A.C. Black jr., Science 211:957, 1981). Large, heritable variations in the sizes of the IIPMF exist between different inbred mouse strains. These non-pathological variations have been shown to be strongly correlated with processes related to learning and memory (W.E. Crusio, H. Schwegler, and I. Brust, Eur. J. Neurosci. 5:1413, 1993).

We gave 12% ethanol in a solution of 30g sucrose/l to pregnant females from the inbred mouse strains DBA/2, BALB/c, and C57BL/6. Surprisingly, their offspring showed neither neuroanatomical changes nor behavioral deficits in a spatial radial-maze task, although a strongly increased prenatal mortality was observed in C57BL/6. These results indicate a possible inter-species difference between mice and rats.

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36.13 CCK INNERVATION OF HIPPOCAMPAL REGIONS IN A REPTILE.

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We studied the distribution of CCK-like immunoreactivity in the cerebral cortex of the lacertid lizard *Psammodromus algirus*. Antisera against CCK-8S (INCSTAR) revealed numerous puncta-like structures (terminals) in the cortical regions of this lizard. Immunoreactivity was largely restricted to the cell layers of the medial, dorsomedial and dorsal cortices, in which the CCK fibers surrounded the cell bodies of principal neurons. In the medial cortex, CCK immunoreactive puncta were more numerous in the outer third of the cell layer. In the dorsomedial cortex, the most lateral portion of the cell layer displayed only a few immunoreactive puncta. Scarce varicose fibers were observed in the deep plexiform layer, especially in the dorsal cortex. The lateral cortex was almost lacking in CCK immunoreactivity.

Electron microscopy showed that the immunoreactive boutons made synaptic contacts on the cell body and proximal dendrites of neurons. These contacts were always of the symmetric type.

The distribution of CCK immunoreactive boutons and the type of synaptic contacts they made in the medial and dorsomedial cortices of *Psammodromus* was similar to the observed in the mammalian dentate gyrus and CA regions. However, in this lizard none immunoreactive soma was observed throughout the cerebral cortex. Therefore, CCK fibers innervating the lizard cortex probably arise from extracortical regions. On the basis of retrograde transport of HRP injected in cortical regions, we suggest that hypothalamic CCK immunoreactive neurons are the source of the cortical CCK innervation.

36.14 THE USE OF AN IN VITRO PREPARATION OF THE ISOLATED AMPHIBIAN CNS FOR TRACT-TRACING

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Many isolated preparations of the CNS have been developed and their success often depends on special features of the preparation that enables it to survive outside the body. A factor that enhances viability of isolated CNS preparations is a decrease in need for oxygen and metabolic substrates often found naturally in non-mammalian species including amphibians.

In the present study an isolated CNS preparation is being used prepared according to a method described by Cochran et al. (1987, Synapse 1: 102-123). Young adult clawed toads, *Xenopus laevis,* were deeply anesthetized with a 0.2% solution of MS 222 and perfused with iced Ringer. The brain and spinal cord were removed and tracers were applied under a dissection microscope. The isolated preparation was subsequently placed in a perfusion chamber, permanently superfused with freshly oxygenated Ringer solution, and processed for visualizing the tracers used, i.e. biotinylated dextran amine (BDA) and fluorescein and rhodamine-coupled dextran amines (FDA, RDA). Examples of experiments will be shown in which the cells of origin of motor pathways to the spinal cord, thalamic and striatal afferents were demonstrated. The data collected in the isolated CNS preparation are directly comparable to findings *in vivo*.

The use of an isolated CNS has many advantages. First, virtually all areas are easily accessible at the same time without the problem of having blood vessels that obstruct access. Second, large lesions and massive tracer applications are possible without survival problems of the animal. The isolated CNS is well-suited for a variety of neuroanatomical techniques. This study was supported by a NATO Collaborative Research Grant (930542) to H.J. ten Donkelaar.

36.15 CA1 RESPONSES TO STIMULATION OF THE RAT NUCLEUS REUNIENS.
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In the stratum lacunosum-moleculare (str. lac-mol.) of hippocampal field CA1, axons from the thalamic midline nucleus reuniens (RE) form asymmetrical synapses on spines (50%) and dendrites (50%). Hence, both pyramidal cells and interneurons presumably receive RE input. To explore this hypothesis, we performed a series of experiments *in vivo*. Stimulating electrodes were placed in RE and evoked field potentials and unit activity were recorded in CA1. Following low frequency (0.1 Hz) stimulation, the depth profile in CA1 consisted of an extracellular field potential that was negative-going in the str. lac-mol., reversed at the border with str. radiatum and was positive-going up to the white matter. Largest (neg. peak) amplitudes were noticed in str. lac-mol. close to the hippocampal fissure and (pos. peak) at the level of the pyramidal cells. Moreover, the occurrence of 2-3 successive peak amplitudes in the field potential appeared frequency (0,6-8 Hz) dependent. Neither changes in stimulus intensity (100-600 μA) nor in frequency (0.1-10 Hz) resulted in the occurrence of a population spike. The latency of the first positive peak (onset stim. artefact to peak amplitude) was shorter in case of rostral RE (15-24 msec) than in case of caudal RE (31-39 msec) stimulation. The absence of a population spike was in line with the lack of synaptically evoked unit activity at the pyramidal cell level. Occasionally, synaptically evoked action potentials (latency 21-23 msec) were noticed in deep stratum radiatum, indicative for the activation of interneurons. Paired-pulse stimuli (0.1 Hz, 100 msec interstimulus-interval, 100-600 μA) resulted in facilitation following moderate and high intensity stimulation, whereas no facilitation or a slight depression was observed following low intensity stimuli. These results indicate that RE stimulation elicits, at least, a subthreshold synaptic potential change of the pyramidal cells, as well as a suprathreshold activation of interneurons in deep stratum radiatum of CA1.

36.16 A FURTHER CHARACTERIZATION OF THE DOPAMINERGIC INNERVATION OF THE ASSUMED 'PREFRONTAL CORTEX' OF THE PIGEON
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Within the last decade a large number of biochemical, immunocytochemical, neuroanatomical and behavioral studies made it likely that the neostriatum caudolaterale (NCL) of the pigeon brain is equivalent to the mammalian prefrontal cortex (PFC). A prevalent function of PFC/ NCL seems to be working memory. A task which requires working memory is 'delayed alternation' and after NCL-lesions pigeons suffer from the same deficits in this task as mammals. It has been shown that dopamine is critically involved in PFC functions. Earlier findings have shown that the NCL receives a strong dopaminergic innervation from tegmental midbrain neurons. Apparently two discrete types of dopaminergic innervation can be distinguished: A 'basket-type' in which fibers densely coil around the perikarya of neurons and a more loosely 'en-passant'-type of innervation. With an antibody directed against DARPP-32, a D1-receptor-associated phosphoprotein, we additionally found a high concentration of dopamine D1-receptors in the NCL by which this area is clearly distinguishable from neighbouring areas. Furthermore there seems to be a slightly stronger prevalence of dopamine D2/D3-receptors in the NCL than in the adjacent telencephalon. Double-labeling experiments with antibodies directed against tyrosine hydroxylase and DARPP-32 or D2/D3, respectively, show that nearly all 'baskets' contain D1-positive neurons and most of them contain D2/D3-positive neurons. Moreover there are many 'baskets' containing GABAergic cells. We are currently working on a network model that serves to relate the working memory function of NCL and its neurobiological structure and suppose that dopamine plays an important role in determining the working mode of the network.

36.17 NUCLEUS PREPOSITUS HYPOGLOSSI PROJECTS TO THE DORSO-LATERAL PERIAQUEDUCTAL GRAY (PAG): A LINK BETWEEN VISUO-MOTOR AND LIMBIC SYSTEMS.
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The PAG forms part of the limbic system. Stimulation in the PAG elicits behavioral patterns used for defence in situations which represent a threat to the animals' survival (such as antinociception, postural and vocal signals and cardiopulmonary responses). Many neurons in the PAG project to the caudal brainstem and receive profuse afferent connections from various limbic structures. However, this is not true for the neurons in the dorsolateral wedge-shaped portion of the PAG (PAGdl). In order to clarify the role of this part of the PAG, it was injected with WGA-HRP in 4 cats to identify its connections. The injection-sites extended into the adjacent superior colliculus (SC). In all 4 cases, a specific group of labeled neurons was found in the contralateral prepositus hypoglossi nucleus (PPH) and ventrally adjacent reticular formation. To determine the exact dorsal midbrain target of these medullary neurons, ^{3}H-leucine was injected into the PPH and adjoining areas in 3 additional cats. In these cases, a pronounced termination of labeled fibers was observed in the contralateral PAGdl, while other parts of the contralateral PAG were devoid of label. Only sparse labeling was found in the intermediate layer of the contralateral SC.

It has been shown that the PAGdl receives afferents from the deeper layers of SC, substantia nigra and various parts of the prefrontal cortex. However, this specific PPH projection to the PAGdl has never been demonstrated. The PPH is known to be involved in control and adaptation of eye- and head-movements. The present results show that the PPH not only projects to visuomotor structures, but also to the PAG. This PPH-PAG connection may play a role in informing the limbic system about ongoing visuomotor activity.

36.18 MULTIDIMENSIONAL SCALING ANALYSIS OF ANATOMICAL CONNECTIONS: EVIDENCE FOR A PROCESSING STREAM CONNECTING THE AMYGDALA, ANTERIOR TEMPORAL AND ORBITOFRONTAL CORTEX.
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Non-metric multidimensional scaling analysis (NMDS) was performed to investigate the patterns of connectivity between individual amygdala nuclei and cortical areas in the primate brain. NMDS analysis was used to analyse the primate corto-cortical connections and to demonstrate objectively that two separate processing streams exist in the cortical visual system (*Young 1992 Nature 358:152-154*). NMDS analysis was performed on a matrix of amygdalo-cortical and corto-cortical connections created from the published literature. Despite the amygdala's connections with all modality specific and association cortical areas (excepting area 4), the NMDS analysis indicated the amygdala's connectivity is most strongly associated with the visual areas in temporal cortex. NMDS also revealed a stream of processing linking anterior temporal cortex, "basolateral" and "corticomedial" nucleic groups of the amygdala and the orbital frontal cortex. Neuropsychological and physiological studies have suggested that these areas are functionally associated in linking visual information to social behaviour, emotion and memory. NMDS treatment of anatomical data shows that connectivity patterns provides objective support for the notion of a functionally integrated socio-emotional system in the primate brain.

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36.19 STIMULATION OF THE MEDIODORSAL THALAMUS-PREFRONTAL CORTEX PATHWAY: IN VIVO TRANSMITTER RELEASE, FOS EXPRESSION AND BEHAVIOUR.
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The excitatory thalamocortical innervation of the prefrontal cortex (PFC) is provided predominantly by the mediodorsal (MDT) and midline paraventricular (PVT) nuclei. These pathways may be involved in cognition and arousal and pathological changes in this pathway have been reported in schizophrenia. Our aim was to develop an in vivo model in which various aspects of the activity of this system could be studied. A microdialysis cannula was implanted in the MDT of male rats. One or two days later the cannula was perfused with Ringer solution. After several hours this was changed for 20 min to Ringer with 0.03 or 0.1 mM bicuculline (GABA-A receptor antagonist), followed by Ringer again. Bicuculline effectively disinhibited thalamic neurons as shown (using in situ hybridization and immunocytochemistry) by a strong increase in the number of Fos-positive neurons. The PVT in particular was sensitive to bicuculline. In the PFC neurons were transsynaptically stimulated, as shown by a concentration-dependent increase in Fos expression.In vivo transmitter relase was measured using a second microdialysis cannula in the PFC. Glutamate and dopamine release were strongly increased (to 200-250%) but the glutamate increase was of a shorter duration. In these experiments the MDT/PVT were stimulated without touching or disturbing the animal, allowing the study of spontaneous behaviour. Rats spent most of their time sleeping, during the stimulation they typically awoke, displayed stationary behaviour and, with the higher bicuculline concentration, also showed increased locomotion and rearing. In conclusion, thalamic neurons were disinhibited and this resulted in increased glutamate and dopamine release, in increased Fos-expression and in arousal. Further studies on the relation between these parameters are in progress.

36.20 DOES AMYGDALA OF LIZARDS INCLUDE THE CAUDAL ADVR?
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The extent of the amygdala in squamate reptiles needs reassesing taking into account that the amygdala is not a pure chemosensory center. In this work the caudal ADVR (ADVRc) of the lizard *Podarcis hispanica* is shown to be a part of the amygdaloid complex in view of: 1) its projections to the hypothalamus and bed nucleus of the stria terminalis (BNST); and 2) its commissural connections via the anterior commissure. The non-olfactory sensory afferents of the ADVRc are then studied. Four main cytoarchitectonic areas are considered in this study: the dorsolateral (DLA) and central (CAN) amygdaloid nuclei (as defined by Martínez-García et al. '93; Brain Behav. Evol. 41:156-62) and the medial (ADVRcm) and central (ADVRcc) caudal ADVR.

Both, anterograde tracing from injections into these four nuclei and retrograde tracing from injections into the hypothalamus show a projection through the stria terminalis to the ventromedial hypothalamic nucleus (VMH) that arises mainly from the ADVRcm and CAN, but also from the ADVRcc. Injections into the ADVRc also show anterograde labeling in the ipsilateral BNST and bilaterally in the ventral anterior hypothalamic area. Moreover, tracer injections into the ADVRc, DLA and CAN reveal that these areas are connected with the opposite telencephalic hemisphere via the anterior commissure. Non-olfactory sensory afferents to these rostral amygdaloid centers arise from the rostral ADVR (ADVRr). Part of this projection shows a rough medio-lateral topography: lateral (visual) ADVRr projects mainly to DLA and ADVRcc, whereas medial and central ADVRr (auditory and somatosensory) mainly project to ADVRcm and ADVRcc. CAN shows a direct input from the ADVRr and an indirect one through the DLA and ADVRc. Thus, ADVRcc and CAN gather all kinds of non-olfactory sensory information. These data suggest that these four structures are comparable, as a whole, to a part of the lateral and basal amygdala of mammals. *Supported by the Spanish DGICyT (PB 91-0643) and IVEI.*

36.21 AgNOR AND CYTOCHROME OXIDASE ACTIVITY IN CA1 AND CA3 HIPPOCAMPAL AREAS DURING POSTNATAL DEVELOPMENT IN RAT.

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NOR are portions of DNA that coding ribosomic RNA and are asociated with different proteins, some argirofilic. These proteins, stained with silver are called AgNOR. Also AgNor are indicators of celular syntetic activity in nonproliferating cells. Cytochrome Oxidase (CO) is a mitochondrial enzime that can be used as endogenous marquer of functional activity in different brain regions.

AgNOR and CO activity was studied in the piramidal layer of CA1 and CA3 Hippocampal areas during postnatal development in rats (Wistar). 24 rats in three groups was used, 14 days old (14D), 21 days old (21D) and Adults (AD). In each animal, we measured nuclear and AgNOR surfaces in 200 cell,number of AgNORs per cell and CO activity. Results show differences between CA1 and CA3 areas in the nuclear and AgNor surface sizes and among ages. Also, CO activity shows differences between CA1 and CA3.

36.22 PONTINE AND MEDULLARY PROJECTIONS TO THE NUCLEUS RETROAMBIGUUS; A WGA-HRP AND AUTORADIOGRAPHIC STUDY IN THE CAT

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The nucleus retroambiguus (NRA) in the cat is a rostrocaudally organized column of interneurons in the ventrolateral part of the lateral tegmental field (LTF), projecting mainly via contralateral pathways. The NRA was found to play a role in expiration, vocalization and vomiting, and possibly, via its projections to the lumbosacral motoneurons, lordosis behavior (VanderHorst and Holstege, J. Comp. Neurol. 1995). This brings up the question which structures control the NRA. One of the most prominent is the periaqueductal gray (PAG). The PAG can be considered as the final integrator of basic functions, such as blood pressure, nociception control, micturition, vocalization, and lordosis behavior. The PAG-NRA pathway might play a crucial role for vocalization and lordosis behavior, especially because more rostral limbic structures do not project to the NRA.

This study deals with the NRA afferents from pontine and medullary sources. In order to determine which pontine and medullary tegmental field neurons project to the NRA, in five adult female cats injections of WGA-HRP were centered on the NRA. Anterograde autoradiographic tracing studies were performed in sixty seven cats (30 males and 37 females) using [^{3}H]-leucine. The combination of these techniques reveals the structures that specifically project to the NRA. The results point to 3 areas which send afferents to the NRA, the parabrachial and Kölliker-Fuse nuclei, the medial part of the medullary lateral tegmental field including the so-called retrotrapezoid nucleus and the Bötzinger complex, and the solitary nucleus. In addition a distinct group of neurons was found in the ventromedial tegmentum at the level of the facial nucleus. The results indicate that, as could be expected, respiratory related cell groups have strong access to the NRA. The cell group in the medial tegmental field might be involved in functions processed by limbic structures rostral to the PAG such as chewing, licking, swallowing, and other with eating and drinking related behaviors.

36.23 OUTPUT FROM DIFFERENT HIPPOCAMPAL FIELDS TO THE SUBICULUM.

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The activation of the different hippocampal fields by perforant path volleys to the hippocampal formation and the following activation of the subiculum were studied by field potential analysis in adult anaesthetized guinea pigs. Impulse volleys in perforant path fibers were obtained by synaptic activation of their neurons of origin.

The earliest response to the perforant path volley was generated in the dentate gyrus, with maximum amplitude in the upper (facing CA1) blade. The dentate gyrus activation was followed by activation of all the hippocampal fields. A population spike-like response was recorded from field CA2. A population e.p.s.p. with a superimposed population spike was recorded from field CA3a, b, with maximum amplitude in CA3a, and from field CA1a,b,c, with maximum amplitude in CA1a. The field CA2 population spike had shorter latency and lower threshold than the potentials evoked in fields CA3 and CA1. The population e.p.s.p.s evoked in fields CA3 and CA1 had similar threshold, the population spike, however, had lower threshold in CA3 than CA1. The hippocampal discharge was followed by activation of the whole rostro-caudal extent of the subiculum. The threshold of the response evoked in the caudal and middle subiculum was higher than that of field CA2 and field CA3, but lower than that of field CA1, population spike. The threshold of the response evoked in the rostral subiculum was similar to that of field CA1 population spike.

The results suggest 1) an "in parallel", instead of sequential, activation of different hippocampal fields by the perforant path input, 2) parallel hippocampal outputs to the subiculum, 3) a major role of fields CA2 and CA3 in the subiculum activation.

36.24 DISTRIBUTION OF NADPH-DIAPHORASE IN THE CENTRAL NERVOUS SYSTEM OF THE FROG.

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The distribution of NADPH-diaphorase was investigated in the CNS of *Rana perezi* by means of a direct histochemical technique.

In the telencephalon, labeled cells are present in the olfactory bulb, pallial regions, septal area, nucleus of the diagonal band, striatum and amygdala. Positive neurons are around the preoptic and infundibular recesses. In the magnocellular and suprachiasmatic hypothalamic nuclei and in the thalamus. Positive fibers and cell groups are present in the pretectal area. The optic tectum have many cells in layer 6, and the torus semicircularis also contains labeled cells and fibers. The nuclei of the mesencephalic tegmentum have abundant labeled cells and a conspicuous cell population is localized medial and caudal to the isthmic nucleus. Scattered neurons are present in the molecular and granular layers of the cerebellum. Numerous cells in the rhombencephalon are distributed in the octaval area, raphe nucleus, reticular nuclei, sensory trigeminal nuclei, nucleus of the solitary tract and, at the obex levels, the dorsal column nucleus. In the spinal cord, abundant labeled neurons are present in all fields of the gray throughout its rostrocaudal extent.

The distribution pattern of NADPH-diaphorase activity in the brain of the frog is very selective and demarks cell groups, fiber tracts and terminal fields and does not correspond with the pattern seen for any other neurotransmitter or neuroactive molecule. In particular, extensive co-distribution ofNADPH-diaphorase and catecholamines is found in the anuran brain. However, double labeling techniques have shown in this study that only restricted co-localization is present in the posterior tubercle and locus coeruleus. This study provides evidence that nitric oxide may be involved in novel tasks, primarily related to forebrain functions, that are already initiated in amphibians.

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36.25 SYNCHRONIZED ACTIVITY IN A CA3 MODEL

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A kinetic population model of longitudinal slices of the hippocampal CA3 region is presented. The model is based on the hypothesis that the behavior of large neuron populations can be adequately described on the statistical level. In this framework (F. Ventriglia, *Bull. Math. Biol* 50 (p 143), 1988), the activity (different levels of subthreshold membrane potential/refractory state) distribution of groups of otherwise not distinguished neurons is considered, and the subpopulations of neurons communicate via packets of action potentials which they can emit and absorb.

Three basic neuron types are taken into account: (i) excitatory pyramidal cells, (ii) inhibitory cells initiating fast ($GABA_A$ mediated) and (iii) slow ($GABA_B$ mediated) IPSP's. The membrane potential distribution of a given neuron population changes according to the corresponding postsynaptic potential. The spatial organization of the interactions follows the anatomical data. The details (parameters) of the model are taken from available rat data.

The model simulates the fundamental electrophysiological behavior patterns of the CA3 region. CA3 pyramidal cells discharge in highly synchronous bursts of action potentials in the absence of inhibition (R.D. Traub and R. Miles: *Neuronal Networks of the Hippocampus*, Cambridge University Press, 1991). The formation of such synchronous bursting activity over a large population of pyramidal cells due to recurrent excitatory synapses and the spreading of synchronized bursts through the entire region are investigated. Gradually increasing inhibition, synchronized population bursts can be prevented.

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36.26 INTRINSIC CONNECTIONS IN THE REPTILIAN DORSAL VENTRICULAR RIDGE

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We studied the connections between different regions of the reptilian anterior dorsal ventricular ridge (ADVR) in a species of lacertid lizard (*Psammodromus algirus*) following two tracing techniques: HRP injections in this structure and crystals of DiI applied directly on fixed brains.

Retrograde HRP labelling demonstrated that at least the caudal part of the ADVR receives a strong projection from rostral neurons widely distributed in the ADVR. Neurons were retrogradely labelled within all medial-to-lateral regions of the ridge. Rostral most labelled neurons were restricted to the dorsal part of the ADVR.

DiI experiments suggested that these connections were largely made through the periventricular zone since DiI crystrals applied on this zone resulted in a labelling of neurons following a similar pattern to HRP injections, whereas DiI crystals applied on deeper zones of the ridge stained neurons the cell bodies of which were restricted to a narrow radial region.

This is the first description of an intrinsic connectivity among different regions of the reptilian ADVR, and it is particularly interesting because the medial-to-lateral regions of the ridge are the targets of different and segregated sensory modalities. This intrinsic connectivity offers the anatomical substrate for a putative sensory integration.

36.27 **CHARACTERIZATION OF VIP-IMMUNREACTIVE INTERNEURONS IN THE DENTATE GYRUS**

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Vasoactive intestinal polypeptide (VIP) was shown earlier to be present in a morphologically heterogeneous subpopulation of GABAergic interneurons in the dentate gyrus, but their input and output characteristics have not been established. Using a new, specific antiserum, VIP-immunoreactive (VIP-IR) cells and axons were visualized in a Golgi-like manner. Three types of VIP-IR cells have been identified on the basis of axonal and dendritic arbor, postsynaptic targets, and colocalization with different neurochemical markers (calcium-binding proteins and cholecystokinin): 1) The axon of the first type projected to the hilus, where it formed a dense plexus of axon terminals restricted to the hilus. The postsynaptic targets of these VIP-positive cells were neurons visualised by immunostaining for substance P receptor (SPR), which is known to label different hilar interneurons. In all cells of this type VIP and calretinin (CR) were shown to coexist, while they proved to be negative for cholecystokinin (CCK). 2) VIP-IR basket cells, innervating predominantly the somata and proximal dendrites of granule cells, were found in str. granulosum and str. moleculare. In this cell type VIP colocalized with CCK, but not with CR. 3) In str. moleculare horizontal VIP-IR cells were found with dendrites and axons restricted to this layer. They established multiple contacts with non-principal cells containing VIP or substance P receptor. In 75% of these cells VIP coexisted with CR, but not with CCK.

On the basis of these observations we conclude that three different types of VIP-IR neurons are present in the dentate gyrus, and are likely to subserve different inhibitory functions, i.e.: 1) synchronization of the activity of hilar neurons or disinhibition of granule cells by specific interneuron-to-interneuron connections, 2) perisomatic inhibition of granule cells, 3) synchronization of interneurons in the str. moleculare.

36.28 SUPRACAPSULAR PORTIONS OF THE RAT EXTENDED AMYGDALA.

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The extended amygdala is characterized by neuronal masses in the centromedial amygdala that are qualitatively symmetrical with cell groupings within the rostromedial forebrain, particularly within the bed nucleus of the stria terminalis. The columns of neurons that interconnect the amygdaloid body with the rostromedial forebrain are an important part of this complex. While in the rat these columns are more numerous ventral to the internal capsule, a significant column of neurons accompany the stria terminalis in its course dorsal to the internal capsule (i.e. the supracapsular bed nucleus of the stria terminalis, BSTS). The existence of the supracapsular cells have occasionally been acknowledged, but their specific anatomy has not been analyzed. We have examined the supracapsular component of the extended amygdala using retrograde tracer injections in specific targets of the extended amygdala. Cells along the lateral corridor of the stria terminalis are invariably labeled from targets that are also innervated by the central amygdaloid nucleus or lateral bed nucleus of the stria terminalis. With large and sometimes multiple retrograde tracers in lateral hypothlamus and brainstem, it is clear that the lateral BSTS forms a nearly continuous column except for along the vertical posterior segment of the stria terminalis. In contrast, only sporadic neurons projecting to targets favored by the medial division of the extended amygdala are seen embedded in more medial portions of the stria terminalis. Ultrastructurally, the neurons in the lateral BSTS are found within a dense neuropil including numerous terminals synapsing on these cells. At least some of these cells appear to be similar to the densely spiny neurons occuring in the lateral part of the central nucleus or lateral BST. While the BSTS represents a minor component of the rat extended amygdala, previous reports indicate that this is more prominent in other species, especially the primate. Supported by USPHS grant NS17743 (LH and GFA) and Consejo Nacional de Investigationes Cientificas Y Technicas, Argentina (CAB and JSO).

37.01 Abstract not received

38.01 THE MODE OF OPERATION OF A VERTEBRATE NEURONAL NETWORK - THE ACTION OF FAST AND 'SLOW' TRANSMITTERS

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Under in vitro conditions the lamprey brainstem spinal cord can be made to produce the motor pattern underlying locomotion. The basic pattern is produced by a network comprised of excitatory glutamatergic and inhibitory glycinergic neurons. The connectivity as well as cellular mechanisms in network neurons play an important role. Co-released dopamine and 5-HT from the same neurons modulate both calcium dependent potassium channels and calcium channels and also affect the presynaptic release of glutamate in certain spinal synapses. The GABA-system ($GABA_B$) modulates neuronal function in a similar fashion on both the pre-and postsynaptic sides, as well as neurotensin and somatostatin. A critical factor in the function of a pattern generating network is the instant of burst termination and also burst onset. A number of complementary cellular mechanisms aid in determining the burst termination, one of which is calcium dependent potassium channels. They act by influencing the point of cessation of plateau potentials during which calcium enters the cell (eg. NMDA) and also spike frequency adaptation via the slow afterhyperpolarisation. The cellular effects of the different modulatory systems will be described as well as the functional consequences on the network level, also utilizing modelling as a tool in the analyses. The different modulatory system can in very specific ways modify the network properties and the coordination.

39. Symposium: H. van der Loos Memorial

WEDNESDAY

39.01 DEVELOPMENT OF THALAMO-CORTICAL PROJECTIONS

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Due to the major contribution of Hendrik Van der Loos the rodent barrel field is one of the best studied model systems for mammalian cortical plasticity. He and his colleagues demonstrated and emphasized the role of the sensory periphery in mammalian cortical development and evolution (Woolsey & Van der Loos (1973) *Science* **179**:395-398; Welker & Van der Loos (1986) *Exp Brain Res* **63**:650-654). These observations inspired many to study interaction between the developing cerebral cortex and thalamus so as to understand the mechanisms by which the sensory periphery influences areal specialization and cytoarchitectonic differentiation of the cortex. I shall review various approaches that reveal some of the mechanisms by which selective thalamic innervation and topographic organisation of the rodent neocortex are achieved during development.

Carbocyanine dye tracing in fixed embryonic rat brains demonstrated that the initial extension of axons from the cortical preplate and the thalamus starts at about E14, and the topography of both may be influenced by their temporal sequences of outgrowth (*chronotopy*). The axon arrays meet and start to fasciculate in the basal telencephalon, beyond which the preplate scaffold may guide the deployment of the thalamic afferents. In co-culture, the cortex appears to exert a remote *growth promoting* influence on thalamic axons from E15; becomes *growth-permissive* to axon invasion at about E20 and expresses a *stop signal*, causing termination in layer 4, from P2-3. This cascade of cortical signals may determine the timing of events *in vivo*. However, any part of the thalamus will innervate any region of developing cortex in culture, without obvious preference, suggesting that the topographic distribution of thalamic fibres *in vivo* does not depend on regional chemospecificity. The puzzling pattern of innervation in the Reeler mutant mouse can be explained with exactly the same algorithm of interaction but in relation to the displaced population of preplate cells.

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39.02 GENETIC ASPECTS OF BARRELFIELD DEVELOPMENT.

Egbert Welker, Institute of Anatomy, University of Lausanne, 1005 Lausanne, Switzerland.

Tonnulae vivant (I presume this is = [ood enough Latin for 'let barrels live')

yrs, H.

"Tonnulae vivant (I presume this is = good enough latin for 'let barrels live')"
Hendrik Van der Loos, 24 August 1993.

In the context of this phrase, and in honour of my friend, I like to present the results obtained from the studies on two series of mice strains that were raised in our mouse colony: those bred for different patterns of mystacial vibrissae and those that lack barrel formation (a strain named *barrelless*).

39.03 CORTICAL ORGANIZATION AND SPECIES DIFFERENCES

Leah Krubitzer, VTHRC, Department of Physiology and Pharmacology, University of Queensland, Australia, and Centre for Neuroscience and Department of Psychology, University of California, Davis, USA.

Throughout this century, remarkable advances in techniques for studying the brain have revealed that the neocortex is composed of a number of functional parts that uniquely interconnect to form processing networks. A number of features of these networks are highly conserved across mammals, so that mammals with very complexly organized brains have areas and nuclei in common with mammals with less complexly organized brains. Examination of a variety of species using a combination of electrophysiological, anatomical and histological criteria for establishing functional subdivisions, allows us to infer which features of the neocortex were established early in mammalian evolution, and to recognize modifications or differences in the neocortex that evolved in different lineages. Comparative analysis in species representing the three major groups of mammalian evolution, eutherians, metatherians, and prototherians, has revealed a common plan of cortical organization that includes several visual, somatosensory and auditory fields as well as areas where information from different sensory modalities converges. Such analysis has also revealed differences in cortical organization that are species specific, and often related to distinct morphological and behaviour specializations of a particular lineage. Our work suggests that the retained plan of organization may act as a constraint on cortical field evolution. Furthermore, differences in cortical organization observed in extant species, often take the same form. This indicates that similar, homologous mechanisms in neural development may mediate the generation of cortical field modifications, and cortical field addition.

39.04 SCULPTING OF AUDITORY CORTEX BY EARLY VISUAL INPUTS.

S.L. Pallas* Baylor College of Medicine, Houston, TX, USA

The many elegant experiments of Hendrik Van der Loos and his colleagues have shown that primary sensory cortex can be profoundly influenced by increases or decreases in sensory stimulation during development. Drawing upon Dr. Van der Loos' experiments for inspiration, we have begun to address how cortical structure and function can be shaped by the *modality* of sensory stimulation.

The retina can be induced to terminate in the auditory thalamus (MGN) by a specific set of lesions on the day of birth in ferrets. This "cross-modal rewiring" procedure results in a primary auditory cortex (AI) which receives visual inputs. My colleagues and I have demonstrated that AI in these animals is able to process its visual inputs in much the same way as primary visual cortex. However, AI's gross connectivity pattern remains the same. Have the visual inputs caused changes in AI's circuitrywhich might explain its visual processing capabilities?

We have recently observed a reorganization of callosal connectivity in AI. Normally, callosal projections in AI are restricted to a specific subpopulation of binaural cells (EE cells) and form a striped pattern coincident with the binaural bands. In the presence of visual input, the bands break up into patches and the number of callosally-projecting cells declines substantially. These results provide the first evidence that changes in sensory modality can actively alter cortical circuitry, and they further suggest that the pattern of local connectivity responsible for functional properties in AI will be altered in the rewired animals.

Additional evidence that the visual inputs cause specific changes in AI's circuitry come from our studies of chemoarchitecture. A specific subpopulation of GABAergic cells, identified by their calbindin content, are markedly increased in number and extent as a result of the early visual input. This change may be responsible for sculpting a two-dimensional visual map and visual receptive field properties from AI.

40.01 EVOKED POTENTIAL SOURCE RECONSTRUCTION RELATIVE TO ANATOMY

H. Buchner, Dep. Neurology, Pauwelsstr. 30, D-52057 Aachen

While evoked potentials have been remarkably successful in experimental and clinical work, the majority of studies used single-channel "peak-picking", i.e., measuring latency and amplitude. A significant advantage comes from source reconstruction, promising information about the location, orientation and magnitude of neuronal sources.

Recently developed techniques allow to determine such sources relative to the individual anatomy of the brain. This techniques makes use of advanced methods of 3D-MR reconstruction and numerical models of the head, i.e., boundary- or finite-element-methods.

This techniques remarkably improve the interpretation of the normal and pathological functioning of the brain by depicting location and magnitude of current generators within the individual brain with high resolution in time and space.

The talk will summarize the actual techniques and give examples in the experimental and clinical field.

40.02 COGNITIVE SUBTRACTION: FACT OR FANTASY?

KJ Friston, PJ Fletcher, T Shallice and CD Frith Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK.

The short history of functional brain mapping has been, almost exclusively, predicated on functional segregation and cognitive subtraction. Cognitive subtraction assumes that distinct and separable processes can be added to a task. The 'extra' brain activations that ensue are then attributed to that component process. Underlying this approach is the conjecture that component processes can be purely inserted or added with no effect on the implementation of extant processing. While simple and powerful this conjecture has never been tested empirically.

We present an analysis of the validity of 'additive factors logic' using Positron Emission Tomography (PET) activation studies. Using a factorial design. we framed our question in terms of the interaction term: Namely if pure insertion is a proper model, for the brain's implementation of cognitive processes, then the interaction term should be negligible. In other words the presence of component process A has no effect on the physiological activation evoked by process B. We tested this null hypothesis using a multivariate, pixel-based analysis of a PET memory study that used primary and secondary tasks.

40.03 MEG IN THE STUDY OF CORTICAL DYNAMICS.

R. Salmelin*, Low Temperature Laboratory, Helsinki University of Technology, 02150 Espoo, Finland

Electric current is a signature of information processing in the brain. Magneto-encephalography (MEG) detects the magnetic signals arising from these currents in the working brain. Contrary to electric scalp potentials, magnetic field is not blurred by the conductivity barriers at the skull and the scalp. Furthermore, MEG is selectively sensitive to activity in fissural cortex. The 3-D locations of the activated cortical sites and the directions of current flow can be deduced from the magnetic field distribution by modelling the head as a spherically symmetric conductor and the sources as current dipoles, which is a reasonable assumption for local activation of a few square cm of cortex. Thus, MEG allows accurate tracking of cortical events both in time and in space fully non-invasively in healthy and diseased brains.

The continuous neuronal activity shows as fluctuating low-amplitude signals all over the cortex. In the rolandic and parieto-occipital areas, these fluctuations form high-amplitude rhythmic oscillations centered at about 10 and 20 Hz. Both evoked responses, time-locked to stimulus onset, and event-related modulation of cortical rhythms are indices of cortical processing. Whole-head MEG has made it possible to map spatiotemporal distribution of cortical activation in a large variety of tasks involving multiple brain areas, e.g., in somatosensation, during voluntary movements, and in cognitive tasks.

Selected examples of cortical activation sequences related to various types of voluntary movements and tasks extending from language comprehension and production to vocalization will be discussed.

40.04 APPLICATIONS AND LIMITATIONS OF FUNCTIONAL MRI

R. Turner, Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, WC1N 3BQ, England

Blood oxygenation level dependent (BOLD) contrast imaging of human brain function using Echo-Planar MRI (EPI) gives good freedom from motion artifact, high SNR/unit time, and adequate spatial resolution. Studies were made of brain activation associated with perceptual and cognitive tasks.

Many cortical areas show a signal change related to task-dependent activity, in images with a spatial resolution of 2.5 mm x 2.5 mm x 5 mm, obtained in less than 100 ms per image. At the magnetic field of 4T fractional changes of MR image intensity up to 25% were observed.

Changes of oxygenation in large draining veins distant from the active neural tissue do not appear to dominate the changes observed, especially when brain tasks activating only a limited volume of grey matter are chosen. This agrees with considerations of dilution, and direct optical observations of functional brain activity in animals via a cranial window. A theoretical limit of about 2 mm resolution is suggested, corresponding to the spatial precision with which CBF is normally controlled.

A study of signal changes in motor cortex M1 during the learning of a complex finger-tapping task showed an increase in activated area, compared with an untrained task, over a period of 3-5 weeks of training, well correlated with the learning curve for this task. This suggests that the trained task comes to be represented by a more extensive neural network in M1 than the untrained task, an instance of medium-term neural plasticity.

Long term plasticity was studied using language tasks in a population of young healthy congenitally deaf subjects, compared with normally hearing subjects. Subjects read English sentences, controlled with nonsense strings of consonants, and viewed American Sign Language sentences presented using a video of a competent signer, controlled with nonsense signs. Significant differences and some striking similarities were found between the two groups, which have profoundly different language experiences.

The two studies demonstrate the remarkable capability of fMRI to map human brain function in detail non-invasively.

41. Symposium: Neurocognitive drugs: the art of affecting the mind

41.01 POPULATION DIVERSITY PREDICTS ADVERSE REACTIONS TO ALZHEIMER'S DISEASE DRUGS.

Y. Loewenstein-Lichtenstein[1], M. Schwarz[1], D. Glick[1], B. Norgaard-Pedersen[2], H. Zakut[3] and H. Soreq[*1]. [1]Dept of Biol Chem, Hebrew Univ, Jerusalem, 91904 Israel. [2]Statens Serum Inst, 2300 Copenhagen, Denmark. [3]Dept of Obst and Gyn, Sackler Faculty of Med, Tel Aviv Univ. Israel.

Serum butyrylcholinesterase (BuChE) from a patient homozygous for the "atypical" BuChE allele and heterozygote individuals or those homozygous for normal BuChE were subjected to inhibition by several anti-cholinesterases, in comparison with recombinant normal or "atypical" human BuChE or acetylcholinesterase (AChE), produced in microinjected *Xenopus* oocytes. The recently approved Alzheimer's disease quaternary amine drug, tetrahydroaminoacridine (THA, tacrine, Cognex) and the currently tested carbamates N-heptyl physostigmine and SDZ ENA-713 reacted faster and/or more efficiently with both native and recombinant normal BuChE than with AChE. Moreover, both native and recombinant "atypical" BuChEs were less sensitive than normal BuChE (by 100-, 30-, 15- and 10-fold) for tacrine, SDZ ENA-713, N-heptylphysostigmine and pyridostigmine, respectively, whether tested alone or in 1:1 mixtures with normal BuChE. These findings imply that AChE would be a relatively vulnerable target for anticholinesterases in carriers of "atypical" BuChE (up to 10% of some populations): Moreover, they may explain some of the symptoms reported recently in tacrine-treated Alzheimer patients, and suggest DNA and serum tests to identify individuals at risk for such responses.

41.02 Abstract not received

41.03 Abstract not received

41.04 ENDOGENOUS CANNABINOID LIGANDS

R. Mechoulam, S. Ben Shabat, L. Hanus and E. Fride. Hebrew University, Medical Faculty, Jerusalem 91120, Israel.
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Arachidonic acid ethanolamide (anandamide) was recently identified by us as a brain constituent that binds to the brain cannabinoid receptor (CB_1). We have shown that anandamide produces many of the pharmacological effects caused by tetrahydrocannabinol (THC) in mice and parallels THC on inhibition of adenylate cyclase. These observations indicate that anandamide is an endogenous ligand-agonist that may serve as a genuine mediator for the cannabinoid receptor. We have recently identified in brain two additional fatty acid ethanolamides that bind to the cannabinoid receptor. The biological role of the anandamides has yet to be established.

A second cannabinoid receptor (CB_2) is present in the spleen. We have now identified in the gut a monoglyceride, 2-arachidonyl-glycerol which was shown to bind to both CB_1 and CB_2 in transfected cells and to inhibit adenylate cyclase in spleen cells.

42. Symposium: Space cognition: visual and motor coordinates

42.01 COORDINATE SYSTEMS FOR REACHING IN THE CEREBRAL CORTEX

F. Lacquaniti, E. Guigon, L. Bianchi, S. Ferraina and R. Caminiti*. Institutes of Physiology, University of Cagliari and University of Rome "La Sapienza", Italy

Reaching is subserved by a cortical distributed system including primarily posterior parietal, dorsal premotor, and primary motor cortices. A vector model of movement direction indicates that reaching is represented in the activity of broadly-tuned directional neurons, as result of a population coding mechanism. However, when parallel movements starting from different initial positions are made, neural activity in the frontal cortical fields changes dramatically. This change predicts the change in orientation of the arm necessary to perform such movements. This suggests that reaching is encoded within a body-centered coordinate system and that the information concerning movement origin and therefore arm posture must be incorporated in any model of arm reaching.

Psychophysical studies as well have suggested that reaching is specified in a body-centered reference frame. One should therefore be able to describe the activity of neuronal populations just by one set of tuning parameters which are independent of the origin of movement. Indeed, we found that the activity of neurons in the superior parietal lobule (dorsal area 5) is monotonically tuned in a body-centered frame whose coordinate define the azimuth, elevation, and distance of the hand in space. Each spatial parameter tends to be encoded in a different subpopulation of parietal neurons, thus offering a neural correlate to the psychophysical observation that these parameters are processed in a parallel way in man.

It remains to be determined how this parietal representation relates to those of frontal cortex and which are the intervening coordinate transformations.

42.02 Abstract not received

42.03 CENTRAL VESTIBULAR PROJECTIONS IN HUMANS AND SPATIAL HEMINEGLECT

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A number of studies have recently shown that vestibular stimulation may temporarily improve spatial hemineglect. The neural basis of these effects has been recently explored in normal human subjects by PET (1).The areas activated by caloric stimulation included the contralateral temporo-parietal cortex, the insula, the putamen, and the anterior cingulate cortex. The behavioral correlate of the stimulation was a contralateral directional error in a pointing task. These findings, which confirm and extend animal data, indicate that the central vestibular projections comprise an extensive neural network, which includes brain regions substantially involved in the representation of extra-personal space (inferior-posterior parietal cortex). The asymmetric activity of such bilateral structures, produced by a unilateral damage, is a neural correlate of hemineglect.

(1) Bottini G, et al.(1994) *Exp Brain Res* **99**: 164-169.

42.04 ENCODING OF SPACE IN EGOCENTRIC COORDINATES. EVIDENCE FROM PATIENTS WITH NEGLECT.

H.-O. Karnath. Department of Neurology, University of Tübingen, Hoppe-Seyler-Str. 3, D-72076 Tübingen, FRG

Eye movements of neglect patients with right parietal lesions were recorded during ocular searching for a (non-existent) target in complete darkness. It was assumed that the part of outer space subjects spontaneously explore with eye movements while no stimulus influences the attention is a direct function of the subject's spatial frame of reference. Fixations were confined almost entirely to the right of the sagittal midplane and biased rightwards within that area. In contrast, control groups without neglect searched equally on both sides with eye movements symmetrically distributed around the sagittal midplane. The whole body of the subjects was then turned 30° to the left and to the right around the earth-vertical body axis. From an egocentric perspective exploration of space by eye movements remained unchanged; under each condition a bias of exploration toward the ipsilesional side was found in the neglect patients. Accordingly, from an allocentric perspective the spatial area explored by eye movements changed along with the subject's body orientation, i.e. it shifted together with the body 30° to the left and 30° to the right, respectively. The spatial distribution of exploratory eye movements changed, however, remarkably with left-sided neck muscle vibration as well as with left-sided vestibular stimulation using ice water calorics. During stimulation the spatial area of exploration was significantly enlarged to the contralesional side and the exploration maximum shifted in the same direction. The results indicate that in darkness the patients' bias of space exploration by eye movements is striktly determined by an egocentric spatial reference frame. Neck proprioceptive as well as vestibular input directly contribute to the computation of the egocentric reference frame. In neglect patients the neural computation of egocentric, body-centred coordinates seems to work with a systematic error resulting in a deviation of the whole spatial reference frame to the ipsilesional side.

43.01 SUBCELLULAR AND SUBSYNAPTIC DISTRIBUTION OF AMPA-TYPE, NMDA-TYPE AND METABOTROPIC GLUTAMATE RECEPTORS IN RAT HIPPOCAMPUS

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Glutamatergic inputs to hippocampal neurones are well characterised and are generally identifiable due to their segregated laminar distribution on the dendritic trees. Thus, the hippocampus provides an opportunity to study the subcellular distribution of glutamate receptors (GluRs) in relation to specific synaptic inputs to relatively homogeneous populations of cells. In order to determine the location of receptors at synaptic and extrasynaptic sites as well as to reveal relative quantitative differences in receptor density at different compartments of the surface of nerve cells, immunogold methods were applied at the electron microscopical level.

Ionotropic AMPA-type GluR subunits (GluRA-D) are highly concentrated in asymmetrical synaptic junctions, and are similarly distributed *in synapses* receiving glutamate from distinct presynaptic sources. The density of immunoreactive AMPA receptor subunits is higher in synapses on interneurones than in synapses on principal cells. Ionotropic and metabotropic GluRs are segregated in excitatory synapses on both interneurones and principal cells. The AMPA-type and NMDA-type (NR1) GluRs are highly concentrated in the main body of asymmetrical synapses, with an abrupt decrease in receptor density at the edge of the synaptic specialisation. However, the postsynaptic metabotropic GluRs (mGluR1α, mGluR1β/c and mGluR5) are always at the periphery of synaptic specialisations. The perisynaptic band of mGluR labelling completely surrounds the postsynaptic membrane specialisation and it also fills the invaginations at "perforated" synapses. Furthermore, the density of *extrasynaptic* mGluR5 is higher in dendritic spines than in dendritic shafts. These results demonstrate that GluRs are highly compartmentalised on the surface of hippocampal cells and the ionotropic and metabotropic GluRs are segregated at excitatory synapses which may provide a structural basis for their differential activation.

43.02 METABOTROPIC GLUTAMATE RECEPTORS IN NEURONAL PLASTICITY AND LEARNING AND MEMORY IN RATS

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Previous work has indicated a possible role of metabotropic glutamate receptors (mGluRs) in hippocampal long-term potentiation (LTP) *in vitro*. Since LTP is widely believed to be a neuronal substrate for learning and memory mechanisms, we have further examined the role of mGluRs in plasticity, namely dentate gyrus LTP *in vivo*, and during learning and memory paradigms by means of the specific mGluR antagonist MCPG and the agonist tADA.

Rats (270-320 g) were chronically prepared with stimulating and recording electrodes in perforant path and dentate granule cell layer, respectively, under nembutale anesthesia (40 mg / kg). An additional guide cannula was also inserted into the lateral ventricle for drug application. After recovery (5-7 days), animals were tested on their capacity to express LTP, or in spatial alternation or brightness discrimination tasks under drug and vehicle treatment.

We found, that the mGluR antagonist MCPG (200 mM/5 μl) prevents LTP expression in the dentate. In contrast the agonist tADA (50 mM/5 μl) facilitated induction and maintenance of LTP. Both compounds effectively blocked spatial alternation when applied pretraining, but had no effect on visual discrimination. Posttraining i.c.v. injection of MCPG had no effect on both paradigms, but tADA caused facilitated retention and prevented further learning in the spatial task. These data strongly indicate that mGluRs are involved in spatial learning, but have no effect on visual learning paradigms. Since both drugs inhibit learning, one is led to the conclusion that the modulation of mGluRs is a prerequisite in spatial, but not non-spatial learning events and saturated stimulation or blocking of mGluRs prevents learning or memory formation.

43.03 ANTIBODIES TO NERVE GROWTH FACTOR RETARD KINDLING AND BLOCK MOSSY FIBER SPROUTING IN ADULT RATS.

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Repeated subconvulsive electrical stimulation of certain areas of the forebrain leads to kindling, a progressive and permanent amplification of evoked epileptiform activity which is a model for human temporal lobe epilepsy. Recent studies have shown that kindling induces synthesis of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) but not neurotrophin-3 (NT-3) in the hippocampus and cortex. Kindling also elicits mossy fiber sprouting and functional synaptogenesis in the supragranular layer, the hilus, and the CA3 region of the hippocampus. Intraventricular administration of antibodies to NGF has been shown to effectively block septohippocampal sprouting in the adult rat, and has been reported to retard amygdaloid kindling. In the present study, we have investigated the role of NGF in both kindling and kindling-associated sprouting. We have confirmed a kindling-induced sprouting of the mossy fibers into the stratum oriens of the CA3 region of the hippocampus, utilizing a new semi-quantitative method of analysis based on Timm staining. We found no signs of hippocampal damage or cell loss with this kindling paradigm, indicating that the increased Timm staining might reflect a purely activity-induced sprouting. Intraventricular infusion of affinity-purified anti-NGF IgGs (which cross-react with NT-3 but not BDNF) resulted in both significant retardation of kindling and inhibition of the kindling-induced mossy fiber sprouting. Conversely, intraventricular infusion of NGF enhanced kindling development and increased mossy fiber sprouting. These results suggest an important role for NGF in both these phenomena.

43.04 CEREBELLAR LONG TERM DEPRESSION MAY NORMALIZE THE EXCITATION OF PURKINJE CELLS: A HYPOTHESIS.

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Long term depression (LTD) of parallel fiber (PF) synapses on Purkinje cells is usually interpreted in the context of a specific theory of motor learning by the cerebellum proposed by Marr, Albus and Ito. Several arguments suggesting that this theory may be false will be presented.

We propose a new hypothesis about the role of cerebellar LTD. It is assumed that under physiological conditions LTD is autoinduced by PF inputs. PF synapses should be able to induce their own depression because they can generate Ca^{2+} influx into the dendrite together with the activation of AMPA and metabotropic receptors. This assumption contradicts evidence against PF-induced LTD from old *in vivo* experiments, but the *in vivo* experimental paradigm is not very sensitive which explains why no PF-induced LTD was recorded.

We propose that plasticity of synapses on P-cells is not involved in motor learning at all. Instead LTD and other forms of Purkinje cell synaptic plasticity are part of a local negative feedback loop which prevents overstimulation of Purkinje cells by PF inputs. This local feedback mechanism normalizes the total excitation of the P-cell at a level of depolarization where the *in vivo* simple spiking rhythm is maximally responsive to changes in PF inputs and where no full-blown Ca^{2+} spikes are generated. The feedback process is initiated by localized elevations of the dendritic Ca^{2+} concentration, which is an indicator of the level of depolarization caused by the synaptic input. LTD involves only a small fraction of activated PF synapses, consisting of the synapses on excessively depolarized regions. In large parts of the dendrite local inhibition is strong enough to balance the PF input and no plasticity is induced. Consequently, it is hard to measure PF-induced LTD unless one records the response to localized PF inputs. The theory explains why it is difficult to induce cerebellar LTD when normal inhibition is present and why inhibitory inputs are potentiated by the same conditions that induce LTD of PF synapses.

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44. Symposium: Mechanisms of neuropathies

44.01 THE CONCEPT OF MOLECULAR MIMICRY IN GUILLAIN-BARRE SYNDROME (GBS).

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GBS is an acute inflammatory polyneuropathy. According to the clinical definition patients develop symmetrical, often severe paresis and areflexia within a period of maximally four weeks. Immune mediated demyelination is the cause of conduction block and clinical deficit in the majority of cases. Within this general concept a large variation of clinical syndromes may be found; in the classical ascending paralytic form weakness may be more proximally, globally or distally distributed and the sensory fibers may be severely involved or completely spared. Moreover, cranial nerve variants exist of which the Miller Fisher syndrome with ophthalmoplegia, ataxia and areflexia is best known. Especially in China a predominantly axonal form in children is seen with late summer outbreaks.

All variants are preceded by clinical infections in about 70% of the cases. Campylobacter Jejuni and Cytomegalo virus are the most common detected organisms. On the other hand antibodies directed against gangliosides present in the peripheral nerve have been detected in up to 30% of the patients. In pure motor GBS anti-GM1 IgG antibodies predominate, whereas virtually all Miller Fisher patients have anti-GQ1b IgG antibodies. It has been demonstrated, that C.Jejuni strains cultured from GBS patients do contain GM1- or GQ1b-like structures in classical GBS or Miller Fisher syndrome, respectively. We subsequently demonstrated, that anti-GM1 IgG antibodies could be strain specifically absorbed by C.Jejuni. C.Jejuni strains cultured from Miller Fisher patients were able to absorb anti-GQ1b antibodies, but not anti-GM1 antibodies. These findings support the hypothesis that the antecedent infection induce auto-antibodies, that result in peripheral nerve damage. Furthermore, that specific antibodies lead to specific syndromes.

44.02 Abstract not received

44.03 DEVELOPMENT OF MODEL SYSTEMS TO STUDY POTENTIAL THERAPEUTIC USES OF NEURONAL GROWTH FACTORS.

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The rational basis for the therapeutic use of growth factors depends upon understanding potential mechanisms of action. We have developed two model systems to understand the neuroprotective effects of nerve growth factor (NGF).

Sodium suramin is a novel chemotherapeutic agent which may alter tumor cell growth by interfering with the interaction of critical growth factors (e.g. EGF and PDGF) with their receptors on cancer cells. Suramin has significant peripheral neurotoxicity which may relate either to interaction with neurotrophin receptors or to interference with glycolipid metabolism. We have demonstrated that suramin binds competitively to the high affinity nerve growth factor receptor ($gp140^{trkA}$) and has two effects. At low concentrations it stabilizes receptor dimer formation and activates the receptor, initiating all down stream NGF signalling events. At this concentration (< 150 µM), suramin potentiates the action of NGF on DRG neurons and induces differentiation and neurite outgrowth from PC12 cells. At high concentrations (> 250 µM) suramin inhibits the action of NGF at the receptor. The latter effect may be overcome with exogenous NGF. The relationship of these changes to suramin cytotoxicity for cancer cells and neurotoxicity will be discussed.

In the second model system, a neurotoxic effect has been demonstrated by exposing DRG tissue culture medium to the core of hemodialyzers. Excess NGF offers complete protection against this effect. The protective effect can be mimicked by addition of catalase and abolished by simultaneous exposure to the specific catalase inhibitor, 3-amino-1,2,4-triazole. This suggests that NGF neuroprotection in this system is mediated by activation of catalase or upregulation of catalase expression.

This type of study will provide a rational basis for the therapeutic application of growth factors.

44.04 ANTI-GANGLIOSIDE ANTIBODIES FROM PATIENTS WITH IMMUNE-MEDIATED PERIPHERAL NEUROPATHIES BLOCK MOTOR NERVE FUNCTIONS

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Raised titres of anti-glycolipid antibodies are present in some forms of peripheral neuropathy particularly multifocal motor neuropathy (MMN), Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS), a variant of GBS. We have examined neuronal function, using the mouse phrenic nerve-diaphragm preparation, after *in vivo* injections of anti-ganglioside antibody positive plasma, purified IgG, or monoclonal antibodies (mabs) cloned from MMN and GBS patients, and following their direct application *in vitro*.

Anti-GM1 ganglioside antibody positive sera or mabs, from MMN or GBS patients, reduced nerve-evoked endplate potential (EPP) amplitudes and resulted in complete absence of EPPs at some endplates, but spontaneous neurotransmitter release (miniature EPPs) was still present. The results suggest an effect on motor nerve conduction. Anti-GQ1b ganglioside positive sera or IgG, from MFS patients, abolished both nerve-evoked EPPs and miniature EPPs (MEPPs) by 200 mins *in vitro*. MEPPs were not restored by ionomycin (normal Ca^{2+}), but α-latrotoxin increased MEPP frequency from 0/sec to >50/sec. These observations suggest that anti-GQ1b antibodies act on the exocytotic mechanism distal to depolarisation-induced calcium uptake.

We conclude that anti-ganglioside antibodies can specifically block motor nerve functions; their mechanisms of action require further study.

45. Symposium: Neurotrophic factors and their receptors

45.01 COMPLEMENTARY ROLES OF BDNF AND NT-3 IN VESTIBULAR AND AUDITORY DEVELOPMENT

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The physiological role of BDNF and NT-3 in the development of the vestibular and auditory systems was investigated by analyses of mice that carry a deletion in the BDNF or NT-3 gene, or mice deficient in both genes. BDNF was identified as the major survival factor for vestibular ganglion neurons. Lack of BDNF and NT-3 did not affect the initial ingrowth of nerve fibers to the vestibular sensory epithelium, but BDNF mutant mice failed to maintain afferent and efferent innervation. In the cochlea BDNF mutants lost only a small portion (i.e. 7%) of their spiral ganglion neurons belonging to type 2 neurons. This deficit caused an absence of afferent innervation to the outer hair cells. NT-3 mutants showed a paucity of afferents and lost 87% of their spiral ganglion neurons, presumably the type 1 neurons which innervate the inner hair cells. Double mutants had an additive loss of neurons, as compared to single mutant mice, lacking all vestibular and spiral ganglion neurons. These results show that BDNF and NT-3 are crucial for inner ear development and, although largely coexpressed in the inner ear, have distinct and non-overlapping roles in the vestibular and auditory systems.

45.02 NEUROTROPHIC FACTORS AND MOTOR NEURONS.

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Using cell cultures of embryonic motoneurons and in vivo models of motoneuron degeneration, a variety of neurotrophic factors has been identified so far, including Ciliary neurotrophic factor (CNTF), Leukemia inhibitory factor (LIF), Brain-derived neurotrophic factor (BDNF), Neurotrophin 4/5, Insulin-like growth factor I and II and, most recently, Glial-derived neurotrophic factor. Quantitative Northern blot analysis and in situ hybridization have shown that in skeletal muscle, the target tissue of motoneurons, Neurotrophin-3 and NT-4/5 are most abundantly expressed. BDNF levels are very low, in particular after birth. After nerve lesion in postnatal rats, NT-4 mRNA expression is rapidly downregulated, whereas the slow increase of BDNF expression occurs in Schwann cells rather than skeletal muscle, suggesting that during postnatal life BDNF expression might only play a role for motoneurons after nerve lesion.

We have established and analyzed mice in which the genes for CNTF and other neurotrophic factors have been disrupted. Whereas CNTF deficient mice develop only relatively mild symptoms of motoneuron degeneration during the postnatal period, and motoneurons are apparently normal in LIF deficient mice, mice with double gene defect for CNTF and LIF show higher rates of motoneuron loss, both during normal postnatal development and after peripheral nerve lesion in 4 week old mice, when motoneuron loss does not occur in control animals during 2 weeks after lesion.

45.03 GROWTH FACTORS AND MESENCEPHALIC DOPAMINERGIC NEURONS

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Following a brief introductory overview of growth factors that may be relevant to the development and rescue of toxically impaired midbrain dopaminergic (DAergic) neurons this talk will focus on members of the TGF-ß superfamily including TGF-ßs, activin A, and GDNF. It will be shown that TGF-ß1, -ß2, and -ß3 are clearly superior to activin and GDNF in their capacities to promote in vitro survival of cultured DAergic neurons and protect them against MPP+ toxicity. TGF-ßs, in contrast to many other cytokines that promote in vitro survival of DAergic neurons do not act via astroglial cells, and their effects are not accompanied by numerical expansion of any cell population present in these cultures. Studies are in progress to reveal a putative in vivo relevance of TGF-ßs for the MPTP-lesioned nigrostriatal system.With regard to GDNF, we will demonstrate that its modest to absent expression in the CNS is in sharp contrast to high levels of expression in many peripheral organs. Our data suggest that GDNF is a typical member of the TGF-ß superfamily in terms of its wide distribution, and that its functions may therefore comprise the typical repertoire of the TGF-ßs, i.e. regulation of cell cycle and tissue modeling through influencing expression of cell surface and extracellular matrix molecules.

Krieglstein K., Suter-Crazzolara C., Fischer W.H. and Unsicker K. (1995) *EMBO J.* 14 (in press).

45.04 NEUROTROPHINS AND BRAIN INSULTS.

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Epileptic, hypoglycemic, ischemic and traumatic insults to the brain induce marked changes of gene expression for the neurotrophins, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), and their high affinity receptors, TrkB and TrkC, in cortical and hippocampal neurons. Glutamate release and calcium influx are the most important triggering factors. Coexpression of BDNF and TrkB mRNA has been demonstrated in many neurons in cerebral cortex and hippocampus. This indicates that neurotrophins can act through autocrine or paracrine mechanisms in addition to their role as classical target-derived trophic factors. The major hypotheses for the functional effects of the insult-induced neurotrophin changes are protection against neuronal damage, stimulation of sprouting and synaptic reorganization, and acute effects on synaptic efficacy. More insight into the regulation and role of the neurotrophins after brain insults should increase our understanding of pathophysiological mechanisms in, e.g., epileptogenesis and cell death, and could lead to new therapeutic strategies.

46.01 IMMUNOCYTOCHEMICAL ANALYSIS OF AMINO ACID TRANSPORT INTO NEURONS AND GLIAL CELLS IN THE RABBIT RETINA USING SPECIFIC ANTIBODIES AGAINST AMINO ACID ANALOGUES AND STEREOISOMERS.
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Neurons appear to be dependent upon extracellular supplies of substrates, for the formation of amino acid transmitters such as glutamate and GABA, and for formation of amino acid-derived compounds such as nitric oxide. To determine which cells in the retina exhibit high-affinity uptake of amino acid transmitters and their precursors, we have developed highly specific antibodies, to molecules such as D-aspartate, D-glutamine and L-NAME. These molecules are not present in significant amounts in the brains of mammals, but are transported by glutamate, glutamine and arginine transporters respectively; thus transport of these molecules into cells can be distinguished immunocytochemically from pools of endogenous molecules. Retinae were isolated from rabbits that had been killed by an overdose of sodium pentobarbital (80 mg/kg, given intravenously). Retinae were incubated with test compounds dissolved in physiological saline, then fixed and processed for immunocytochemistry, using 0.5 µm-thick semithin sections. This paradigm resulted in labelling of specific classes of cells, with high resolution. Examination of serial semithin sections permitted the identification of endogenous molecules. Thus, for instance, D-arginine was strongly accumulated in a subset of retinal neurons, including, amongst others, some GABAergic amacrine cells, and revealed a population of amacrine cells which contained neither GABA nor glycine.

We believe that this immunocytochemical approach to the analysis of amino acid transport will be a powerful tool in analysing both the cell specificity and any activity-dependence of such transport systems.

46.02 DOWNREGULATION OF MUSCARINIC- AND 5-HT_{1B}-MEDIATED MODULATION OF [^{3}H]-ACETYLCHOLINE RELEASE IN SLICES FROM THE DENERVATED RAT HIPPOCAMPUS WITH SEPTAL GRAFTS.
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Two weeks after fimbria-fornix lesions, rats received intrahippocampal suspension grafts of fetal septal tissue (G). Sham-operated (S) and lesion-only rats (L) served as controls. Between 6.5 and 8 months later, hippocampal slices were used to assess [^{3}H]-Choline ([^{3}H]-Cho) accumulation and electrically evoked [^{3}H]-Acetylcholine ([^{3}H]-ACh) release in presence of atropine (1µM), oxotremorine (0.01µM-10µM), mecamylamine (10µM), methiothepin (10µM), 2-Me-5-HT (10µM) and CP 93129 (0.1µM-100µM), or without any drug. In L rats, the accumulation of [^{3}H]-Cho was reduced to 46% of normal and the release of [^{3}H]-ACh to 48% (% of tissue content). In G rats, these parameters were increased to 62% and 130% of control, respectively. Mecamylamine, methiothepin and 2-Me-5-HT had no effect on [^{3}H]-ACh release. Atropine increased [^{3}H]-ACh release in all groups, but this effect was larger in S rats than in L and G rats. Oxotremorine decreased [^{3}H]-ACh release, but in L rats, this effect was lower than in S rats. CP 93129 decreased [^{3}H]-ACh release, this effect being lower in G rats than in S and L rats. These data 1) confirm hippocampal cholinergic terminals to possess inhibitory muscarinic and 5-HT_{1B} receptors, and 2) show these receptors to be still operative in the cholinergic terminals spared by the lesions or derived from the grafts. However, the muscarinic receptors in L and G rats and the 5-HT_{1B} receptors in G rats show a downregulated sensitivity as compared to that found in S rats. In G rats, these downregulations may contribute to (or reflect) increased cholinergic function by reducing the cholinergic and serotonergic inhibitory tonus at the cholinergic terminal.

46.03 NOREPINEPHRINE MODULATES THE SPIKING ACTIVITY OF RED NUCLEUS NEURONES IN THE RAT: OPPOSITE EFFECTS MEDIATED BY α_2 AND β ADRENOCEPTORS.
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Previous studies have shown the presence of significative amounts of norepinephrine (NE) in the red nucleus of both humans and rats, although very little is known about the electrophysiological effects of NE in this structure. Therefore, we have tested the effects of NE on the spontaneous spiking activity of rat red nucleus neurones by using an *in vivo* extracellular recording technique. Microiontophoretic applications of NE modified the background firing rate in 56 out of 73 neurones. Three distinct patterns of response to NE were observed in different cells: in 52% of the responding neurones NE produced a decrease of the mean firing rate, while 34% of neurones responded to NE by increasing their spiking activity. In 14% of cells NE exerted a biphasic inhibitory/excitatory response. The effects of NE were fully reversible and dose-dependent. From histological examination, neurones responding to NE with either pure excitation or pure inhibition were found to be scattered throughout the red nucleus, while biphasic inhibitory/excitatory effects appeared to be segregated in the outer lateral portion. The inhibitory effect of NE was mimicked by the α_2 receptor agonist clonidine that had no effect on the cells excited by NE. In line with this, the α_2 receptor antagonist yohimbine completely blocked the inhibitory effect of NE, while being unable to antagonise the excitatory response. The excitatory effect of NE was blocked by the ß receptor antagonist timolol and mimicked by the ß receptor agonist isoprenaline, that was uneffective on those cells in which NE induced inhibitory responses. The α_1 receptor agonist phenylephrine was unable to mimick any of the effects of NE. Taken together, our results indicate that the inhibitory effect of NE on the firing rate of rat red nucleus neurones is mediated by α_2 receptors, while ß receptors are responsible for the excitatory effect.

46.04 THE CALCIUM PERMEABILTY OF GLIAL AMPA RECEPTORS IS DEVELOPMENTALLY REGULATED.
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In acute hippocampal slices of juvenile rats (P2 to P16) hilar glial precursor cells were identified by their position, their small size and their typical current pattern including voltage-gated Na^+- and K^+-currents. The properties of AMPA receptors present in these cells were investigated using the whole-cell configuration of the patch-clamp technique. At a V_h of -70 mV the application of kainate (400 µM) evoked inward currents of 218 pA (median, range 16 to 1540 pA; n = 40). The kainate-induced currents were inhibited by DNQX (10 µM), Zn^{2+} (2 mM) and Evans Blue (10 µM), and potentiated by cyclothiazide (100 µM) indicating their mediation by AMPA receptors. Steady-state current-voltage (I-V) relations were determined using the voltage-ramp method. In physiological salt solution the currents induced by excitatory amino acids reversed their polarity at -1.2 ± 1.2 mV (SEM; n = 28) indicating the activation of non-specific cation channels. To estimate the Ca^{2+} permeability of these receptors, I-V relations were determined in a Na^+ free solution containing 40 mM Ca^{2+}. The reversal potentials showed a wide variation ranging from -63 to +1 mV. The corresponding P_{Cs}/P_{Cs} permeability ratio ranged between 0.09 and 2.10 as calculated by the modified constant field equation for biionic conditions. A plot of the reversal potentials obtained in 40 mM Ca^{2+} as a function of the age of the cells showed a negative correlation (r = 0.59; n = 21; p < 0.01) indicating that the Ca^{2+} permeability of AMPA receptors in hilar glial precursor cells decreases with progressing age. It is speculated that Ca^{2+}-permeable AMPA receptors might be used in the developing hilus for the glial cell processes to find their targets, as e.g. the excitatory synapses. In the mature hilus, a low rate of Ca^{2+} influx following the activation of AMPA receptors might be sufficient to stabilize the glial contribution to the synaptical structure.

46.05 INFLUENCE OF BUFFER KINETICS ON THE FIRING PROPERTIES OF A PURKINJE CELL MODEL WITH REALISTIC CALCIUM DYNAMICS
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We have previously used computer modeling studies to characterize the electrophysiology of cerebellar Purkinje cells (De Schutter and Bower, J. of Neurophysiology: 71, 375-400, 1994). However,this compartmental model had primitive (single-pool) calcium dynamics. We have now incorporated more realistic calcium handling, and updated channel kinetics, into this Purkinje cell model. Calcium diffuses radially between cylindrical shells, with buffers incorporated, and with channels and pumps in the outer shell. K-Ca channels are coupled to the calcium in the outer shell. We simulate responses to somatic current injection. At moderate current injections, we find that a typical pattern of slow dendritic Ca bursting can only be obtained if most of the calcium buffer has slow kinetics (relaxation time on the order of 100 ms). The burst period increases rapidly upon increasing the proportion of fast buffers, which are known to dominate Ca buffering in the cytoplasm of other cell types. Also, K-Ca channels must be sensitive to calcium on the order of 1 uM to drive dendritic bursting. Given these conditions, typical dendritic bursting is obtained for 2-3 seconds. In this model, large gradients of calcium do not develop within spiny or smooth dendritic compartments due to their narrow diameter. We are exploring an alternative hypothesis that K-Ca channels and Ca channels are clustered such that K-Ca channels are exposed to localized peaks of high "domain" calcium. Regarding channel properties, a very high density of somatic NaF channels and a low density of somatic CaP channels are both required to properly reproduce somatic spiking. Supported by NFWO (Belgium) and NIMH grant 1-R01-MH52903-01.

46.06 A PRESYNAPTIC SOMATOSTATIN RECEPTOR WITH A NOVEL AGONIST PROFILE MODULATES SYMPATHETIC TRANSMITTER RELEASE BY AN INHIBITION OF N-TYPE CALCIUM CHANNELS.
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Cultures of chick sympathetic neurons represent a useful model for the investigation of presynaptic receptor systems, since transmitter release occurs exclusively at axons and/or axon terminals. The present study aimed at identifying presynaptic somatostatin (som) receptors in this preparation.

Overflow of previously incorporated [3H]noradrenaline triggered by electrical pulses (40mA, 0.5s, 1Hz) was reduced by som-14 in a concentration-dependent manner with a maximal inhibition of 43% at 10nM and an IC_{50} of 0.6nM; som-28 was equipotent (IC_{50}: 0.4nM) and equieffective. MK-678 also displayed an inhibitory action (IC_{50}: 5nM), whereas octreotide was ineffective at concentrations up to 1µM. None of the som receptor subtypes cloned so far showed such a dissociation between the effects of these two agonists. The inhibiory action of som-14 was significantly larger when present for 4min as compared to 8 or 16min, indicating a rapid desensitization of the receptor involved. In neurons pretreated with pertussis toxin (100ng/ml for 24h), som-14 had no effect. Electrically evoked overflow in the presence of 3µM BayK 8644 from neurons treated with ω-Conotoxin GVIA (3µM for 24h), which occurs independently of N-type calcium channels, was not affected by som-14.

In whole-cell recordings of calcium currents som-14 reversibly inhibited the ω-conotoxin-sensitive component. The inhibition comprised a slowing of activation kinetics and a reduction of steady-state current amplitudes. The effect was abolished by a pretreatment of the neurons with pertussis toxin, but not altered by inclusion of peptide inhibitors of either cyclic AMP-dependent proteinkinase or proteinkinase C in the pipette solution. The inibitory action of som-14 was attenuated by large depolarizing prepulses, an effect which is taken as an indication to a direct interaction between activated G protein subunits and calcium channels.

These results show that chick sympathetic neurons possess presynaptic somatostatin receptors which display a novel agonist profile and rapid agonist-induced desensitization. Activation of these receptors reduces transmitter release by an inhibition of N-type calcium channels. The effect is mediated by G proteins of the G_i/G_o subtype, but apparently independent of proteinkinases A or C.

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46.07 "INCREMENTAL" CAFFEINE-INDUCED CALCIUM RELEASE IN MOUSE SENSORY NEURONES.

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Cytoplasmic free calcium concentration ($[Ca^{2+}]_i$) was measured in indo-1/AM loaded dorsal root ganglion neurones acutely isolated from 3 months old mice. While investigating caffeine-induced Ca^{2+} release from internal ER stores we have found that the amplitude of release was determined by (i) caffeine concentration, (ii) intraER releasable Ca^{2+} content and (iii) cytoplasmic Ca^{2+} concentration which preceded caffeine application. Submaximal caffeine concentrations (1 - 4 mM) were able to induce $[Ca^{2+}]_i$ elevation only after charging of the ER stores by conditioning depolarization-induced Ca^{2+} entry. Moreover, if submaximal caffeine concentrations were applied in a sequence, only the first application was effective, however, succeeding application of supramaximal caffeine concentration (20 mM) evoked large $[Ca^{2+}]_i$ transient. Such an "incremental" caffeine-induced Ca^{2+} release was observed only at resting $[Ca^{2+}]_i$; at elevated $[Ca^{2+}]_i$ (> 400 nM) submaximal caffeine concentrations evoked a full-size Ca^{2+} release, and 20 mM caffeine applied afterwards produced a minor $[Ca^{2+}]_i$ elevation. Observed "incremental" caffeine-triggered Ca^{2+} release presumably reflects gradual nature of Ca^{2+} -induced Ca^{2+} release in nerve cells.

47. Oral Session: Sensory systems

47.01 SOMATOTOPIC ORDERING OF EVOKED HIGH-FREQUENCY (600 HZ) NEUROMAGNETIC FIELDS RECORDED NON-INVASIVELY FROM THE HUMAN PRIMARY SOMATOSENSORY CORTEX. G. Curio*, B.-M. Mackert, M.Burghoff #, W. Müller #, P.Marx. Dept. of Neurology, Universitätsklinikum Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, and # Physikalisch-Technische Bundesanstalt, Abbestr. 2-12, 10587 Berlin, Germany

INTRODUCTION: Based on a new dc-SQUID magnetometer (2.5 fT/√Hz white noise level) a burst of oscillatory 600 Hz somatosensory evoked fields (SEF) could be detected non-invasively over the human primary somatosensory cortex upon conventional median nerve electric shock stimulation (Curio et al., Electroenceph. clin. Neurophysiol., 91, 483-7, 1994). Here, the weaker ulnar nerve response was studied in comparison. **METHODS:** Using 49 axial first order gradiometers (70 mm baseline) on a hexagonal grid (30 mm interchannel distance) early SEF were mapped (0.5-1500 Hz analog filter; 4 kHz ADC) over the scalp contralateral to conventional repetitive (9/sec) electric shock stimulation of either median or ulnar nerve at wrist. After averaging (n=9000) a digital 428 Hz high-pass filter was applied off-line. **RESULTS:** For median as well as ulnar nerve stimulation dipolar N20 field patterns were recorded reflecting the somatotopy of the primary cortical EPSP response in S-I. A significant 600 Hz burst activity could be isolated not only from the median N20 proper but also from the ulnar one despite its lower signal strength. For both nerves the field patterns for N20 and burst peaks were congruent indicating the possibility for a comparative somatotopic source analysis. **CONCLUSION:** Evoked 600 Hz neuromagnetic fields from human S-I could be demonstrated for median as well as for the weaker ulnar nerve response. Since these bursts presumably reflect mainly a repetitive discharge of thalamocortical neurons, a non-invasive study on possibly differential contributions of subcortical (burst) vs. cortical (N20) activities to human neuroplasticity may become feasible.

47.02 PROCESSING OF TACTILE INFORMATION IN THE HUMAN IPSILATERAL PRIMARY SOMATOSENSORY CORTEX

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Cortical representations of cutaneous tactile stimuli applied to peripheral limbs are supposed to be strictly contralateral at the primary somatosensory cortex SI.

We investigated with a 122-channel whole-scalp neuromagnetometer whether afferent cutaneous information from the human hand also reaches ipsilateral SI. In six healthy right-handed subjects (22 - 34 years), right and left median nerves were alternately stimulated once every 1.5 s at the wrists with 0.3 ms electric constant current pulses. In the rest condition, the subject received no extra stimuli whereas in the two other conditions, in addition to median nerve stimulation, the first three fingers and palm of either the left or the right hand were continuously brushed with a rough sponge.

Median nerve stimuli evoked typical short-latency somatosensory evoked fields (SEFs) in the contralateral hemisphere. SEFs were adequately explained by one or two time-varying equivalent current dipoles in the hand SI cortex. In all subjects, continuous tactile stimulation of one hand altered the SEFs to stimulation of the other hand, maximally at around 35 ms. This effect was more pronounced in the left than right hemisphere.

Our findings indicate that activation of cutaneous afferents from the hand significantly modifies neuronal activity in the human ipsilateral SI. We suggest that the effect is mediated via interhemispheric transcallosal pathways.

47.03 CHARACTERIZATION OF CORTICOTHALAMIC PROJECTIONS BASED UPON THEIR TARGET CELLS AND POSTSYNAPTIC RECEPTORS

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The synaptic organization of corticothalamic projections - anterogradelly labelled with *Phaseolus vulgaris* leucoagglutinin - from different visual cortical areas were analysed in the dorsal lateral geniculate nucleus (dCGL) and lateral posterior nucleus (LP) of the rat and cat. It was found that in cats corticothalamic projections from different visual cortical areas in the same target regions (from area 17 and 18 in the dCGL) and the cortical projections from the same area in different visual thalamic nuclei (from area 17 in dCGL and LP) exhibit specific, differential synaptic organization pattern, ie. they innervate variously the two types of thalamic neurons, the principal cells and the interneurons, characterized by postembedding GABA immuncytochemistry.

In rats the two morphologically distinct types of corticothalamic boutons (small and giant boutons) exhibit a clear difference in their type of postsynaptic glutamate receptors. The small terminals - constituting the majority of corticothalamic boutons and found both in dCGL and LP - establish asymmetrical synapses with mGluR1a-immunopositive dendrites with immunometal particles concentrated at the periphery of their postsynaptic membranes. In contrast, synapses formed by giant boutons in the LP were always mGluR1a-immunonegative.

These results indicate, that similarly to the parallel, functionally and morphologically distinct pathways and channels existing in the retinothalamocortical system, there are parallel pathways and channels in the corticothalamic feedback also.

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47.04 BILATERAL RECEPTIVE FIELDS IN RAT SOMATOSENSORY NEURONES AFTER LESION OF THE CORRESPONDING CONTRALATERAL CORTEX.

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This study describes the transhemispheric induction of plastic changes by contralateral cortical lesions in rats. Previously this phenomenon had been shown after unilateral peripheral injuries, the cortical changes extending within minutes from the specific cortical representational area to the corresponding ipsilateral cortical area. In the present study, the right hindpaw cortical representational area of adult male rats was ablated selectively and 3 to 4 weeks later, responses of single units in the left hindpaw representational area to stimulation of ipsilateral and contralateral paws were recorded under urethane anaesthesia. The majority of units were found in layers IV and V.

Lesions of the contralateral representational area produced a significant 26 % increase in the number of neurones in the hindpaw representational area responding to contralateral hindpaw stimulation. The percentage of neurones demonstrating a short latency response characteristic of pyramidal neurones to both contralateral and ipsilateral hindpaw stimulation also increased, demonstrating that transcallosal connections were not necessary for transhemispheric plasticity or for appearance of neurones with bilateral receptive fields.

The results suggest that lesioning causes pre-existing thalamocortical connections subserving neurones with bilateral receptive fields to become functional or for new connections to develop. This expansion of central receptive fields is somatotopically specific (e.g. to either hindpaw) and may occur at the expense of other contralateral somatosensory inputs.Thus undamaged brain tissue contralateral to the lesion 'takes over' some functions of the damaged area and this may have therapeutic relevance to different neurological disorders.

47.05 TOPOGRAPHIC ASPECTS OF STIMULUS INDUCED RECEPTIVE FIELD PLASTICITY IN ADULT CAT VISUAL CORTEX. *Eysel UT, Eyding D, Schweigart G. Ruhr-Universität Bochum, Institute of Physiology, 44780 Bochum, Germany

Long-term potentiation has been shown in the visual cortex both of rat and cat *in vitro*. Recently, we observed an associative LTP-like phenomenon in adult cat visual cortical neurones *in vivo* when synchronously activating suprathreshold inputs from the receptive field and subthreshold inputs from regions outside the RF when the cortical target site of the latter was locally inactivated at the same time by GABA microiontophoresis. The RF size increased by recruiting the previously unresponsive RF region (Eysel, Soc. Neurosci. Abstr. 20, 838, 1994). Here we ask the question whether the effects can be obtained for regions close to the RF without inactivation of intracortical lateral signal processing and whether the effects are specific with regard to stimulus location. In adult cats anaesthetised with a mixture of oxygen, nitrous oxide and halothane we have recorded extracellularly from single cells in cat area 17. The receptive fields were mapped in steps of 0.5 degrees with on-off stimuli of optimal orientation. PSTHs with averages of 100 responses were sampled. Thus, the response profile of the RFs was obtained and regions on two opposite sides just outside the RFs were determined. The RF and one of the regions outside of the RF were synchronously stimulated with 1/s on-off stimuli for 60 minutes. The two opposite regions outside the RF were repetitively tested thereafter. In 5/12 cases no effect was observed, in 7/12 the previously unresponsive region that had been costimulated with the RF proper displayed suprathreshold responses. However, this effect was only specific in 4/7, in 3/7 the RF had as well expanded to the opposite side.

The results provide evidence that LTP-like changes cannot be elicited in all neurones under standard experimental conditions in the adult cat visual cortex *in vivo*. However, among the cells showing enlarged RFs after associative stimulation there is a slight bias towards stimulus specificity.

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47.06 ARE THE SAME ATTENTIONAL MECHANISMS USED FOR TARGETS DEFINED BY COLOR, ORIENTATION AND MOTION?

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Previous studies have shown that the N2pc component of the event-related potential (ERP) waveform reflects an attentional filtering process that operates during color and form discrimination, and the present study sought to determine if this same attentional process is used for targets defined by motion. We recorded ERPs from young adults in a visual search paradigm using stimulus arrays composed of either 8 vertical green bars moving in a downward direction (homogeneous arrays) or 7 of these bars and 1 bar that differed in its color, orientation, or direction of motion (pop-out arrays). One of the three pop-out types was the target for a given trial block, and the homogeneous arrays and other pop-out types served as nontargets. A robust N2pc component was observed for all three target dimensions, indicating that the same neural attentional systems are used across dimensions. In addition, we found that motion pop-outs elicited an N2pc component even when another feature was the target, whereas color and orientation pop-outs elicited an N2pc only when they were targets. This result suggests that motion pop-outs might automatically attract attention, even when they are not task-relevant. Together, these results indicate that: a) information from the parvo and magno streams converges before the stage of attentional filtering indexed by the N2pc component; and b) stimuli within the magno stream may attract attention more automatically than stimuli within the parvo stream.

47.07 INTERAREAL SYNCHRONIZATION BETWEEN THE VISUAL, PARIETAL AND MOTOR CORTEX OF THE AWAKE CAT. P. R. Roelfsema*, A. K. Engel, P. König and W. Singer, Max-Planck-Institute for Brain Research, Deutschordenstr. 46, 60528 Frankfurt, Germany

It has been proposed that synchronization with a millisecond precision plays an important role in the integration of distributed neuronal activity. In anesthetized cats synchronization between neuronal responses occurs within a single visual area, and also between different visual areas. Recent studies in awake monkeys have uncovered interareal synchronization between the somatosensory and motor cortex, and even between the visual and motor cortex. This suggests that synchronization may play a role in the coordination of motor activity by sensory feedback. In the present study, we investigated the interactions between transcortical field potentials of the visual, parietal and motor cortex of the awake behaving cat using cross-correlation analysis. The cats were trained to push and release a lever in response to visual stimuli. In the episodes that the animals paid attention to the visual stimuli, precise synchronization occurred between various areas of the visual cortex. These interactions were particularly strong in the interval between the visual stimulus and the subsequent behavioral response. Interactions between areas of the visual, parietal and motor cortex were also characterized by synchronization with a millisecond precision. However, when the animals were rewarded with food, synchrony was lost and large phase shifts occurred between 10 Hz EEG rhythms that developed simultaneously in the visual and parietal cortex. These changes in the interactions were also observed in spike triggered averages of the transcortical field potentials computed for interareal combinations. The enormous changes in the pattern of interactions under different behavioral conditions indicate that the interareal interactions are highly flexible, and suggest that interareal synchronization may play an important role in visuomotor integration.

47.08 ROLE OF CAT ANTERIOR SUPRASYLVIAN SULCAL CORTEX IN LINE ORIENTATION DISCRIMINATION

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Increased levels of 2-deoxyglucose (2DG) uptake in the visual cortex of cats trained to a high level of proficiency at line orientation discrimination, implicate cortex forming the banks of the anterior half of the lateral suprasylvian (LS) sulcus as a major component in the circuit underlying line orientation discrimination.

We have tested this proposition by implanting cooling probes bilaterally into LS sulcus of two cats previously trained to make line orientation discrimination of better than 7 degrees for lines with a length of 12 degrees and a width of .2 degrees.

Cooling impaired line orientation discrimination performance. In cold blocks of trials the staircase reached asymptote at a lager orientation difference than during warm or rewarm blocks of trials. Cooling to 8 degrees Celsius resulted in an increase in orientation difference of 25 to 60 %, whereas cooling to 1 and 2 degrees, and blocking of a greater region of cortex, further increased the orientation difference by 100 to 200 %. The increase in orientation difference could not be attributed to decreased detection of the stimuli because the cats showed good stimulus control during all blocks.

These results are consistent with those obtained using 2DG that implicate the anterior half of LS sulcus in the line orientation discrimination circuit.

48. Oral Session: Ion channels and transmission

48.01 SYNAPTIC VESICLES IN CENTRAL SYNAPSES COMPRISE TWO FUNCTIONALLY DISTINCT POOLS.

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Synaptic vesicle exocytosis is distinguished from other forms of cellular secretion by the unique temporal properties, fundamental to its function in mediating fast synaptic transmission. While little is known about the mechanisms that account for distinctive features of neurotransmitter release, it can be assumed that neuron-specific proteins are involved.

In the present study we studied the role of synapsins by introducing synapsin-specific antibodies into the presynaptic region of lamprey reticulospinal synapses. The release sites in these glutamatergic synapses are uniquely accessible for experimental manipulation, as the presynaptic axon is unbranched and make en passant synapses from its main trunk. We found that clusters of vesicles at synaptic release sites are composed of two pools, a distal pool containing synapsin and a proximal pool devoid of synapsin and located adjacent to the presynaptic membrane. Presynaptic injection of synapsin antibodies resulted in the loss of the distal pool, without any apparent effect on the proximal pool. Depletion of this distal pool was accociated with a marked depression of neurotransmitter release evoked by high frequency (18-20 Hz), but not by low frequency (0.2 Hz) stimulation. Thus the synapsin-associated pool of vesicles appears to be required to sustain release of neurotransmitter in response to high-frequency bursts of impulses.

48.02 **DIFFERENTIAL EXPRESSION OF P- AND Q-TYPE CALCIUM CURRENTS DURING EARLY DEVELOPMENT OF SENSORY NEURONS.**

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Analysis of neuronal development has emphasized the importance of voltage-activated Ca^{2+} currents (I_{Ca}) during the initial period of differentiation. Whether the new identified non L, non N high-threshold calcium current subtypes are present in early embryonic neurons and developmentally regulated is still unknown. To resolve these issues, we used the whole-cell patch-clamp technique to record calcium current in dorsal root ganglion (DRG) neurons acutely dissociated from mouse embryos during development. We report dramatic in vivo changes in the expression of P-, Q- and R-type calcium currents between embryonic day-13 and day-15, respectively before and after the period of target innervation. All three current were distinguished on the basis of their sensitivity to AgaIVA. Since R-type was stable over this developmental span, Q-type expression increased 2-3 fold and P-type current disappears completely. These data show that P-, Q- and R-type calcium current are expressed by early embryonic DRG neurons, are developmentally regulated and are probably involved in specific key developmental events including natural neuron death and onset of synapse formation.

48.03 EXPRESSION OF LOW-VOLTAGE ACTIVATED CALCIUM CHANNELS FROM RAT SUBCORTICAL NUCLEI IN *XENOPUS* OOCYTES

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Xenopus oocytes were injected with mRNA obtained from the thalamo-hypothalamic complex of adult rats and fractionated in sucrose gradient; 25 - 30 S fractions diluted in water to concentration 1 mg/ml were used. Double micro-electrode technique was used voltage clamping. In 60% out of 110 injected oocytes a Ba^{2+} current was expressed after 4 days with peak amplitude of 120-150 nA, which became activated by depolarizations to -70 mV from holding potential -120 mV and reached maximum between -30 and -20 mV. It was subjected to steady-state inactivation (half-value at -78 mV). The current could be specifically depressed by La^{3+} (K_d = 0.48 μM), flunarizine (K_d = 0.42 μM) and amiloride (K_d about 0.5 mM) but were not sensitive to high concentrations of ω-Aga-IVA (10 μM), ω-conotoxin GVIA (20 μM) or verapamil (10 μM); they revealed some sensitivity to nifedipine (K_d about 10 μM). By such pharmacological properties they could be easily differentiated from about one order smaller high-voltage activated currents appearing in some of the injected oocytes. All described characteristics are identical to those for T-type channels in hypothalamic neurones *in situ*, in which such channels are present in high density in adult animals (Akaike, Kostyuk & Osipchuk, 1989). The only difference of the expressed channels was a considerable slowing-down of their time-dependent inactivation, which might be caused by changes of channel subunit composition occuring during expression. Thus injections of mRNA obtained from identified neuronal structures may be an effective way for expression of low-voltage activated calcium channels in an artificial system.

48.04 **Cl^--DEPENDENT GATING OF THE VOLTAGE-DEPENDENT CHLORIDE CHANNEL, ClC-0**

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The *Torpedo* Cl^- channel, ClC-0, is the first cloned member of an expanding gene family of "ClC" chloride channels. Although lacking the typical voltage-sensor found in cation channels, gating of ClC channels is clearly voltage-dependent. ClC-0 has a "slow" gate operating on both protochannels of the double-barreled channel, and a "fast" gate acting on single protochannels. We expressed ClC-0 in oocytes and studied the fast gate in isolation. We found that channel opening is strongly facilitated by $[Cl^-]_{ext}$. Other less permeable anions can substitute for Cl^- with less efficiency. The nominal gating charge remains ~1 throughout. Cl^- conductance shows an anomalous mole fraction behavior with NO_3^-/Cl^- mixtures, suggesting a multi-ion pore. Gating shows a similar anomalous behavior, tightly linking permeation to gating. Eliminating a highly conserved lysine residue (K519) located at the C-terminus of D12, changed kinetics, $[Cl^-]_{ext}$-dependence, and halide-selectivity of gating, and altered pore properties such as ion selectivity, channel conductance, and rectification. Taken together, these results strongly suggest that voltage-dependence of gating in these channels is conferred by the permeating ion itself, acting as the "gating-charge".

48.05 SIMULTANEOUS PRE- AND POSTSYNAPTIC RECORDINGS AND CALCIUM MEASUREMENTS AT A FAST GLUTAMATERGIC SYNAPSE.

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The medial nucleus of the trapezoid body (MNTB) is involved in the localization of sound. Each principal cell is excited by a large presynaptic terminal, called the calyx of Held. We studied synaptic transmission in transversal brainstem slices of the rat MNTB. Slices were visualized with infrared differential interference contrast video miscroscopy. Large, excitatory postsynaptic currents (EPSCs) were evoked in voltage-clamped MNTB neurons upon stimulation of the trapezoid body. Transmission was calcium-dependent, the amplitudes of the EPSCs were reduced by cadmium or low extracellular calcium. We made patch clamp recordings from the terminal and used a fast CCD camera and the fluorescent calcium-sensitive dye Calcium Green-5N to measure the presynaptic Ca^{2+} transient evoked by a single action potential. The calcium transient was much larger in the calyx than in the preterminal axon, suggesting that the calcium channels are preferentially located in the terminal.

To study the effect of manipulations of the presynaptic cytoplasm on neurotransmitter release we made simultaneous whole-cell patch-clamp recordings of the terminal and the postsynaptic cell. When the presynaptic terminal was perfused with a solution with a low concentration of the calcium buffer BAPTA, no rundown in the size of the orthodromically-evoked EPSCs was observed. In contrast, when the presynaptic pipette solution contained 1 mM BAPTA, which is not sufficient to block facilitation, the size of the EPSCs was rapidly reduced following the establishment of the whole-cell configuration in the terminal. This suggests that the endogenous mobile calcium buffer capacity in these terminals is low. In conclusion, the possibility to make simultaneous pre- and postsynaptic recordings makes the MNTB an excellent preparation for the study of presynaptic release mechanisms.

48.06 **NEURONAL G PROTEIN GATED INWARD RECTIFIER CHANNEL EXPRESSED IN *XENOPUS* OOCYTES.**

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Neuronal function is modulated in part by regulation of G protein-gated inwardly rectifying potassium channels (Velimirovic et al, PNAS 1994; 92:1590-4). The recently cloned brain inward rectifying potassium channel, GIRK2 was coexpressed in *Xenopus* oocytes with GIRK1, a related homolog present in brain. The size of the resulting ACh-activated current was up to 10-fold larger than either GIRK1 or GIRK2 expression alone. This current sharply inwardly rectified and was K^+-selective. Current expressed by coinjection of GIRK1, GIRK2 and m2 receptor was blocked by extracellular Ba^{2+} and Cs^+ in a voltage-dependent manner. Single channel recordings from cell-attached and inside-out patches revealed a channel amplitude of 32 pS in symmetrical 140 mM $[K^+]$. The open time histograms of the channel were fitted by a single exponential (τ = 1.1 ms). GTPγS applied from the intracellular side of the patch activated the channel. These data suggest that the brain inward rectifying potassium channel underlying the mechanism of slow synaptic inhibition is a heteromultimer comprised of at least two different subunits. Many neurotransmitters modulate this channel in the fashion similar to the m2 agonists action demonstrated here. This fact, and the ability of neuronal cells to differentially express receptors and G proteins, greatly amplifies the potential for signalling in the central nervous system.

48.07 ROLE OF CALCINEURIN IN Ca^{2+}-INDUCED RELEASE OF ALL MAJOR NEUROTRANSMITTERS: EFFECTS OF ANTI-CALCINEURIN ANTIBODIES AND PHOSPHATASE INHIBITORS IN PERMEATED SYNAPTOSOMES.

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Several phosphoproteins such as B-50/GAP-43 have been implicated in Ca^{2+}-induced release of neurotransmitter vesicles. Recently, we have suggested that protein dephosphorylation rather than phosphorylation is important after the Ca^{2+} trigger in this release process. Therefore, we investigated the role of Ca^{2+}/calmodulin-dependent phosphatase calcineurin (CaN) and protein dephosphorylation in the molecular mechanism underlying Ca^{2+}-induced neurotransmitter release. We introduced CaN-neutralizing antibodies (IgGs) into streptolysin-O-permeated synaptosomes from rat cerebral cortex and measured the release of glutamate (glu), noradrenaline (NA) and neuropeptide cholecystokinin-8 (CCK). The vesicular nature of Ca^{2+}-induced glu release (obtained by an elevation of free $[Ca^{2+}]_i$ from 10^{-8} to 10^{-4} M) was demonstrated by its complete block by the light chain fragment of tetanus toxin at 300 nM. Specific poly- and monoclonal anti-CaN IgGs, that inhibited CaN-mediated dephosphorylation of protein kinase C-substrates B-50 and MARCKS, inhibited Ca^{2+}-induced release of glu, NA and CCK from permeated synaptosomes. Control IgGs were without effect. Introduction of okadaic acid (1 μM), an inhibitor of phosphatases 1 and 2A, into permeated synaptosomes did not significantly inhibit Ca^{2+}-induced release of glu, NA or CCK. Inhibitor-2 and microcystin were also without effect on Ca^{2+}-induced NA release, indicating that phosphatase 1 and 2A are not involved in this release process. Altogether, these data identify CaN as a key protein phosphatase involved in the regulation of Ca^{2+}-induced exocytosis and/or vesicle recycling of all major neurotransmitters.

48.08 PRESYNAPTIC MODULATION OF NORADRENALINE RELEASE FROM CHICK SYMPATHETIC NEURONS BY CONCANAVALIN A.

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Concanavalin A (Con A) is frequently used to investigate synaptic plasticity, since this lectin is known to modulate e.g. neurite outgrowth, neuronal responses to glutamate and acetylcholine, and the coupling of electrical synapses. However, reports on presynaptic effects are rare, and therefore Con A was applied to cultures of chick sympathetic neurons which release previously incorporated [3H]noradrenaline exclusively at axons and/or axon terminals.

Con A reduced electrically evoked (40mA, 0.5s, 3Hz) overflow in a concentration-dependent manner with an IC_{50} of 0.2μM and maximal effects (30% inhibition) at 3μM. Overflow evoked by 25mM potassium was reduced to a similar extent (20%) by Con A. The inhibition by Con A was time-dependent, being more pronounced after 2 than after 8 or 12min of application. The effect of Con A was irreversible in a buffer containing sucrose, but complete recovery was obtained by adding methyl-mannopyranoside. Likewise, no inhibition was seen when Con A was applied in a methyl-mannopyranoside-solution. Pretreatment of neurons with either pertussis or cholera toxin (100ng/ml for 24h) did not alter the effect of Con A. The dimeric analogue, succinyl-Con A, failed to mimick the action of tetrameric Con A. Hence, the inhibition by Con A may involve clustering of glycoproteins without the activation of presynaptic neurotransmitter receptors commonly coupled to G_i/G_o type G proteins.

Con A has been shown to enhance potassium and to reduce calcium channel currents. Both effects might form the basis for a decrease in transmitter release. However, Con A had no effect in whole-cell recordings of either potassium or calcium currents of chick sympathetic neurons.

An alternative site of action for Con A is provided by neurexins, glycoproteins highly enriched at presynaptic nerve terminals. Neurexin Iα constitutes the site of action for α-latrotoxin which triggers exocytosis. In fact, pre-exposure of chick sympathetic neurons to Con A (3μM) reduced the α-latrotoxin-induced transmitter release by about 30%, but the lectin failed to alter overflow triggered by the addition of calcium once α-latrotoxin had bound.

Thus, Con A may affect synaptic transmission by a presynaptic inhibition of transmitter release possibly at the level of neurexins.

49.01 N-TERMINAL CYSTEINES ESSENTIAL FOR GOLGI SORTING OF B-50 (GAP-43) IN PC12 CELLS.

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B-50 (also known as GAP-43, F1, p57, pp46 and neuromodulin) is a neuronal, calmodulin binding PKC-substrate that accumulates presynaptically during growth. It is synthesized as a highly hydrophilic protein on free ribosomes in the cytosol and associates with membranes, rapidly after its synthesis. Tight association of B-50 to membranes is thought to be accomplished via palmitoylation of two cysteine residues at positions 3 and 4.

We have examined the subcellular distribution of the B-50 protein in pheochromocytoma (PC12) cells, using confocal laser scanning microscopy. Administration of Nerve Growth Factor (NGF) leads to differentiation of PC12 cells to sympathetic neuron like cells, a process that is accompanied by an enhanced B-50 expression. Whereas proliferating PC12 cells contained very low levels of B-50 immunoreactivity (BIR) located in the cytosol, enhanced expression of B-50, induced by either NGF administration or transient transfection with rat B-50 cDNA, led to Golgi sorting and membrane targeting of BIR.

To assess the importance of the N-terminal cysteine residues for B-50 localization in PC12 cells, we compared the subcellular distribution of BIR in cells transiently transfected with wild type and mutant (Ser_3Gly_4)B-50 cDNA. PC12 cells, transiently transfected with Ser_3Gly_4 B-50 cDNA showed a cytosolic distribution of BIR. We conclude that Cys_3 and Cys_4 are essential for accumulation of BIR both at the plasma membrane and in the Golgi apparatus of PC12 cells.

49.02 REGIONAL BRAIN ABLATION: EFFECTS ON IMMUNE RESPONSES AND MONOAMINE CONTENT IN LEFT-BIASED RATS

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This study was designed to evaluate the consequences of regional brain ablations on immune reactions and monoamine content in left-biased rats. Lesions in ipsilateral frontal (FC), parietal (PC) and occipital (OC) regions were performed by the aspiration method in male Wistar rats (250-300 g), previously tested for brain laterality. After two weeks of recovery, rats were sensitized with bovine serum albumin (BSA) in complete Freund's adjuvant. On day 14 and 21 after the immunization rats were bled and skin tested with BSA for Arthus and delayed hypersensitivity skin reactions. Anti-BSA antibody levels were determined by ELISA method. On day 22 after the immunization monoamine concentrations were determined in the brain and lymphoid tissues by high-performance liquid chromatography with electrochemical detection. On day 14, but not on day 21 after the immunization, Arthus skin reactions to BSA in PC- and FC-lesioned animals were decreased in comparison with other experimental groups. Delayed skin reactions were decreased after FC-ablation both on day 14 and 21 in comparison with other groups. Regional ablations of the left neocortex were also accompanied by marked changes in norepinephrine, dopamine and serotonin levels in the cerebral cortex, hyppocampus, hypothalamus and lymphoid tissues (thymus and spleen). These results showed that immune reactions and monoamine levels in left-biased rats are changed after ipsilateral regional ablations. (Supported by Ministry of Sciences and Technology of Serbia.)

49.03 EFFECTS OF METABOLIC INHIBITION ON MEMBRANE POTENTIAL AND ION CHANNELS IN RAT ASTROCYTES.

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The effects of metabolic inhibitor 2,4-dinitrophenol (DNP) on membrane potential (Em) and I-E curves of rat astrocytes were studied with patch clamp technique (whole cell recordings). Cells from newborn rats were incubated 13-18 days before experimentation. In normal external solution (3 mM K^+) E_m was -72 ± 1.1 (n=21) and the membrane conductance (g) was 42 ± 3.7 nS (n=21). The cells immediately depolarized to -52 ± 6.7 mV (n=4) in the presence of 1 mM DNP and g decreased by 25%. These effects were reversible. Block of K^+ conductance with tetraethylammonium chloride (TEA, 10 mM) depolarized the cells to -65 ± 2.4 mV (n=5), and addition of DNP caused a further depolarization to -29 ± 3.2 mV (n= 5). Replacement of the intracellular solution with a Cl^- free solution had only small effect on E_m (-71 ± 3.3 mV, n=6). However, the depolarizing effect of DNP was diminished, E_m was -67 ± 4.8 mV (n=6). These results show that the rapid depolarizing effect of metabolic inhibition in astrocytes is more prominent when K^+ channels are blocked, and dependent on intracellular Cl^-, which suggests a change in Cl^- conductance.

This work has been supported by the Swedish Medical Research Council (project no. 14X-4255).

49.04 ORDERED EXPRESSION OF IMMUNE-RELATED ANTIGENS BY PHAGOCYTIC MICROGLIA IN THE FACIAL NUCLEUS OF THE RAT*.

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Application of 50 µl 4% Fluoro-Gold (FG) to the whisker pads of rats yields a stable retrograde labeling of facial motoneurons. Following a subsequent resection of 10 mm from the facial nerve, the phagocytic microglia assume the fluorescent label from the decaying FG-preloaded neurons (Angelov et al., GLIA 13:113-129; 1995). Combining this vital labeling of neuronophagic microglia with immunochemistry for established microglial markers (OX-6, OX-18, OX-42, ED1 and ED2) we traced the expression of immune-related antigens on active neuronophages 14-224 days post resection (DPR).

We found that the expression of immunomolecules by phagocytic microglia took place in an ordered fashion: OX-42 (CR3) immunopositive cells appeared first (14 DPR) and comprised the bulk of the microglial clusters till 56 DPR. OX-18 (MHC class I) and OX-6 (MHC class II) immunopositive microglia occurred later (28-56 DPR) and disappeared by 112-224 DPR. During the later postoperative survival periods (56-224 DPR) the phagocytic microglia started to express an antigen present in cells of the monocyte- macrophage lineage (ED1-positive) and most interestingly, some small round macrophages with perineuronal localization were found ED2-positive (ED2 is considered a classical marker for the "immunologically inert" perivascular cells.

Confirming the functional continuum between activated and phagocytic microglia, this time-dependent expression of immunomolecules by neuronophages provides evidence that there is no single immunophenotype of phagocytes in the rodent CNS.

• Supported by the Uhrmacher Foundation

49.05 EFFECTS OF LEUCINE-ENKEPHALIN (LEU-ENK) ON ADJUVANT ARTHRITIS IN LEWIS, DARK AUGUST AND WISTAR RATS

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It is well established that neuropeptides, and opioids in particular, may affect a number of immunological functions. In this study, the immunomodulatory effect of Leu-Enk on adjuvant arthritis was investigated. Eight-week old, male Wistar, Lewis and Dark August (DA) rats were immunized for adjuvant arthritis by a single intradermal injection of complete Freund's adjuvant (CFA, 50 µl/rat) in the basis of the tail. Treatment groups were intraperitoneally (i.p.) injected with 0.2 mg/kg of Leu-Enk or saline (n=7-9 rats per group) 1 hour before immunization and then every other day until day 21. Reinduction of arthritis was performed 52 days later, after full recovery of animals, by injection of 50 µl of CFA in the left hind foot pad. All rats were daily observed for appearance and duration of arthritis. Clinical arthritic score was evaluated for each paw as follows: 0, no arthritic changes; 1, edema; 2, edema and nodules on 1-2 fingers; 3, edema and nodules on 3-4 fingers; and 4, edema and arthritic changes on all fingers. During reinduction, the injected paw was not scored. The following results were obtained: a. treatment with Leu-Enk markedly increased the severity (clinical score and aggregate clinical score) and duration of adjuvant arthritis in Lewis rats, but did not affect the disease following reinduction; b. in DA rats treated with Leu-Enk arthritis appeared significantly later than in saline controls, and the severity of arthritis was markedly suppressed after induction as well as after reinduction of arthritis; c. Leu-Enk did not affect adjuvant arthritis in Wistar rats. These data suggest that modulation of immune responses by opioids may significantly vary among responders. (This work was supported by the Ministry of Science and Technology, of the Republic of Serbia).

49.06 EXPRESSION AND PURIFICATION OF WILD-TYPE AND SER41 B-50/GAP-43 MUTANTS IN ESCHERICHIA COLI

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In order to gain more insight into the biochemical and physiological properties of B-50, we employed a bacterial expression system to produce large quantities of wild-type B-50 and its two PKC phosphorylation site mutants B-50^{Ala41} (non-phosphorylated form) and B-50^{Asp41} (mimicking the phosphorylated form).

B-50 and its mutants (Nielander et al., J. Neurochem. 55, 1442, 1990) were cloned in frame in the IPTG sensitive pQE30 expression vector (Qiagen) using PCR. The cloned products were sequenced for PCR artifacts. The use of this vector adds 6xHis tag to the N-terminus of the protein enabling purification of the recombinant product by Ni^{2+}-affinity chromatography. Induction of recombinant B-50 synthesis in the bacteria by IPTG prevented cell division. Bacteria expressing an out of reading frame B-50 cDNA did not show this inhibition of growth, indicating that B-50 is toxic to the cells.

His-tagged recombinant products were bound to a Ni^{2+}-NTA-resin, washed with 20 mM imidazole and collected from 500 mM imidazole eluates. On Western Blot these purified products showed one clear B-50 immunoreactive band of the expected size and some minor bands.

The purified preparations were further identified by electron spraying mass spectrometry. The measured molecular mass of the recombinant wtB-50 was 25344.6, the B-50^{Ala41} 25323.8 and B-50^{Asp41} 25410, closely corresponding to the theoretical MWs based on the masses of the individual aminoacid residues (Errors: wtB-50 0.04%, B-50^{Ala41} 0.06%, B-50^{Asp41} 0.05%).

49.07 GLUTAMATE INDUCES CALCIUM-UNCOUPLING OF NEURONAL MITOCHONDRIA: PROTECTION BY PYRUVATE AND MALATE. R. Pereira, F. Ruiz, M. Villalba, G. Alvarez, E. Bogónez* and J. Satrústegui. Departamento de Biologia Molecular. Centro de Biología Molecular "Severo Ochoa". C.S.I.C. - Universidad Autónoma de Madrid. Cantoblanco. 28049-Madrid. SPAIN.

One of the immediate events linked to Ca^{2+} influx via NMDA receptors in hippocampal neurons is a Ca^{2+}-dependent acidification (Hartley and Dubinsky, *J. Neurosci.* 13, 1993, 4690-4699; Irwin et al, *J. Neurosci.* 14, 1994, 1352-1357; Wang et al. *J. Neurophystol.* 72,1994, 2563-2569). This acidification does not result from H^+ influx, but rather from an intracellular H^+ source. We have investigated the nature of this process in hippocampal and cerebral cortex neurons (9-11 DIV) and have found that glutamate-induced acidification is inhibited by rotenone, unaffected by oligomycin and mimicked by the uncoupler FCCP (plus oligomycin, F/O), indicating that it results from Ca^{2+}-uncoupling of mitochondria, a process in which H^+ efflux is coupled to Ca^{2+} uptake rather than ATP synthesis. This is supported by the fact that, following exposure to glutamate, the uncoupling effects of F/O (as manifested in a pH drop), largely disappear. Pyruvate and malate (P/M) increase the contribution of neuronal mitochondria to calcium homeostasis in hippocampal and cerebral cortex cells (Villalba et al. *J. Biol. Chem.* 269, 1994, 2468-2476). We have found that the addition of P/M protects hippocampal and cerebral cortex neurons against excitotoxicity induced by 30 min exposure to 100 M glutamate. Moreover, $[Ca^{2+}]_i$ levels during and after glutamate exposure were reduced when neurons were incubated in the presence of P/M. Interestingly, when P/M were added shortly before (5 min) or even together with glutamate, the resulting pH drop was decreased and a subsequent challenge with F/O was now manifested in a substantial acidification. These results suggests that pyruvate plus malate protect hippocampal and cerebral cortex neurons against glutamate excitotoxicity at least in part by attenuating Ca^{2+}-uncoupling of mitochondria, an initial step in the cascade of events triggered by glutamate.

49.08 CELL PROLIFERATION AND APOPTOSIS IN THE POST-NATAL CEREBELLAR CORTEX OF THE RABBIT. L. Lossi, M. Piccinini, S.Ghidella, L. Bonfanti* and A. Merighi. Dipartimento di Morfofisiologia Veterinaria, Via Nizza 52, I-10126 Torino, Italy

In early post-natal life, cell proliferation is known to occur in the cerebellar cortex, where differentiation of granule cells takes place from the external granular layer (EGL) which appears during late embryonic development and persists for about 3-4 weeks after birth (Altman, 1972, *J.Comp.Neurol.* 145:353). It is well known that the number of granule cells is regulated to match the established number of Purkinje cells and that a massive loss of granule cells occurs during the third to fifth post-natal week in mice and rats, with the formation of synapses between the parallel fibers and the dendrites of the Purkinje neurons. However, it was recently reported that in the mouse, granule cells undergo massive programmed cell death (apoptosis) at earlier post-natal stages (Wood et al., 1993, *Neuron*, 11:621). We report here our results on cell proliferation and apoptosis in the post-natal cerebellar cortex of the rabbit. Post-natal rabbits (from P0 to P60) were injected intraperitoneally with bromo-deoxyuridine (BrdU) to label proliferating cells and killed 60 minutes after. For each animal, one half of the cerebellum was used for genomic DNA extraction and analysis, while the second half was processed for the immunocytochemical detection of the BrdU-labelled nuclei and for the *in situ* visualisation of fragmented nuclear DNA, a biochemical hallmark of apoptotic cells. After injection of BrdU, labelled nuclei were visualised mainly in the EGL. Fewer positive nuclei vere dectected also in the molecular and inner granular layer (IGL). Proliferation reached its maximum at P5. Nuclei containing fragmented DNA were detected in the EGL and IGL and peaked at P5-P10. Analysis of genomic DNA following agarose gel electrophoresis confirmed that DNA fragmentation to nuclosome-sized oligomers was not detectable at P0, become visible at P5-P10 and was reduced at P15. The temporal relationship between BrdU incorporation and DNA fragmentation was further investigated by Southern blotting experiments. Our results indicate that apoptosis occurs prior to the establishment of synaptic contacts with the Purkinje neurons and may help to tailor the granule cell number together with different mechanisms of cell death taking place at later developmental stages.

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49.09 GLIOCYTE-LYMPHOCYTE INTERACTIONS: AN IN VITRO MODEL. P. Bongioanni*, C. Fioretti, F. Gemignani, F. Lombardo. Scuola Superiore di Studi Universitari e di Perfezionamento Sant'Anna, Pisa, Italy.

A relatively new role for gliocytes concerns their ability to serve as immunocompetent cells within the central nervous system (CNS). Gliocytes have been shown to internalize, process, and present soluble antigens (Ag_s) to T lymphocytes. In search for better understanding the relationships between human gliocytes and lymphocytes, the *in vitro* effects on their own biological and biochemical mechanisms resulting from their mutual interactions have been studied, by using co-culture techniques, and determining some biochemical and immunological parameters. Primary glial cell cultures were established from human neurosurgical specimens: by using an indirect immunofluorescence technique, the percentage of cultured glial fibrillary acidic protein $(GFAP)^+$ cells (i.e. gliocytes) was evaluated. Lymphocyte cultures were prepared from multiple sclerosis (MS) or myasthenia gravis (MG) patients, and from healthy controls. Following a 48 h-incubation, the cell number was counted, glial class II major histocompatibility complex (MHC) Ag, and neural cell adhesion molecule (N-CAM) expression, interferon (IFN)-γ and tumor necrosis factor (TNF)-α receptor binding were evaluated in gliocyte and lymphocyte cultures, separately. Then, after an additional 24 h-incubation of both cell types together (co-cultures) or separately (control cultures), the same biological parameters were re-evaluated. The amounts of several cytokines (interleukin (IL)-1α, IL-2, IL-6, IFN-γ and TNF-α) in cell culture supernatants were determined after both the first 48h-incubation and the additional 24h-incubation. Our findings of remarkably increased receptor density and enhanced cytokine production in the case of gliocytes co-cultured with lymphocytes from MS patients (as compared to glial cells co-cultured with lymphocytes from MG patients or healthy controls, or cultured alone) point out the existence of mutual interactions between gliocytes and lymphocytes, at least *in vitro*, particularly in those neuro-immunological diseases involving the CNS.

49.10 MAINTENANCE OF NEURONAL HOMEOSTASIS: THE ROLE OF ANION EXCHANGE PROTEINS IN REGULATION OF INTRACELLULAR pH. G.J.C.G.M. Bosman*, C.H. Vollaard and W.J. De Grip. Department of Biochemistry (Fac. Med.), University of Nijmegen, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands.

At least three members of the anion exchanger (AE) gene family are present in human neurons, as revealed by RNA, immunohistochemical, and immunoblotting analysis. The AE expression level increases during development and aging, and in degenerative neurons in brain areas affected by Alzheimer's disease. The exact nature of these changes is not clear, but resembles the age-related breakdown of AE1 in erythrocytes. As in erythrocytes, aging- or degeneration-related breakdown of AE proteins probably also affects anion transport in neurons. In order to establish the possible effects of AE breakdown on neuronal function, we determined expression and function of AE proteins in various neuroblastoma cell lines. Analysis of RNA, as well as immuno(histo)chemical analysis, showed that AE1 and AE2 are expressed by neuronal cells. Measurement of intracellular pH with a fluorescent probe revealed that anion (chloride/bicarbonate) exchange is the major mechanism by which intracellular pH is regulated. Dysfunction of AE proteins may thus profoundly disturb neuronal homeostasis.

49.11 QUANTITATION OF CYTOKINE mRNA EXPRESSION IN PERIPHERAL NERVE BY SEMIQUANTITATIVE COMPETITIVE REVERSE-TRANSCRIPTION PCR. O. Bourde*, R. Kiefer, H.-P. Hartung and K.V. Tovka, Dept. of Neurology, Univ. of Würzburg, Würzburg, Germany

Cytokines may be critically involved in regulating cellular interactions in the diseased peripheral nervous system. The quantitation of specific mRNA species is complicated by low abundancy of cytokine mRNA's and low amounts of total RNA within the peripheral nerve. We have applied and modified a highly sensitive semiquantitative PCR method for the quantification of IL-6 mRNA in the rat and human peripheral nervous system. For quantification, a synthetic sense RNA containing either human or rat IL-6 PCR primer sequences was used (Bouaboula et al., J.Biol.Chem. 267:21830, 1992), allowing the distinction between PCR products from natural IL-6 mRNA and synthetic RNA by their different length. Both the rat and human synthetic sequence, originally used as competitive templates during PCR, could also internally calibrate the preceding steps of RNA extraction and reverse transcription. Thus, natural mRNA and synthetic standard RNA were proportionally co-extracted, co-reverse transcribed and co-amplified by PCR. PCR products were analysed by radioactive Southern blot hybridization and densitometry of autoradiography bands, thus greatly improving the sensitivity. Applied to the rat peripheral nerve, the method allows the detection of very low amounts of IL-6 mRNA already in normal nerves. Following rat sciatic nerve transection, preliminary results suggest an early and strong upregulation of IL-6 mRNA both in the proximal and distal nerve stump already 12 hours after transection. Prompted by preliminary results also in human nerves, suggesting a differential expression of IL-6 mRNA in inflammatory and non-inflammatory neuropathies, the method will also be useful to study cytokine expression in pathologic tissue specimens from human sural nerve biopsies.

49.12 HETEROGENEITY OF THE EXTRACELLULAR SPACE REVEALED BY LECTIN CYTOCHEMISTRY IN THE RAT BRAIN: LIGHT AND ELECTRON MICROSCOPIC STUDIES. G. Brückner*, K. Brauer, W. Härtig, J. Kacza, J. Seeger and K. Welt. University of Leipzig, Paul Flechsig Institute for Brain Research, Jahnallee 59, D-04109 Leipzig, and Institute for Anatomy, Liebigstr. 13, D-04103 Leipzig, FRG

The neuronal microenvironment as a communication channel may be determined substantially by extracellular matrix proteoglycans influencing the functional properties of the neuron-glia interface. The present study was focused on 'perineuronal nets' to characterize the heterogeneity of extracellular matrix zones in several brain regions. Proteoglycan components were detected in neocortex, cerebellar nuclei, medial septum, reticular thalamic nucleus and piriform cortex using the N-acetylgalactosamine-binding plant lectin *Wisteria floribunda* agglutinin (WFA). Lectin-binding material was visualized by peroxidase cytochemistry directly or after photoconversion in dilated extracellular spaces around neuronal somata and dendrites, axon initial segments and unmyelinated axonal bundles. The labelled areas in perineuronal nets varied in shape and size, being very large in cerebellar nuclei and some of the cortical non-pyramidal neurons. They were distinct, but smaller in the septal region and rather slender in the thalamic reticular nucleus. By semiautomatic quantitative evaluation the extent of extracellular spaces was defined in the neocortex. The WFA-labelled extracellular compartments were found to be significantly larger than unlabelled extracellular spaces. These findings suggest that the volume of the extracellular space in the brain is extremely different and corresponds with molecular properties of the extracellular matrix. The specialized extracellular microenvironment may provide a high ion buffering capacity mainly for neurons involved in rhythmogenesis and/or motor functions. (Supported by the Deutsche Forschungsgemeinschaft, Br 1208/2-2)

49.13 TRANSCRIPTIONAL CONTROL OF THE HUMAN PRODYNORPHIN GENE BY CREM PROTEINS. Carrión, A. M*., Mellström, B., and Naranjo, J.R. Instituto Cajal, 28002 Madrid, Spain.

The expression of the rat prodynorphin gene is finely controlled by at least five regulatory sites located in its promoter. We have studied the regulation of the human prodynorphin gene in NB69 cells, a human neuroblastoma, that express prodynorphin gene in basal condition and can be induced with forskolin. In this system, we characterized the prodynorphin transcriptional start site by primer extension analysis. Furthermore, using transient transfection we identified a fragment of human prodynorphin promotor, which subcloned in a reporter plasmid, had all the regulatory signals necessary for basal and inducible expression. Band shift gels showed the existence of four AP1/CRE elements, three in the distal region and one in the proximal region with respect to the cap site, and one AP1 element close to transcriptional start site. Point mutations and deletion analysis of the human prodynorphin promoter indicates that: a) the absence of each regulatory element modifies the basal expression of the reporter construct; and b) the minimal inducible promoter includes the AP1/CRE element downstream from the cap site. Transactivation experiments with several transcription factors and the minimal inducible promoter, suggests that αCREM is implicated in the activation of the human prodynorphin gene.

We conclude that all the cis regulatory elements participate in transcription of the prodynorphin gene in basal conditions, while the proximal AP1/CRE element is sufficient for the induction by forskolin or α-CREM in the NB69 neuronal cell line.

Work was supported by grant DGICYT PM92/0018.

49.14 TPA PRE-TREATMENT REDUCES APOPTOTIC CELL DEATH INDUCED BY CISPLATIN (CDDP) EXPOSURE IN SH-SY5Y HUMAN NEUROBLASTOMA CELL LINE.

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Growth, differentiation and death are controlled by a complex series of steps in signal transduction pathways which can greatly overlap. To study the relation between neuronal cell differentiation and apoptosis, we treated SH-SY5Y cells with TPA (16 nM), with CDDP (2 μg/ml) alone, and with both drugs in combination. Pre-treatment with TPA induced a reduction in cell proliferation rate and neuronal differentiation of the SH-SY5Y cells. CDDP alone induced dose-related cell death, measured by the release of LDH and the MTT method, morphologically characterized by apoptotic changes and electrophoretically by DNA fragmentation. Treatment of TPA-differentiated SH-SY5Y cells with CDDP resulted in a marked reduction of apoptosis. Concomitant treatment of SH-SY5Y cells with TPA and PKC inhibitors, as staurosporine (20 nM) or H7 (50 μM), determined an increasing in cell death after exposure to CDDP, respect to those pre-treated with TPA alone. These findings suggest that PKC activation is an important step in neuronal differentiation and also partly inhibits apoptosis.

49.15 EXPOSURE TO ELECTRIC STRESS DIFFERENTIALLY AFFECTS PRIMARY AND SECONDARY HUMORAL IMMUNE RESPONSE TO BOVINE SERUM ALBUMINE (BSA)

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The aim of this study was to investigate the effects of inescapable intermittent electric stress on primary and secondary antibody responses to BSA in 8-week old male Wistar rats. Stressed animals (ES, n=20) received 80 unpredictable tail shocks (intensity 1 mA, duration 5s, intervals between shocks 5-120s) during 80-90 minutes. Control rats (C, n=20) were handled in an identical manner but recieved no shock. The first electric shock was applied 1 hour before intraperitoneal (i.p.) immunization with BSA (1 mg/0.5 ml of saline/rat) and then for four consecutive days. Half of the rats from the ES (n=10) and C (n=10) groups were exposed to electric stress 43 days later, 1 hour before secondary immunization with the same dose of BSA, and then for two consecutive days. So, during secondary immunizations four groups were formed: ES-ES, ES-C, C-ES and C-C. Animals were bled on days 7, 16, 46, 51 and 63 by cardiac puncture under ether anesthesia. Anti-BSA antibody levels in rats subjected to electric stress during primary immunization were significantly suppressed in comparison to control animals. After secondary immunization, the suppressive effect of stress was recorded only in rats that experienced stress during primary immune response, i.e. in ES-C and ES-ES groups. Humoral immune response in rats subjected to stress only during secondary immunization (C-ES) did not differ from controls (C-C). These results suggest that the prolonged suppressive effects of stress may be due to alterations of immunological memory. (This work was supported by the Ministry of Science and Technology of the Republic of Serbia).

49.16 ASSYMETRIC DISTRIBUTION OF BRAIN MONOAMINES AND IMMUNE REACTIVITY IN LEFT- AND RIGHT-BIASED RATS AFTER REGIONAL BRAIN ABLATIONS

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We report here that assymetrical modulation of immune reactions in male Wistar rats (200-250 g) is associated with rotational bias and region of cerebral cortex. Rats assigned as left- and right-rotators in cylindrical Plexiglass rotometer were subjected to the ablation of ipsilateral frontal (FC), parietal (PC) and occipital (OC) cortex. Intact (IC) and sham-lesioned (ShL) rats served as controls. Two weeks after the operation all rats were immunized with bovine serum albumin (BSA) in complete Freund's adjuvant. Hypersensitivity skin reactions and antibody production to BSA 14 and 21 days after the immunization were compared between left- and right-biased rats. Also, biogenic amine distribution was analysed in cerebral neocortex, hippocampus, hypothalamus as well as in thymus and spleen and compared between left- and right-biased rats. Left-biased IC, ShL and OC rats showed more intense Arthus and delayed hypersensitivity skin reactions and antibody production to BSA in comparison with their right-biased counterparts, both on day 14 and 21 after the immunization. FC ablation decreased immune reactivity to BSA in left- and increased in right-biased rats. Also, the results showed that assymetrical monoaminergic concentrations exist in the rat brain, and that regional brain ablations in the left- and right-biased rats caused marked changes in norepinephrine, dopamine and serotonin levels in different brain areas. (Supported by Ministry of Sciences and Technology of Serbia.)

49.17 CULTURED HIPPOCAMPAL NEURONS MAY SECRETE A COMPOUND INHIBITING PHA-INDUCED LYMPH CELLS PROLIFERATION.

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We report preliminary data strongly suggesting that cultured hippocampal neurons secrete a compound that inhibits phytohemoagglutinin (PHA) - induced proliferation of periferal blood mononuclear cells (PBMC). Rat hippocampal neurons were cultured in vitro, and their culture medium was collected after 4 to 14 days in vitro (DIV). Rat PBMC' s were stimulated with PHA. Coincubation with neuronal culture medium significantly decreased PHA - induced proliferation ($p = 0.0091$ Wilcoxon test). In the absence of PHA stimulation, no significant differences were found between proliferation with and without culture medium ($p = 1$). Moreover, when culture medium was obtained from cultures subjected to 24-hours anoxia it no longer had any effect on PHA - induced proliferation ($p = 0.919$). Also pure culture medium (i.e., in which no neurons had been cultivated) equally had no effect, thus ruling out an aspecific effect of culture medium itself. The degree of inhibition of PHA- induced proliferation was inversely proportional to culture age. The data suggest that central neurons may secrete a compound acting as a PHA - antagonist whose possible role could be protection against PBMC - mediated immunological reaction. Whatever the mechanism of action, the responsible compound is lost or inactivated after neuronal anoxia. It is more evident in younger than in older cultures, perhaps indicating a generally decreased ability of older neurons to protect themselves.

49.18 **DIFFERENTIAL EXPRESSION AND LOCALIZATION OF STATHMIN AND SCG10 IN THE CHICK EMBRYONIC RETINA.**

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To identify genes involved in the process of neuronal selection, we used differential DNA-DNA competitive hybridization during specific developmental stages. We have cloned 55 partial cDNAs of genes expressed in the chick retina during synapse formation and developmental cell death. One of the subtracted clones encoded the phosphoprotein stathmin. Subsequent cloning of its neuronal homologue SCG10 was performed. Northern blot analysis revealed that both transcripts were developmentally regulated and transiently induced during neuronal selection in embryonic retina. Then, we found that their expression was regulated by electrical activity in the visual pathway. In situ hybridization indicated that both mRNAs were mainly expressed in ganglion and amacrine cells, which is consistent with the protein localization revealed in immunocytochemistry experiments using specific antibodies. Finally, immuno-fluorescent stainings showed a differential localization of both proteins in primary retinal cells in vitro: while stathmin was expressed in cell body and in the proximal part of processes, SCG10 was localized mainly to the Golgi complex and the growth cones of developing neurons. These data suggest a differential role for stathmin and SCG10 in the development of specific neuronal cell types in the chick embryonic retina.

49.19 **HYPOTHALAMIC REGULATION OF PRO-OPIOMELANOCORTIN BIOSYNTHESIS IN THE INTERMEDIATE PITUITARY OF THE AMPHIBIAN *XENOPUS LAEVIS***

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In the South-African clawed toad *Xenopus laevis*, background adaptation is regulated by α-MSH, a POMC-derived peptide. After transfer of the animal from a black to a white background, secretion of α-MSH from the intermediate pituitary lobe is inhibited by the hypothalamic neurotransmitters NPY, dopamine and GABA. To study a possible coördination between the regulation of α-MSH secretion and the regulation of expression of its precursor protein, the rate of POMC biosynthesis was determined by radioactive amino acid incorporation after *in vitro* treatment of the neurointermediate pituitary with NPY, apomorphine (dopamine D_2-receptor agonist), baclofen ($GABA_B$-receptor agonist) and isoguvacine ($GABA_A$-receptor agonist). An almost complete inhibition of POMC biosynthesis was observed after 24 hours of NPY or apomorphine treatment, while baclofen and isoguvacine gave a maximal inhibition of 34% and 52% respectively after 3 days of treatment. Superfusion experiments analysing α-MSH secretion showed that prolonged treatment with the GABA-receptor agonists results into desensitisation of the GABAergic mechanisms. These observations suggest differential actions of the secreto-inhibitors on POMC biosynthesis in the *Xenopus* intermediate pituitary, indicating a major role for dopamine and NPY while the GABAergic mechanisms have no longterm function in this process.

49.20 α-TRINOSITOL REDUCES APOPTOSIS IN NEURONS AND GLIAL CELLS OF CULTURED, ADULT MOUSE SUPERIOR CERVICAL GANGLIA.

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Apoptosis in various tissues is revealed by the presence of DNA-breaks, which can be studied on histological sections with an in situ nick-labelling method, using terminal deoxynucleotidyl transferase and biotinylated dUTP. When superior cervical ganglia (SCG) from the adult mouse are cultured, several neurons and adjacent satellite cells can be shown by this method to undergo apoptotic changes within 24 h in serum-free medium. The factors eliciting the apoptosis are not known but may include abrupt loss of target derived survival factors or transient anoxia.

The myo-inositol phosphate analogue α-trinositol (D-myo-inositol-1,2,6-triphosphate) has been shown to possess certain pharmacological attributes, for instance anti-inflammatory properties. Furthermore, specific inositol phosphate binding sites have been detected in several organs, including brain tissue. In the present study α-trinositol at various concentrations was tested for effects on SCG apoptosis. After culturing of SCG for 48 h with 20 μM α-trinositol there was a marked decrease in the number of apoptotic neurons as compared to paired control cultures (ratio α-trinositol / control: 0.45±0.14, mean ±SEM, n=3, $p<0.05$). A similar reduction was seen in satellite cell apoptosis.

Although its mechanisms of action are not clarified, α-trinositol has been suggested to interfere with endogenous inositol phosphates to affect calcium fluxes. Calcium is important for the apoptotic reaction and the use of calcium-free medium has been shown to prevent apoptotis in cultured, adult mouse peripheral ganglia. Therefore, inhibition of apoptosis by α-trinositol might have been brought about by interference with calcium fluxes in both neurons and satellite cells of the SCG.

49.21 HYPERACTIVITY OF CORTICOTROPIN-RELEASING HORMONE (CRH) NEURONS IN MULTIPLE SCLEROSIS (MS) PATIENTS.

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Studies on the experimental allergic encephalomyelitis (EAE), an animal model for MS, showed that the hypothalamus-pituitary-adrenal (HPA)-axis is involved in the susceptibility for and recovery from the disease. Both in EAE and MS, corticosteroid administration quells the symptoms of the acute relapse. Endocrine studies indicate that the HPA-axis is hyperactive in MS, as appears from the elevated plasma cortisol and ACTH levels, enlarged adrenal and increased hypothalamic CRH cell numbers in this disease. In the present study, we determined the degree of activation of the CRH cells in the paraventricular nucleus (PVN) of hypothalamus in MS patients in comparison with controls, using a double staining immunocytochemical procedure on postmortem material. AVP co-expression is increased in the CRH neurons when HPA-axis is hyperactive. We determined the number of CRH cell profiles and the proportion of CRH cells co-localising vasopressin (AVP) as measures for activation. The 3 fold increased number of CRH cells and the 4.5 fold increased proportion of CRH cells co-localising AVP showed that there was indeed an hyperactivation of CRH neurons in MS. We also showed for the first time the strong negative feedback effect of high peripheral corticosteroid levels on the hypothalamic CRH cells since this caused both AVP co-localising and non-co-localising CRH cells to disappear. (Brain material was obtained from the Netherlands Brain Bank. This study was supported by the Foundation Friends of MS Research grants # 92-111 and # 94-188).

49.22 FRAMESHIFT MUTATIONS AT HOTSPOTS IN VASOPRESSIN TRANSCRIPTS IN RAT AND HUMAN POSTMITOTIC NEURONS.

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Mutations in DNA underlie carcinogenesis, inherited pathology and aging and are generally thought to be introduced during meiosis and mitosis. Here we report that in post-mitotic neurons specific frameshift mutations occur at high frequency (in the order of 10^{-2} to 10^{-3} as compared to 10^{-4} to 10^{-6} per gene in somatic cells). These mutations were identified in vasopressin (VP) transcripts in magnocellular neurons of the VP-deficient homozygous Brattleboro rat and predominantly consist of a GA deletion at GAGAG-motifs. In homozygous Brattleboro rats substituted with VP for 40 weeks and displaying a normalized water balance a 25% reduction in the number of VP cells displaying a GA deletion was found. This indicates that the diseased state of the Brattleboro rat, resulting in a permanent activation of VP neurons, enhanced the mutational rate. Using antibodies against peptides predicted from the +1 reading frame of VP mRNA, immunocytochemical evidence was obtained for similar events in the hypothalamus of wild-type rats and human. These data have revealed hitherto unrecognized somatic mutations in non-dividing neurons. Such mutations are not restricted to the VP gene and may occur more widely in neuronal systems affecting other neuronal genes.

49.23 INTRACELLULAR pH (pH_i) REGULATION IN CULTURED MICROGLIAL CELLS FROM MOUSE BRAIN

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Microglia, the resident macrophages of the CNS are activated by any injury or pathologic event. The signal cascade controlling the multi-step activation from the resting to the fully activated form are at present unknown. pH could interfere with such as cascade twofold: firstly, extracellular pH changes are observed in many pathologic events including ischemic insults; secondly, intracellular pH changes might be part of a signal cascade.We therefore set out to study basic mechanisms by which intracellular pH is controlled or affected in microglial cells from embryonic mouse brain using the pH-sensitive fluorescent dye BCECF-AM. We used a classical approach to acidify cells by a pulse of NH_4^+ (4-5 min; 20 mM) and studied the subsequent pH_i recovery. In HCO_3^--free saline, pH regulation was dependent on extracellular [Na^+] and sensitive to amiloride indicating the involvement of the Na^+/H^+ exchanger. In HCO_3^- - containing solution amiloride slightly slowed but did not block pH_i recovery; in Na^+-free saline, however, the recovery was completely blocked. The involvement of a Na^+ -dependent Cl^-/HCO_3^- exchanger was infered from the observation that removal of Cl^- or application of 1 mM furosemide decreased the recovery rate. The recovery (in the presence of HCO_3^-) was completly blocked in the presence of 1 mM DIDS suggesting the additional presence of a Na^+/ HCO_3^- exchanger. We conclude that microglial cells express a distinct set of pH regulatory carriers which act in concert for pH_i homeostasis.

49.24 NITROARGININE ATTENUATES AMMONIA TOXICITY AND AMMONIA-INDUCED ALTERATIONS IN BRAIN METABOLISM.

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We propose that acute ammonia toxicity is mediated by activation of NMDA receptors. MK-801, a selective antagonist of these receptors, prevents ammonia-induced depletion of ATP and death of animals. It seems therefore that, following activation of NMDA receptors, the subsequent events in ammonia toxicity should be similar to those involved in glutamate neurotoxicity. Inhibitors of nitric oxide synthase, e.g. nitro-arginine (NArg), prevent glutamate toxicity. We therefore tested whether NArg prevents ammonia toxicity and ammonia-induced alterations in brain energy metabolism. NArg prevents partially (≈ 50%) death of mice induced by acute ammonia intoxication. NArg also prevents partially ammonia-induced depletion of brain ATP. It also prevents completely the rise in glucose and pyruvate and partially that in lactate. This indicates that NArg attenuates acute ammonia toxicity and ammonia-induced alterations in brain energy metabolites.

49.25 **A RELIABLE METHOD FOR GOLGI STAINING OF RETINA AND BRAIN SLICES.**

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Although the Golgi method is generally considered to be one of the most unpredictable neurohistological techniques, we have recently shown that the quality of the results depends on the levels of hexavalent (Cr^{VI}) and trivalent (Cr^{III}) Chromium that are achieved in the tissue during chromation. This levels could be accurately predicted by the pH increase of the chromation fluid (J. Histochem. Cytochem. 42, 393-403, 1994). Moreover the formation of an adequate Golgi precipitate depends on the diffusion of the chromation fluid and silver nitrate solution into the tissue. This fact could explain why Golgi staining renders poor results when performed in tissue sections.

In the present study we evaluate the ability of our approach to obtain reproducible results of Golgi impregnation in aldehyde-fixed retina and brain slices. These specimens have been selected because of the well known difficulty to achieve good quality of Golgi staining. Rabbit retinas and brain slices from rat were stained with different Golgi-aldehyde techniques. In all cases, the temperature was held at 10 °C throughout the procedure, and we used the pH as criterion for the endpoint of the chromation process. Our results showed that pH could be considered a reliable criterion to predict the quality of neuronal impregnation, although each formula reach the best impregnation at different pH.

49.26 **THE EFFECTS OF HALOPERIDOL, CHLORPROMAZINE AND CLOZAPINE, AND THEIR INTERACTIONS WITH d-AMPHETAMINE ON SCHEDULE-CONTROLLED AND SCHDULE-INDUCED BEHAVIOUR**

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Food deprived rats develop excesive drinking when they are exposed to an intermittent food schedule. This behaviour has been termed schedule-induced polydipsia (SIP). It has been proposed that SIP is a member of the class adjunctive behaviours. It is know that d-amphetamine increases operant behaviour at the same doses that decreases SIP. The purpose of this study was to investigate the pharmacological mechanisms of the effects of d-amphetamine on SIP and on lever pressing. Eigth male Wistar rats were used. Food was delivered in the operant boxes according to a Fixed-Time Fixed-Interval 30 s schedule. When all rats developed SIP, d-amphetamine (0.1-3.0 mg/kg), haloperidol (0.01-3.0 mg/kg), chlorpromazine (0.03-5.6 mg/kg), clozapine (1.0-10.0 mg/kg), and the combinations of d-amphetamine with doses of the antagonists were administered. There were two randomised sequences of doses for each drug and for each combination. During combinations studies antagonists were given 30 min and d-amphetamine 10 min before testing. The four substances, dose-dependently decreased SIP and operant behaviour. Haloperidol (0.03-0.1 mg/kg) shifted to the rigth the dose-dependent curve of d-amphetamine on operant behaviour. On the other hand, haloperidol (0.03-0.1 mg/kg) had no effect on the dose-dependent curve of d-amphetamine on SIP. The effects of clozapine (1.0-3.0 mg/kg) were similar to haloperidol. However, chlorpromazine (0.03-0.3 mg/kg) shifted to the right the dose-dependent curve of d-amphetamine on SIP and operant behaviour. The present results will be discussed in relation to the receptors involved in the effects of d-amphetamine on both kinds of behaviours.

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49.27 MBP GENE EXPRESSION AND MYELIN COMPACTION IN MATURE OLIGODENDROCYTES ARE ALTERED BY bFGF **IN VITRO**

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Almost pure oligodendrocyte (OL) cultures, containing at least 90 ± 5 % of mature (MBP+) OL, were obtained by cytosine arabinoside (ARA-C) treatment of cells derived from 40 -day-old mixed cultures from newborn rat brain (1) After withdrawal of ARA-C, treatment of the cells with bFGF for3days tended to reverse at least part of the mature OL population back to less mature traits. This was characterized by : (i) a drastic decrease in MBP mRNA level ; (ii) a pronounced decrease of the percentage of cells immunolabelled with anti-MBP (50 %), anti-MOG (50 %) or anti-PLP (40 %) antibodies ; and (iii) a loss of compaction of myelin-like membranes synthesized in vitro. These results point out to a previously unsuspected plasticity of mature OL, and suggest that if bFGF is secreted in vivo after a demyelinating lesion, it will allow remyelination to complete only after this factor has returned to low levels.

(1) Fressinaud et al. (1993). Dev. Biol. 158 : 317-329

49.28 HYPOGLYCEMIA-EVOKED IMMEDIATE EARLY GENE EXPRESSION IN NEURONS AND GLIA OF THE HIPPOCAMPUS: NOVEL PATTERNS OF FOS, JUN AND KROX INDUCTION IN EXCITOTOXIC INJURY.

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In the hippocampus, there is a graded vulnerability of different neuronal subpopulations to undergo hypoglycemia-induced degeneration. We investigated if the induction of immediate early gene (IEG) encoded transcription factors after hypoglycemia reflects the different grades of neuronal vulnerability. The expression profile of 7 IEG-encoded proteins was studied in the rat hippocampus after severe insulin-induced hypoglycemia with 30 min of EEG isoelectricity and various survival periods for up to 42 h. Immunocytochemistry was performed using specific antisera for c-FOS, FOS B, c-JUN, JUN B, JUN D, KROX-24 and KROX-20. To define the type of glial cells with IEG induction, co-expression of c-FOS and glial marker proteins (GFAP, OX-42) was studied by confocal laser scanning microscopy. Up to 3 h after glucose replenishment, differential temporospatial induction of IEG-encoded proteins of the *fos*, *jun* and *Krox* families was observed in moderately injured neuronal subpopulations including the majority of dentate granule cells and CA3 neurons. At later timepoints, however, a delayed and persistent c-JUN expression was found in severely but reversibly injured CA1 neurons. Similar to experimental models of central and peripheral axotomy, selective c-JUN induction in these neurons most likely reflects an initial event in the regeneration process of sublethally injured neurons. In contrast to other models of excitotoxic injury such as ischemia and epilepsy, a marked IEG expression was also observed in astrocytes as assessed by confocal laser scanning microscopy.

49.29 ROLE OF VAGAL AFFERENTS IN ENDOTOXIN-INDUCED ACTIVATION OF THE HYPOTHALAMUS-PITUITARY-ADRENOCORTICAL AXIS AND FOS EXPRESSION IN THE RAT BRAIN

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Systemic administration of bacterial endotoxin causes activation of accesory immune cells and induces brain-mediated adaptive responses described as non-specific sickness symptoms. Among these, an activation of the hypothalamus-pituitary-adrenocortical (HPA) system occurs. It has been questioned as to whether the immune system-to-brain communication runs through a humoral or neuronal pathway. In order to elucidate the role of vagal afferents in the activation of the HPA system, we studied the effects of subdiaphragmatic vagotomy on ACTH and corticosterone responses in the rat after endotoxin administration. Fos induction in the neuroendocrine and autonomic centers of the brain was also assessed. Rats received either sham operation, complete transection of the subdiaphragmatic vagal nerve (SDVAGX), or transection of the hepatic branch only (HPVAGX). After two weeks of recovery, endotoxin or vehicle was injected i.p. (20 and 250 μg/kg). Blood (for hormone assays) and brains (for Fos immunocytochemistry) were collected after decapitation two hours later. Subdiaphragmatic vagotomy, but not hepatic branch transection alone, blocked and attenuated the ACTH response after administration of 20 and 250 μg/kg endotoxin, respectively. Paradoxally, the corticosterone response to either dose of endotoxin was unaffacted by vagotomy. The endotoxin-induced Fos immunoreactivity in CRH-containing neurons of the paraventricular nucleus of the hypothalamus was concomitantly suppressed in SDVAGX animals. These findings suggest that the functional activation of the CRH neurosecretory cells and the ACTH response to a low dose of endotoxin is completely mediated through vagal afferents. The responses to high dose of endotoxin appear to involve additional neuronal or humoral pathways yet to be elucidated.

49.30 IMMUNOPATHOGENESIS OF BRAIN ATROPHY IN BORNA DISEASE.

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Borna disease (BD) is a virus-induced meningoencephalitis with marked pathology in the limbic system and the cerebral cortex. Borna disease virus (BDV) is a highly neurotropic nonsegmented negative-strand RNA virus that occurs in a variety of species from birds to primates and probably in man. BD can vary from subclinical disease to severe disturbances of movement and behavior. Severe inflammatory reactions cause tissue destruction and cortical brain atrophy leading to chronic debility and cachexia. After experimental infection of the rat, intraparenchymal $CD8^+$ T cells, MHC class I antigens on BDV-infected neurons and numerous nerve cell lesions were present. A field-induction of microglia was paralleled by a dramatic increase of tumor necrosis factor (TNF α & β), and interferon-γ (IFN-γ) located on inflammatory cells and brain cells, as well as by high activities of superoxide dismutase (SOD) as an indicator for the presence of free radicals. Since BDV has no acute cytopathic effects, we provide evidence that the presence of $CD8^+$ T cells within the brain parenchyma, the expression of MHC class I antigens on neurons and the production of toxic immune-mediators play a major role for immunopathological brain tissue destruction.

49.31 GM-CSF STIMULATES IN VITRO PROLIFERATION OF ASTROCYTES DERIVED FROM SIMIAN MATURE BRAINS.

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In the brain, granulocyte-macrophage colony stimulating factor (GM-CSF) may be released by infiltrated cells of the immune system including T and B lymphocytes and mononuclear phagocytes, but also by nervous system resident cells such as microglia and astrocytes. Astrocyte-secreted GM-CSF may play an important role in enhancing the local inflammatory response to central nervous system (CNS) injury and in recruting microglia and activated macrophages. In this study, we demonstrated that GM-CSF, as TNFα and IL-6, stimulates *in vitro* proliferation of simian astrocytes in primary cultures. Results were confirmed by blocking experiments performed with a specific neutralizing mAb directed against GM-CSF. Furthermore, we demonstrated that GM-CSF mediates its effect on these cells through the α subunit of the GM-CSF receptor which is constitutively expressed at the membrane of the cultured simian astrocytes as assessed by immunofluorescence. GM-CSF effects on astrocytes could be involved in astrocytosis, a hallmark of various neurological injuries and in inflammatory processes in an autocrine manner.

49.32 TRIPLE IMMUNOFLUORESCENCE LABELLING OF CALCIUM-BINDING PROTEINS IN RAT AND MONKEY BRAIN. W. Härtig*, K. Brauer, G. Seeger and G. Brückner. Paul Flechsig Institute for Brain Research, University of Leipzig, Jahnallee 59, D-04109 Leipzig, FRG

Calcium-binding proteins like parvalbumin (PARV), calbindin-D_{28k} (CALB) and calretinin (CR) are established markers of neuronal populations in the central nervous system, which were previously demonstrated by cytochemical single and double staining only. The simultaneous detection of PARV-, CALB- and CR-immunoreactivity (-ir) by conventional indirect immunofluorescence labelling was impossible until yet because non-cross-reacting primary antibodies from three different animal species were not available. To circumvent this problem, we applied a simple, but sensitive technique to rat brain sections - based on the concomitant use of digoxigenylated mouse-anti-PARV, biotinylated mouse-anti-CALB and rabbit-anti-CR. Subsequently, these antibodies were revealed by a cocktail containing green fluorescent fluoresceinated anti-digoxin, red fluorescent Cy3-tagged streptavidin and blue fluorescent AMCA-goat-anti-rabbit. Alternatively, the detection of CALB and CR with unmodified primary antibodies was followed by the use of digoxigenylated or biotinylated anti-PARV and its visualization by appropriate fluorochromated immunoreagents. Such techniques were also applied to cortical tissue of the rhesus monkey *Macaca mulatta* and gave more informations than conventional detection methods, for instance regarding the co-expression of calcium-binding proteins in neuronal subpopulations. The established triple-staining techniques were mainly applied to the mapping of PARV, CALB and CR in the rat basal forebrain. This part of our study was complemented by dual peroxidase labelling of PARV- and CR-ir as well as of PARV- and CALB-ir. The complex demonstration of these calcium-binding proteins provided new insights into structural and functional organization of the investigated brain regions. (Supported by the DFG, grant 1376/2-1)

49.33 MECHANISMS OF GLUTAMATE INDUCED ASTROGLIAL SWELLING

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The activation of metabotropic glutamate receptors (mGluRs) by 1-aminocyclopentane-1,3-dicarboxylic acid (1S, 3R-ACPD) or ibotenate induced a rapid cell volume increase in primary cultures of type 1 astroglial cells from cerebral cortex of newborn rat. These relative volume changes and parallell Ca^{2+} transients in single cells were examined by microspectrofluorimetry after loading the cells with fura-2/AM and varying the excitation wavelengths between the isosbestic point of the probe and its ion sensitive wavelength. L-AP4 evoked an astroglial swelling but few or no cytosolic Ca^{2+} transients. No rapid swelling was observed after stimulation of ionotropic Glu receptors.
The Glu induced volume increase was unaffected by gluconate or amiloride, partially blocked by Glu carrier-blockers and totally blocked by ketamine. The Glu or L-AP4 induced volume increases were blocked by $BaCl_2$ or furosemide. Tetraethylammoniumchloride-1-hydrate blocked the Glu and 1S,3R-ACPD induced astroglial swelling but the voltage-dependent L-, N- or T-type Ca^{2+} channels were not primarily involved in the Glu, 1S,3R-ACPD or L-AP4 induced swelling.
MGluRs induce IP_3 synthesis, intracellular Ca^{2+} increase and the opening of a delayed outward K^+ rectifier, and along another route activate a G_i-protein and open an inward K^+ rectifier. One Na^+-K^+-$2Cl^-$-cotransporter and a Na^+-K^+-ATPase is activated and so is also an electrogenic Na^+-dependent Glu carrier. Thus, Glu induced astroglial swelling is not only the result of the above mechanisms, but requires another, until now unidentified mechanism, probably some ketamine sensitive K^+-outflux or Na^+-influx.

49.34 GLYCOGEN PARTICLES IN RODENT AND OVINE PRIMARY CULTURED ASTROCYTES. B. Guicheux[(1)], V. Vergé[(1)], M. Caldani[(2)], O. Richard[(1)], A. Duittoz[(3)], and T.K. Hévor*[(1)]. (1)Laboratoire de Physiologie, Jeune Equipe 268, Université d'Orléans, F-45067 ORLEANS Cedex 2. (2)Unité de Neuroendocrinologie sexuelle, INRA PRMD, F-37380 NOUZILLY. (3)Laboratoire de Neuroendocrinologie, Université de Tours, Parc de Grandmont, F-37200 TOURS. (France).

Astrocytes play a major role in glucose metabolism in the brain. These cells have been intensively cultured and the cultures have become a model for the study of the carbohydrate metabolism in the brain. It is generally believed that the carbohydrate pathways are weaker in the astrocytes than in the hepatocytes. The aim of this study is to know whether or not astrocytes are able to synthesize glycogen upto the highest degree of organization, as well as hepatocytes. A comparative study has been undertaken using the primary cultures of astrocytes from two different species, i.e. rat and sheep. The cultures were made in the Dulbecco's Modified Eagle's Medium supplemented or not with foetal calf serum. When the glucose concentration was 5g/l in the medium, the glycogen deposition was of α-particle type, as in hepatocyte. Large particles of this polysaccharide were seen in the cytoplasms of the astrocytes. In some parts of the cells, single particles were seen. In other parts, many particles laid together in clear areas, without a surrounding membrane. When the astrocytes were submitted to methionine sulfoximine which is a drug that enhances glycogen content in the brain, the size of the latter areas notably increased. These results show that astrocytes cultured from the brain of two different species of mammals have the potentiality for synthesizing the highest form of glycogen α-particles, as well as hepatocytes.

49.35 REGIONAL BRAIN ABLATIONS AND EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

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In the present study we assesed onset and developement of experimental allergic encephalomyelitis (EAE) and hypersensitivity skin reactions to old tuberculin in right- and left-biased rats after ipsilateral ablations of frontal (FC), parietal (PC) and occipital (OC) neocortex. Lesions were performed by the aspiration method in Wistar rats (250-300 g) previously tested for brain laterality. After recovery rats were immunized intradermally in the hind footpad with 0.1 ml of emulsion containing guinea pig spinal cord in complete Freund's adjuvant. In addition rats received subcutaneos injection of Bordetella pertussis in the dorsum of the same foot, as an additional adjuvant. Animals were observed daily for clinical signs of EAE. Skin-testing with old tuberculin was performed on day 14 after the immunization. Brains and spinal cords of all animals were examined for mononuclear cell infiltrates characteristic of EAE. Both left- and right-biased PC- and FC-lesioned animals had increased incidence and severity of clinical and histopathological signs of EAE. Arthus and delayed hypersensitivity skin reactions to old tuberculin were significantly reduced in left-biased PC-lesioned rats. These results suggest that frontal and parietal neocortical ablations have influence on immune reactivity and development of EAE. (Supported by Ministry of Sciences and Technology of Serbia.)

49.36 THE ROLE OF CENTRAL D1 AND D2 DOPAMINERGIC RECEPTORS IN MODULATION OF HUMORAL IMMUNE RESPONSES IN THE RAT

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Catecholamine dopamine (DA) has been reported to be involved in regulation of immune functions. In this study we discussed the role of D1 and D2 types of central DA receptors in immunoregulation, investigating the influence of dopaminergic antagonists with different selectivity towards the type of dopaminergic receptors on humoral immune response in the rat. Male Wistar rats were immunized with sheep red blood cells (SRBC) and treated daily with intraperitoneal (i.p.) injections of fluphenazine (0.05, 0.5, 1 and 2 mg/kg b.w.) or sulpiride (0.1, 1 and 2 mg/kg b.w.) for 5 days. Control animals were treated with saline. On day 4 after immunization animals were sacrificed, the spleen cells were processed for a direct plaque forming cell (PFC) assay, and the titers of anti-SRBC antibody were determined in the sera. The treatment with 0.5, 1 and 2 mg/kg b.w. of fluphenazine (mixed antagonist of D_1 and D_2 receptors) induced a pronounced suppression of PFC response, and the doses of 1 and 2 mg/kg b.w. decreased hemagglutinin production. Sulpiride (selective D_2 antagonist) did not affect either PFC response or antibody production. Thus, only simultaneous blockade of D_1 and D_2 receptors decreased humoral immune response in the rat, while selective D_2 blockade did not exert such an effect, what led us to assumption that synergistic action of D_1 and D_2 receptors is required for dopaminergic modulation of the immune response. (Supported by Ministry of Sciences and Technology of Serbia.)

49.38 CHRONIC VERSUS ACUTE COCAINE-INDUCED IMMEDIATE EARLY GENE EXPRESSION IN RAT BRAIN.

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The immediate early genes *c-fos, egr-1,* and *c-jun* belong to a class of inducible genes, that are rapidly and transiently expressed, independently of protein synthesis. Activation of these genes is likely to play a key role in the transduction of short lived signals into long-lasting changes in cell function. The *egr-1* gene has been shown to be induced by synaptic activity. It is also known for playing a crucial role in neuronal plasticity in the hippocampus.

Cocaine produces its stimulatory effect by elevating 5-HT, DA and NA neurotransmission. We measured the induction of the immediate early genes in the rat brain in response to cocaine, using *in situ* hybridization. Wistar rats were treated acutely or chronically (1 injection/day, 10 days, i.p.) with 20 mg/kg cocaine, and sacrificed 45 minutes after the last injection. In saline treated rats, expression of *egr-1* could only be noticed in the cortex, hippocampus and cerebellum. Acute cocaine injection produced a dramatic expression of this gene in the fronto-parietal cortex, nucleus accumbens, caudate-putamen and in the ventromedial part of the hypothalamus. In chronically treated rats, however, this gene induction was nearly totally abolished, whereas the expression of *egr-1* in the cortex and hippocampus was not affected. The induction of *c-fos* was also abolished by the chronic cocaine treatment. Studies of the involvement of the 5-HT neurotransmission in the cocaine-induced gene expression are presented, using 5-HT receptor antagonists, or fluoxetine, a selective inhibitor of 5-HT reuptake. In order to correlate the behavioral effects of drug treatment with gene induction, the rats were tested in the place preference paradigm, since cocaine is well known to reliably produce a positive conditioned place preference.

49.39 BRAIN ENKEPHALIN-DEGRADING AMINOPEPTIDASE ACTIVITIES: A FLUORIMETRIC ASSAY.

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This communication decribes a fluorimetric method for determinating enkephalin-degrading aminopeptidase activities using Tyr-2-naphthylamide as substrate and puromycin as specific inhibitor of the membrane-bound MII form. This assay is based on Greenberg's method that enables us to measure soluble and membrane-bound (puromycin sensitive and insensitive) activities in discrete areas of the rat brain without employing radiosisotopic methods. Through several test, we have established the incubation time in 30 minutes and the substrate concentration in 1 ml/100 ml. Measuring Leu-, Ala-, Lys-, Arg- and Tyr-2-naphthylamide degradation with and without inhibitors (puromycin and bestatin), we have found that tyrosine and alanine derivates from naphthylamides are the most specific substrates for determining enkephalin-degrading aminopeptidase activities. In this sense, or results show that the relative activities obtained from the two membrane-bound aminopeptidases using Tyr- or Ala-2-naphthylamide as substrate is very similar to those obtained by other authors when the membranes are incubated with tritiated leu-enkephalin. The rest of aminoacil-2-naphthylamides seem to be hydrolyzed by other enzymes distinct from the enkephalin-degrading aminopeptidases. Finally, the results obtained through inhibition assays show puromycin as an important biological tool in the determination of both membrane-bound enkephalin-degrading aminopeptidase activities.

49.40 INHIBITION OF MYELIN FORMATION BY LONG-TERM CULTURED ASTROCYTES.

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To investigate the influence of astrocytes on neural regeneration we explanted mouse cerebellar tissues on astrocytes in culture which had been maintained in a 24-well plate for 2 to 12 weeks. The cerebellar tissue maturation was observed up to 20 days after explantation. Myelination occurred vigorously in the tissue explanted on 2- to 4-week-old astrocytes, but was poorer in the tissue explanted on astrocytes older than 4 weeks, and no myelin sheath was formed on 12-week-old astrocytes. However, immunostaining using anti-neurofilament protein antibody revealed that axons in the tissue explanted on 12-week-old astrocytes developed equally as well as those explanted on 2-week-old astrocytes. As astrocytes were maintained longer, they became fibrous, hypertrophic and more deeply immunostained with anti-glial fibrillary acidic protein antibody, being analogous to reactive astrocytes. These results suggest that astrogliosis may inhibit remyelination but not axonal regeneration.

49.41 **AN AGE-RELATED GFAP EXPRESSION IN ASTROCYTES PROLIFERATING IN THE INJURED RAT BRAIN.**

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In the cerebral hemisphere of newborn, 6, 14 and 30-day-old rats a lesion was made. The lesion volume was proportional to the brain size. At different intervals following the injury ^{3}H-thymidine was injected and the animals survived four hours after the injection. Brain sections were immunostained for glial fibrillary acidic protein (GFAP) and subjected to autoradiography. Thereafter, numbers and locations of GFAP-immunopositive (GFAP+) and autoradiographically labeled (labeled) astrocytes were recorded.

In rats injured neonatally, no labeled GFAP+ astrocyte was found. In the group of 6-day-old rats only occasional labeled GFAP+ astrocytes were recorded. In 14-day-old rats, the spatio-temporal pattern of reactive proliferation of GFAP+ astrocytes resembled that seen in 30-day-old rats.

The proliferative response of astrocytes to brain injury in neonatal rats was already described in quantitative studies (Janeczko, Brain Res. 456:280, 1988 and 564:86, 1991). The present study, however, provides evidence that the reactive astrocytes proliferating in the rat brain do not express GFAP during the first postnatal week.

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49.42 SENILE BUT NOT LESION-INDUCED INCREASE IN THE RAT BRAIN GFAP CONTENT IS MODULATED BY PHOSPHATIDYLSERINE (PS)

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One of the hallmarks of astrogliosis is an increase in the level of glial fibrillary acidic protein (GFAP). Although being a common event in the CNS, gliosis is not a stereotypic phenomenon. The differences in gliotic response, dependent on the character of its stimulus may be expressed eg. in different response to pharmacological treatment. The aim of this work was to compare the susceptibility to phosphatidylserine treatment of the two forms of astrogliosis: lesion-induced (7 days after lateral fimbria transection-FF) and age-associated. It was previously demonstrated that PS diminishes some age-induced impairments (Pepeu et al. Neurosci Res Comm suppl 12, 1993). Using quantitative immunoblotting we have measured GFAP content in the septum (sp) and hippocampus (hp) - structures undergoing intense gliosis after FF lesion, and in the striatum, corpus callosum, hp and sp from aged brains. Following groups of animals were used: (1) 3-month old (mo), saline-treated (sal); (2) 3-mo PS-treated; (3) 24-mo sal; (4) 24-mo PS-treated; (5) 3-mo FF sal; (6) 3-mo FF PS-treated. PS was administered ip 15mg/kg for 8 days. The results show that: (1) PS further increases elevated GFAP content in aged brain (2) PS does not affect GFAP level neither in the adult controls nor in the adult FF-lesioned animals. The data indicate that PS might influence only the astrocytes activated by a chronic, age-related process but not by acute stimulation. It remains to be verified whether the upregulation of astrogliosis in aged brain by PS is correlated with its beneficial effects on neurons.

49.43 **A NON-RADIOACTIVE *IN SITU* HYBRIDIZATION DOUBLE-LABELING METHOD.**

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In Situ hybridization (ISH) for 2 species of mRNA in central nervous tissue is usually performed by combining radioactive with non-radioactive techniques. In the present study, we developed a protocol for simultaneous double-labeling ISH with 2 non-radioactively labeled cRNA probes for preproenkephalin (ENK) and for the dopamine D_2 receptor (D_2). During *in vitro* transcription digoxigenin(DIG)-UTP or biotin(BIO)-UTP were incorporated into the cRNA probes. After hybridization, DIG and BIO were visualized employing antibodies for DIG and BIO, biotinylated secondary antibodies, avidine-biotin complex (Vector) and HRP or alkaline phosphatase (AP) as reporter enzymes. Substrates for AP were BCIP/NBT and for HRP DAB-Nickel followed by silver intensification. Detection through AP proved the most sensitive, for either DIG or BIO. However, use of AP in a simultaneous double ISH was not possible. Therefore, AP was combined with HRP. Optimal conditions were: simultaneous hybridization with DIG-UTP labeled cRNA for D_2 and BIO-UTP labeled cRNA for ENK. First, ENK probe was visualized with a 5 step method (mouse anti-biotin, biotinylated horse anti-mouse, anti-biotin, biotinylated horse anti-mouse, avidine-biotin complex, DAB-Nickel and silver intensification according to Merchentaler), next D_2 probe was visualized with anti-DIG labeled with AP, followed by BCIP/NBT incubation. Strict control of incubation times allowed for excellent resolution between the two mRNAs and quantification of double- and single-labeling.

49.44 BLOOD TO BRAIN TRANSPORT OF ^{3}H TIAZOFURIN IS PARTIALLY MEDIATED BY THE ADENOSINE TRANSPORT SYSTEM. S.S. Jovanović*, Z.B. Redžić, I.D. Marković, D.M. Mitrović and Lj.M. Rakić. ICN Galenika Institute, Biomedical Research Dept. and Institute of Biochemistry, School of Medicine, Belgrade, YUGOSLAVIA

Our previously conducted studies demonstrated the slow and saturable penetration of tiazofurin (a purine nucleoside analogue) through the blood-brain barrier (BBB). The aim of this study was to investigate whether tiazofurin blood-to-brain transport is mediated by the adenosine transport system. Therefore, the in situ brain vascular perfusion method in guinea pig was applied. The addition of 0.2 mmol/l of adenosine to perfusing medium caused significant decrease of [^{3}H] tiazofurin influx into the brain. Unidirectional transport constant K_{in} decreased from 2.61 ±0.21 µl/min/g in control (adenosine-free) group to 1.81±0.25 µl/min/g with perfusing medium containing adenosine. The difference between these K_{in} values was statistically significant ($p<0.01$). However, the complete inhibition was not achieved (only 30.76% of control K_{in} values). Similar results were obtained after addition 0.025 mmol/l of dipyridamole (inhibitor of nucleoside transport across biological membranes) into the perfusing medium. In this group K_{in} was 1.44 ± 0.43 µl/min/g (44.83% of inhibition).

Results explained above indicate that [^{3}H] tiazofurin blood-to-brain transport is mediated by the adenosine transport system, but only partially. It seems that another transport system, different from adenosine ones, takes part in tiazofurin unidirectional blood-to-brain transport.

49.45 PRENATAL VASOPRESSIN ADMINISTRATION INDUCES CHANGES IN BEHAVIORAL ASYMMETRY IN RATS

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The development of brain asymmetry during prenatal ontogenesis could depend on different sensitivity of right and left hemispheres to some factors of intrauterine environment. These factors can shift a ratio of individuals with right- and left-sided brain asymmetries in the population of animals. The asymmetry of tail-posture in newborn rats as well as the behavior in T-maze of adult individuals are regarded as the features of functional brain asymmetry. As we have shown previously i.v. injection of arg-vasopressin induces postural asymmetry (flexion of right hind limb) of adult rats. In the present work we have revealed that intraamniotic injections of 1-deamino-8-D-arginine-vasopressin (DDAVP) on the 14-th day of gestation resulted in a significant increase in the number of newborn rats with right-sided tail posture. This effects had a dose-dependent character in the range of doses of DDAVP from 0.3 fmoles up to 1 pmole per embryo. Analyzing the behavior of adult rats (3 months) subjected to prenatal administration of DDAVP we have found a significant increase ($p<0.01$) in the frequency of right-sided choices in T-maze in the offspring of treated animals when to compare with control. Thus, we can conclude that prenatal administration of DDAVP has lateralized effect on the developing rat brain and the result of this influence could be revealed during neonatal and late postnatal ontogenesis.

49.46 **MULTIPLE SCLEROSIS PATIENTS CEREBROSPINAL FLUID INCREASES NEURONAL SODIUM CURRENT INACTIVATION.** **Hubertus Köller*, Jochen Buchholz and Mario Siebler. Dept. of Neurology, Heinrich - Heine - University, P.O. Box 10 10 07, D - 40001 Düsseldorf, FRG**

During an acute relapse of multiple sclerosis a great number of immunologically active molecules has been identified in cerebrospinal fluid (CSF). The role of these substances, however, in neuronal dysfunction is unclear. We investigated the effect of CSF-MS compared to CSF from patients with noninflammatory neurological diseases on membrane currents of cultured cortical neurons from embryonic rat. We found an increase in Na^+ current (I_{Na}) inactivation by a shift of the h_∞ curve to more hyperpolarizing potentials by 9.3 mV. This effect was reversible after wash and could be abolished by CSF-MS heat inactivation. The degree of the shift, induced by CSF from different patients, ranged from 4.3 mV to 17.6 mV and correlated with the IgG index, but not with the degree of pleocytosis, protein or albumin content.

We concluded that during an acute relapse of MS, diffusible factors are released into the CSF which reduce neuronal excitability. These factors may well contribute to transient neurological symptoms seen in patients with "active" MS.

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49.47 IMMUNOHISTOCHEMICAL DETECTION OF THE PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA) IN HUMAN NEURONS: FACT OR ARTIFACT?

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PCNA is auxiliary protein of δ-DNA-ase, that is detected in nuclei of proliferating cells within the G1, S and G2 phases of mitotic cycle. Material it study was consisted of 78 biopsy specimens of human brain tissue, that were surgically removed "en block" with brain damages, including 46 glial neoplasm's, 8 arteriovenous malformations, 3 epileptic foci et c.t. All paraffin -embedded specimens were treated with antibodies against to PCNA (clone PC-10, Boehringer). Strong positive immunostain of the neuronal cytoplasm's and processes was detected in all 78 biopsy specimens. We observed immunostain with PCNA antibodies in neurons from different regions - cortex, basal ganglia, cerebellum, brain stem et. c.t. Also we detected differences in intensity of expression : immunostain was more weak in neurons that located in perifocal zone of brain damage. We have at least two explanations for these findings.

1. Immunostain of neurons with PCNA antibodies is the result of cross reaction with products of degradation of the neurofilaments.

2. Syntheses of PCNA is carried out in neuronal cytoplasm during all life of neurons, but transport of PCNA into nuclei of mature neurons is blocked. In our opinion, further studies of these hypotetic blocking mechanisms should be useful for investigation of neuronal regeneration.

49.48 THREE YEARS CYCLICITY IN THE APPEARANCE OF MULTIPLE SCLEROSIS (MS) - FACT OR COINCIDENCE?

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During our systematic follow-up of 167 patients with definite MS, hospitalized in the period from 1980 - 1995, we have noticed an interesting observation that the number of new registered patients with MS showed a marked increase every three years. The number of new discovered MS patients in the years 1983, 1986, 1989 and 1992 was 18, 19, 18, 17, respectively, while in years between, the number varied from 1 to 8. Apart from well known spatial clustering of cases of MS, there are instances of clustering in time. To our knowledge, the only similar three years clustering in time refered to Faroe Island, where a large number of British troops were stationed in 1940. MS appeared abruptly in 1943 and disappeared almost as abruptly in 1960. Since MS is a relapsing disease which may be due to a single or recurrent viral infections it remains to be seen whether human requires two different antigens or a single antigen to evoke T-cells and demyelinating antibodies and whether this process is somehow connected to three years incubation period.

49.49 BEHAVIORAL PROFILE AND SUSCEPTIBILITY TO INDUCTION OF ADJUVANT ARTHRITIS IN DA, LEWIS, WISTAR, AND AO RATS

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The aim of this study was to investigate the relationship between behavioral performances of different strains of rats and their susceptibility to induction of autoimmune disease. For this purpose, three inbred rat strains (DA, AO, and Lewis) and one outbred strain (Wistar) with different susceptibility to induction of adjuvant arthritis (AA) were used. The behavior of rats was tested in the open field, Porsolt swim test, and interspecies aggression test (mouse killing). DA rats exhibited the lowest activity in the open field test, according to the number of lines ceossed and the number of rears. AO rats showed pronounced grooming behavior in the open field in comparison with other strains of rats. In the Porsolt swim test, DA and AO rats had shorter immobility time compared to Lewis and Wistar rats. In the mouse killing test, only Wistar and AO rats exhibited aggression. Ten days after the last behavioral test, animals were immunized with single intradermal injection of complete Freund's adjuvant (0.6 mg of BCG/rat) in the basis of the tail. Animals were scored daily for clinical signs of AA. Clinical severity of the disease was evaluated for each paw as follows: 0, no arthritic changes; 1, edema; 2, edema and arthritic nodules on 1-2 fingers; 3, edema and nodules on 3-4 fingers; and 4, edema and nodules on all fingers. AO rats were resistant to induction of AA, while DA rats exhibited the highest incidence and mean clinical score as well as prolonged duration of the disease in comparison with Lewis and Wistar rats. These data suggest a possible correlation between open field activity and susceptibility to induction of AA in rats. (Supported by the Ministry of Science and Technology of the Republic of Serbia).

49.50 INTRACELLULAR CALCIUM MOBILIZATION AS RESPONSIBLE FOR REGULATION OF PROTEIN SYNTHESIS INITIATION.

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The rate of protein synthesis is regulated by calcium in a wide variety of cell types. Mobilization of sequestered calcium by hormones or other agents from endoplasmic reticulum cause inhibition of protein synthesis and disaggregation of polysomes, which is characteristic of decreased rates of polypeptide-chain initiation. The phosphorylation of the α subunit of initiation factor 2, eIF-2α, is one of the best documented mechanism implicated in the inhibition of translation at the initiation step. One of the mechanism of increasing the cytosolic calcium concentration, is originated by opening intracellular Ca^{2+} channels as those activated by inositol 1,4,5-trisphosphate ($InsP_3$), which is produced following activation of phospholipase C. In the present study, we have analyzed the accumulation of [^{3}H]Inositol phosphates ([^{3}H]IPs), phosphorylation of eIF-2α and translational rates in primary cultures of neurons from cortex of 18 days old rat embryos. In the presence of extracellular Ca^{2+}, all the compounds tested stimulated [^{3}H]IPs formation (A23187 > quisqualate > glutamate > carbachol > N-methyl-D-aspartate (NMDA) = KCl). In EGTA-calcium-free medium KCl and NMDA responses were abolished. EGTA, which acts as a extracellular extractant, and A23187, both fostering the passage of calcium across the ER membrane to cytoplasm, significantly increased the levels of eIF-2(αP) from 14% to 26% and inhibited protein synthesis rate (36% and 58% respectively). No changes were observed with the other agents tested in the phosphorylation state of eIF-2α and translational rates. Our results suggest that eIF-2α phosphorylation and inhibition of translation are independent of extracellular Ca^{2+} influx through voltage or receptor-operated Ca^{2+} channels, and are regulated by intracellular Ca^{2+} mobilization independent of IP_3-receptor stimulation.

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49.51 THE N-TERMINUS OF SCG10 DETERMINES ITS TARGETING TO MEMBRANES AND TO THE GOLGI COMPLEX.

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SCG10 is a neuron-specific, growth-associated protein that belongs to the same gene family as the ubiquitous phosphoprotein stathmin. Whereas stathmin is localized in the cytosol, SCG10 is membrane-associated. Previous studies have suggested a role for stathmin in intracellular signalling for proliferation and differentiation of various cell types. The specific function of SCG10 is unknown, but since many structural features are shared between the two proteins, SCG10 might perform a similar function in signal transduction in developing neurons and the plasticity of the adult nervous system. Although stathmin and SCG10 share 74% amino acid identity, they differ in their N-terminal region. SCG10 has an extension of 34 amino acids containing a string of 12 hydrophobic amino acids. In order to analyse the difference of localization of the two proteins and to investigate the importance of this N-terminal domain, we transfected a COS-7 cell line, and parallely injected primary neurons in culture, with vectors expressing different types of constructs. We subsequently revealed the localization of the proteins by subcellular fractionation and immunocytochemistry using specific antibodies. The transfected wild type stathmin is widely distributed throughout the cytoplasm, in neurons as well as in COS cells, whereas SCG10 localizes exclusively to the membranes and to the Golgi complex. A mutant of SCG10 lacking the N-terminal part has the same pattern of distribution as wild type stathmin. In contrast, a chimeric protein in which the amino terminus of SCG10 was fused to stathmin distributes like wild type SCG10. Similarly, a fusion protein containing the N-terminal amino-acid sequence of SCG10 and a heterologous protein, the beta-galactosidase enzyme, is also targeted to the Golgi. These experiments show that the amino terminus of SCG10 is necessary and sufficient for localization of the protein to the membrane and to the Golgi complex.

49.52 DIFFERENT EXPRESSION OF MEMBRANE CONDUCTANCES IN CULTURED RAT CORTICAL ASTROCYTES INDUCED BY INTRACELLULAR CYCLIC-AMP ELEVATION.

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The expression of membrane ionic currents in rat cortical astrocytes was investigated with the patch-clamp technique in control condition and after short term (4-24 hours) or long term (1-3 weeks) treatment of the cultures with 250 μM dibutyryl-cyclic-AMP. Outward sustained time- and voltage-dependent potassium (K^+) currents were evoked by depolarizations above -40 mV in control astrocytes and in both short and long term treated cultures. They were partially blocked by extracellular application of 10 mM TEA and the current density remained unchanged in all the three experimental conditions. In contrast, time- and voltage-dependent inward currents elicited by hyperpolarizations from an holding potential of -60 mV and induced by the activation of two different conductances were recorded only in long term treated astrocytes. The first one was associated to the activation of an inwardly rectifying K^+ conductance because 1) it displayed a quasi istantaneous activation kinetic and for membrane potentials lower than -120 mV showed a time- and voltage-dependent inactivation; 2) it was reversibly blocked by extracellular 0.1 mM Ba^{2+}; 3) the reversal potential of the currents changed in function of the extracellular K^+ concentration and went along with an increase of the conductive property. The second had a slower activation time course and did not inactivate even for large hyperpolarizations. It was not affected by 0.1 mM Ba^{2+} and by the change of intra- and extracellular monovalent cations content but was sensible to the change of chloride ions and thus was identified as a chloride conductance. These two conductances might be involved in the process of the extracellular K^+ buffering via the mechanism of the "local accumulation".

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49.53 USE OF CAPILLARY DEPLETION METHOD IN STUDIES OF AMINO ACIDS AND DRUGS DISTRIBUTION BETWEEN BRAIN ENDOTHELIUM AND PARENCHYMA.

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In most transport studies it is of considerable interest to determine the distribution ratio between the endothelial compartment (pellet) and brain parenchyma (supernatant). The determination of that ratio could be important for endogenous substances as well as drugs. Therefore, the capillary depletion method (Triguero et al. 1990) was applied to investigate the transport of three small neutral amino acids (^{3}H l-serine, ^{3}H l-alanine and ^{14}C l-proline) and a drug that is a nucleoside analogue (^{3}H tiazofurin). After in situ brain vascular perfusion, endothelial cells were separated from brain parenchyma and the concentration ratio between the two compartments determined for each examined substance after different perfusion times. The obtained results showed a significant increase of pellet/supernatant ratio in time for all three amino acids studied ($p<0.05$ between 1 and 6 min for both l-alanine and l-serine and $p<0.05$ between 1 and 3 min for l-proline). Higher ratios were probably due to very slow increase of volume of distribution in postvascular compartment (brain parenchyma), in comparison with the vascular compartment. However, pellet/supernatant ratio of tiazofurin significantly decreased in time ($p<0.01$ between 1. and 15. min). It seems that after achieving initial equilibrium between blood and endothelial cells, a steady increase of the tiazofurin concentration in brain parenchyma occurs.

These results show that although transport studies demonstrated the increase in brain uptake of the examined substance in time, it may not necessarily be due to the increase in penetration of that substance in brain parenchyma.

49.54 INTERLEUKIN-2 DIRECTLY MODULATES THE EXPRESSION OF THE CHOLINERGIC PHENOTYPE IN RAT SEPTAL CELL CULTURES.

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We recently demonstrated that interleukin-2 (IL-2) increases choline acetyltransferase (ChAT) activity in embryonic septal rat neuronal cell cultures (Soc. Neurosci. Abst. 285.15, Miami 1994). The maximal increase in ChAT activity was observed at a concentration of IL-2 (10^{-11}M) and after 5 days in culture with a cell density of 250000 cells/cm^2 and under serum free-conditions. To investigate if this effect is due to an increase in the survival and growth of cholinergic cells or to a direct increase in ChAT activity per cholinergic neurons, acetylcholinesterase (AChE) staining was used to visualize cholinergic cells. Cultures were prepared by dissecting the septa of 17-day old rat embryos. After mechanical dissociation, cells were grown in a chemically defined serum-free medium in poly-L-lysine coated wells. Cultures were kept at 37°C (5% CO_2) for 5 days, IL-2 (10^{-14}M to 10^{-8}M) being added immediatly after plating. AChE staining was according to the well established method of Tago *et al.*. The total length of the neurites of the AChE-positive neurons, the number of primary neurites by cell and the size of the pericaryon were measured using a computerized image analyser. Additionaly, to adress the specificity of the IL-2 effects, other cytokines (IL-4, IL-7 and IL-15) expressed in the CNS and likely acting through some of the subunits of IL-2 receptor were tested. No significant changes in the morphological parameters and number of AChE-positive cells were observed in presence of various concentrations of either IL-2, IL-4, IL-7 and IL-15, and ChAT activity was only significantly increase by IL-2. Hence, IL-2 apparently acts by directly increasing the synthetic activity of the cholinergic neurons ; not its survival or growth. Interestingly, IL-2 was also found effective to stimulate ChAT activity under serum or serum-free conditions. Taken together, these results provide further evidence suggesting that IL-2 can directly modulate the activity of the cholinergic neuron in the rat brain (Supported by FRSQ and MRCC).

49.55 CGANGES IN THYMOCYTE SUBSETS INDUCED BY INTRACEREBRO"ENTRICULAR ADMINISTRATION OF SOMATOSTATIN:

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This study was performediin order to investigate the influence of centraly applied somatostatin-28 (SRIH-28) on the expression and relative proportion of $CD4^-$ $CD8^-$ (DN), $CD4^+$ $CD8^+$ (DP), $CD4^+$ and $CD8^+$ (SP)cells in the rat thymus. In-bred male AO strain rats, four weeks old, were cannulated and treated intracerebroventriculary (icv) with SRIH-28 (1 ug/5 ul) in three doses every second day. Controls were treated with saline in an identical manner as experimental animals. Thymuses were aseptically removed and thymocytes were prepared for FACS analysis. The results shown that SRIH-28 caused changes in thymocyte subsets: the percent of DP cells was slightly decreased, the percent of SP cells was moderate increased, while percent of DN cells was significantly increased (about 100%) with respect to control group of animals. The results suggested that SRIH-28 icv applied in peripubertal period can be involved in the regulation of early stages of T cells differentiation. (Supported by the Ministry of Science and Technology of the Republic of Serbia).

50.01 CHOLINESTERASE INHIBITORS INCREASE SECRETION OF APPs IN RAT BRAIN CORTEX. E. Giacobini*, F. Mori and A. Buznikov. Southern Illinois Univ. Sch. Med., Dept. Pharmacology, P.O. Box 19230, Springfield, IL 62794-9230 USA

We have demonstrated that cholinesterase inhibitors (ChEI) can alter the release of amyloid precursor protein (APP) from superfused brain cortical slices of the rat. Three ChEI, both reversible and irreversible, were tested for their ability to enhance the release of nonamyloidogenic soluble derivatives (APPs). APP gene expression was also studied. ChEI included: physostigmine, heptyl-physostigmine and 2,2-dichlorovinyldimethyl phosphate (DDVP), at concentrations producing cholinesterase inhibition ranging from 5% to 95%. All three ChEI elevated APPs release significantly above control levels. Electrical field stimulation significantly increased the release of APPs within 50 min. Similar increase was observed after muscarinic receptor stimulation with bethanechol. Activation of protein kinase C with phorbol-12-myristate-13-acetate (100 nM) increased APP mRNA expression. Tetrodotoxin completely blocked the effect of electrical stimulation. These findings suggest that administration of ChEI to Alzheimer disease patients may have a neuroprotective effect by activating normal APP processing. [Reference: Mori, F., Lai, C-C., Fusi, F. and Giacobini, E., Cholinesterase inhibitors increase secretion of APPs in rat brain cortex. NeuroReport, 6(4), 1995]

50.02 GROWTH HORMONE SECRETION IN PRIMARY DEGENERATIVE DEMENTIA: CORRELATIONS WITH COGNITIVE IMPAIRMENT. M.V.Gianelli*, G.Murialdo, S.Porro, G.P.Solinas, P.Tosca, C.Parodi, E.Di Paolo, P.Costelli,. Dep. of Endocrinological & Metabolic Sciences, Univ. of Genova, Viale Benedetto XV, 6-16132 Genova, Italy.

Changes in brain peptides and neurotransmitters are thought to elicit alterations of Growth Hormone (GH) secretion in dementia. With a view to detecting correlations between neuroendocrine and clinical data, baseline GH levels and the hormone responses to GH-Releasing Hormone (GHRH) - administered alone or after pyridostigmine pretreatment - were evaluated in 17 patients, aged 52 to 83, with primary degenerative dementia, quantified by CDR (Hughes et al., 1982) and MMSE (Folstein et al., 1975).

Statistical differences in basal GH levels were found to be correlated to disease severity, rates being lower in mild dementia and higher in more severe cases. GH responses to GHRH were significantly higher in (mild to moderate) patients than in controls after pyridostigmine pretreatment, but not after infusion of GHRH alone. In patients with mild to moderate DAT basal levels were lower, but GH responses to GHRH higher than in both more severe patients and in healthy controls. Pyridostigmine did not potentiate GHRH effects in the more severe cases.

The scores at Rey's 15 words test for memory function were correlated inversely with GH baseline levels and directly with GH peaks after GHRH. No correlations were found between GH data, age, disease duration and scores at other psychometric assessments such as MMSE, Raven's Matrices, Verbal Fluency or WAIS tests.

50.03 CLEAVAGE OF β-APP IN RAT HIPPOCAMPUS: EFFECTS OF ISCHEMIA AND NMDA RECEPTOR STIMULATION

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Abnormal proteolytic degradation of β amyloid precursor protein (β-APP) may result in accumulation of potentially neurotoxic β amyloid (βA). Both βA and β -APP accumulate in brain in several neurodegenerative disorders including ischemia. The role of various receptors in regulation of β-APP processing has been suggested. The aim of this study was to establish early changes in the expression of some domains of β-APP in the rat hippocampus after 10 min forebrain ischemia (Pulsinelli's 4VO model) and to determine if NMDA receptors and Ca^{2+} ions regulate proteolysis of β-APP in superfused rat hippocampal slices. Separation of the hippocampal proteins by electrophoresis followed by their Western blot analyses using antibodies against some domains of β-APP in the early postischemic period (2 h after 4VO) demonstrated significant decrease in the immunoreactivity of the membrane-bound and cytosolic βA and the C-terminal fragment of β-APP, whereas extracellular β-APP domains remained unchanged. One and 7 days later the enhanced immunoreactivity of all β-APP domains was noted. To detect the role of NMDA receptors in modulation of β-APP processing in brain, adult rat hippocampal slices were superfused with NMDA containing media, and immunoreactivity of soluble β-APP derivatives was measured in dialysates. 100 μM and 250 μM NMDA induced a release of amino-terminal β-APP derivatives and a fragment of βA, which was dose-dependent, sensitive to 1 μM MK-801 and 100 μM CPP, and to Ca^{2+} presence. Release of carboxy-terminal fragments of β-APP was not detected. These data indicate that ischemia and NMDA receptor stimulation induce cleavage of β-APP in brain. Mechanisms of these effects will be discussed.

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50.04 DIFFERENTIAL IMMUNOREACTIVITY TO PARVALBUMIN, CALBINDIN-D28K, AND CALRETININ, IN THE SOMATOSENSORY CORTEX OF NORMAL C57BL/6 AND MUTANT *MDX* MICE. M. Santarelli§, M.E. Dell'Anna§, D. Carretta§, F. Pinto§, G. Zito#, A. Granato# (*), and D. Minciacchi§. Department of Neurological and Psychiatric Sciences§, University of Florence; Institute of Neurology§, University of Udine; Institute of Anatomy#, Catholic University, Rome; Italy.

The localization of calcium-binding proteins parvalbumin, calbindin-D28k, and calretinin, has been examined in the somatosensory cortex of normal and dystrophin deficient *mdx* mice. In both groups, parvalbumin-immunoreactive neurons were present in all layers except layer 1. Differences were evident in the amount and distribution of immunostained cells: parvalbumin-positive neurons were more numerous in *mdx* and showed a less clear laminar segregation compared to normal mice. In all animals, the prominent calbindin-D28k-immunoreactive cell population was represented by lightly stained neurons in layers 2 and 3; a band of darkly stained neurons was also present in layers 5 and 6. In *mdx*, calbindin-D28k-positive cells were more numerous especially in deep layers. The distribution of calretinin-immunoreactive neurons was comparable in both groups: positive neurons were mostly confined within the supragranular layers. The different patterns of expression of parvalbumin and calbindin-D28k we describe in the somatosensory cortex can be explained as alterations in the Ca^{++}ion metabolism of cortical neurons. Altered Ca^{++}ion regulation has been already reported in cerebellar granule neurons of *mdx* mice. In addition, high levels of parvalbumin have been associated with protection of neurons against ischemia, neurodegenerative disorders, and stimulation-induced cell death. Cells that do express parvalbumin could be less susceptible to death, especially during *ontogenesis*. The increase of parvalbumin expression in somatosensory cortex could thus reflect differences in the processes of developmental remodeling.

50.05 CYTOSKELETAL ASSOCIATED PROTEINS IN ALZHEIMER'S BRAIN ARE SIGNIFICANTLY INCREASED IN THE POST-TRANSLATIONAL MODIFICATION O-LINKED N-ACETYLGLUCOSAMINE OVER AGED MATCHED STROKE AND NORMAL CONTROLS

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We show that the O-GlcNAC modification, which we have previously shown to exist on the cytodomain of amyloid precursur protein (APP) (1), is significantly increased on cytoskeletal associated proteins in Alzheimer's versus-age matched control brain. Interestingly the increase in O-GlcNAc modification is largely restricted to areas of the brain that are known to be affected most drastically in Alzheimer's disease. For example there is a significant difference between Alzheimer's and normal brain in the frontal cortex, basal forebrain and hippocampus while in the cerebellum (an area of the brain that is not affected by amyloid plaques and neuronal death in Alzheimer's) the observed difference is not significant.

We are further investigating this exciting finding to identify the specific protein(s) that are hyper-N-acetylglucosaminylated and to determine the role it may play in the development and etiology of Alzheimer's disease.

1. Griffith et al. J. Neurosci. Res. in press

50.06 OBSERVATIONS ON THE MOTONEURONE SURVIVAL IN THE SPINAL CORD AFTER BLOCKING THE NEUROMUSCULAR ACTIVITY 5-6 DAYS POSTNATALLY ON L-DOPA TREATED RATS

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Motoneurone survival depends on their functional interaction with the muscle they innervate. Prevention of neuromuscular transmission with a-BgTx postnatally induces motoneurone death, while if the same interuption occurs 5-6 days later no motoneurone death is noticed. In this study the neuromuscular activity of edl rat muscle was blocked at 5-6 days after birth, for 7 days with a-BgTx; half of the animals were then treated with L-dopa postoperatively for 14 days, while the rest were treated with vehicle. 8 wks later the motoneurone pool of this particular muscle was studied with HRP. The L-dopa treated animals showed a 40% reduction of the motoneurones compared to non L-dopa treated. Morphometric analysis of the whole muscles showed an 11% reduction in the number of fibres (2685±27), and the whole muscle area was reduced to 1626 μ^2. The oxidative fibres comprised the 74.4% compared to 63 % of the controls. The tetanic tension of these animals was 39.4% less than the non L-dopa treated; the time to peak was 19.3 %, and the half relaxation time was 26.7 % increased compared to controls. The results indicate that L-dopa, acting as NorAdr precursor may cause overexcitation of the motoneurones disconnected from their target via spinal a_1 adrenergic receptors. The immature neurones may not withstand this overexcitation and die.

50.07 THE TRANSIENT NEUROLOGIC DISORDERS IN PATIENTS WITH INTRAHEPATIC PORTAL HYPERTENSION

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Purpose: The aim of this presentation is to study transient neurologic disorders in the patients with intrahepatic portal hypertensions (PH).

Methods and materials: Neurologic and EEG alterations were studied in 68 patients with liver cirrhosis and PH at the age from 16 to 68 years. The reduce of functional reserve of liver by criteria of Child and Turkotte (1964) was slight in 32,4% of cases, middle - in 38,2% and pronounced in 29,4% of patients. In 32,4% of patients there were surgical portosystemic shunts, in the most cases - splenorenal anastomosis.

Results: One or more episodes of acute hepatic encephalopathy (HE) were in the past in 14,3% of patients. 29,4% patients had a daytime sleepiness, 20,5% - syncopes, not at the time of a hemorrhage from the varicose gastroesophageal veins, 17,6% - panic attacks, 13,2% - episodes of vasoparalytic headache, 13,2% - transient tremor. In 25% of the patients there were commonly rare paroxysmal with polymorphic neurologic disorders: ataxia, dysphasia, dystonic phenomenon, emotional changes and sometimes - with seizures or altered state of consciousness. There was no paroxismal activity in EEG at the interattack periods, but these forms of activity was observered at the time of fits in 2 cases. HE, daytime sleepiness and transient tremor were more common in the patients with a more lengthy time of clinical manifestations of PH and a more low levels of proteins in the blood. There were some correlations between the different paroxysmal disorders. Attacks with polymorhpic neurologic disorders, daytime sleepiness, transient tremor and vasoparalytic headache often were connected with those factors, which provoked an acute HE.

Conclusion: Such transient neurologic disorders have toxico-metabolic character and some of its are connected with epileptic mechanisms.

50.08 APOLIPOPROTEIN-E BINDS ALZHEIMER'S DISEASE AMYLOID PROTEIN PRECURSOR

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Apolipoprotein E (ApoE), particularly the e4 allele, is genetically linked to the incidence of Alzheimer's disease. *In vitro*, ApoE has been shown to bind β-amyloid (Aβ), an amyloidogenic proteolitic product of amyloid precursor protein (APP). In order to investigate the possibility that ApoE could bind directly to APP, we have engineered a vector for the recombinant expression in high quantities of a maltose binding protein (MBP)-APP fusion protein, which is specifically retained by an affinity column. Using this column as a model system, we have found that both ApoE3 and ApoE4 in form of VLDLs purified from human sera bind to MBP-APP, but not to MBP alone. Binding to APP was inhibited when ApoE-containing VLDLs were preincubated with peptide Aβ(1-28), but not with peptides Aβ(1-15) and APP_{695}(582-596). However, no SDS-resistant APP-ApoE complexes could be detected under the experimental conditions employed. These results indicate that native ApoE is able to bind APP, and suggest that although ApoE-APP binding seems to be mediated by the same residues of Aβ implicated in ApoE-Ab binding, the mechanisms of interaction may be different. The physiological relevance of the interaction of ApoE with APP is still unknown; however, it could play a relevant role similar to the interaction with the VLDL receptor, and could precede the formation of ApoE-Aβ complexes, hence mediating the generation of amyloidogenic fragments.

50.09 DISTRIBUTION AND METABOLISM OF [14C]-CABERGOLINE, A POTENT D2 AGONIST, IN THE RAT BRAIN.

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Cabergoline,1-[(6-allyl-ergoline-8β-yl)carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea, (CB), is a highly specific D2 agonist currently under clinical evaluation in Parkinson's disease. In this study the tissue distribution of radioactivity was investigated in brain areas, adrenal and pineal glands, adeno-and neurohypophysis 1 and 8h after 3.5 mg/kg [^{14}C]-CB p.o. (free base). Moreover, the metabolism of CB in these tissues was evaluated 8h after 5.8 m/kg [^{14}C]-CB p.o. The experiments were carried out in accordance with the EECD guidelines for animal treatment. Female Sprague-Dawley rats (180-200g) were used. Total radioactivity was determined by LSC after adequate preparation of the samples. The metabolic profile was determined by radio TLC after acetone extraction. The concentrations of total radioactivity at 8h, corrected for blood contamination, were 82,114, and 92 ngeq. CB/g w.w. tissue in the striatum, hypothalamus, and hippocampus, respectively, being 2-7 times higher than the values obtained 1h post-dosing. In the pineal and adrenal glands, neuro-and adenohypophysis 2.1,5.4,4.4 and 3.8 μgeq. CB/g w.w., respectively, were found 8h post-dosing. These values were ca.100 times higher than those found 1h after administration. In all investigated areas 78-91% of the radioactivity present 8h after the administration was CB while the N-demethylated derivative amounted to 3-13%. In the striatum, hypothalamus, hippocampus and n. accumbens, CB concentrations were 377, 506,199, and 137 nM, respectively. Assuming a linear dose-concentration relationship, the striatal value 8h after 0.5 mg/kg CB p.o. would be 33 nM which is ca.20 times higher than the IC_{50} value ([^{3}H]-NPA binding *in vitro*). It has been shown previously (Eur.J. Pharmacol.,187,399,1990) that this dose causes a displacement of 23% of [^{3}H]-NPA binding *in vivo*. Studies are in course to evaluate the possible non linearity of the dose-concentration relationship.

50.10 TRANSGENIC MOUSE MODELS OF NEUROLOGICAL DISORDERS DUE TO GLYCINE RECEPTOR DEFECTS.

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The inhibitory glycine receptor (GlyR) is a ligand-gated ion channel mediating post-synaptic inhibition in the vertebrate central nervous system. GlyR is a pentameric protein composed of three α and two β subunits. Several isoforms of the α subunit have been isolated whereas only one β subunit has been identified. Mutations in the α1 subunit which mediates ligand binding are associated with the human neurological disorder Hereditary Hyperekplexia. Several murine mutants carrying mutations in one of the two subunits have been identified.

In order to investigate the value of these mutants as models of human disease, we attempted to rescue the mutant phenotype with α1 and β subunit transgenes from other species. So far, we successfully rescued the *spa* mutation by introduction and expression of a rat GlyR β transgene. This experiment provided proof that the defect in the murine β gene is indeed causal to the phenotype. It also showed that species barriers can be overcome, and most importantly that small amounts of GlyR expression are sufficient to fully accomplish the glycinergic pathway. Moreover, a transdominant negative receptor mutant (Chi 1), previously characterized in the *Xenopus* oocyte system (Kuhse et al. Neuron 11, 1049, 1993) was introduced as a transgene. Expression of this gene apparently interferes with correct α1 β assembly and induces a partial phenotype reminiscent of the recessive phenotype observed in *spd* mice.

50.11 SHORT-TERM AND LONG-TERM EFFECTS OF A REPETITIVE MOTOR TRAINING IN THE REHABILITATION OF STROKE PATIENTS

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In the rehabilitation of stroke patients physiotherapeutic strategies and the type of performed movements vary frequently, although the latest neurophysiologic findings imply that the repetitive execution of the very same movement may be of special value in motor learning. According to Asanuma and Keller (1991) repetition of movements induces long term potentiation (LTP) phenomena in the sensorimotor cortex that facilitate the excitation of respective subsets of motor cortex neurones activating the particular muscles involved in the movement. LTP may be an explanation for the striking improvement of biomechanical as well as functional motor parameters we saw in 60 hemiparetic stroke patients who underwent a stereotyped repetitive hand training.

In order to demonstrate facilitation/LTP-phenomena immediately after the execution of a repetitive movement we examined 20 healthy subjects and 10 hemiparetic stroke patients by the means of transcranial magnetic stimulation. Subjects were asked to carry out dorsal extensions at the wrist for 2 min with two different velocities (48BpM and 96 BpM respectively). Transcranial magnetic stimulation was performed at 1.2 threshold intensity before and after the movement periods. A significant facilitation of the amplitudes of our target muscle, the extensor carpi radialis muscle, was found only while subjects performed the movement slowly (48 BpM). Further results, the presumed neuronal mechanisms and the implications for motor learning and physiotherapy will be discussed.

50.12 ANTINEURONAL ANTIBODIES IN RETT SYNDROME

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In the last years much evidence has accumulated regarding the presence of antibodies to neurons in paraneoplastic syndromes and in several progressive neurological disorders. In some cases the antigens have been discovered and a possible autoimmune mechanism has been hypothesized in the pathogenesis of these syndromes. Therefore we have investigated the presence of antibodies to neurons in sera and cerebro spinal fluid (CSF) of patients with Rett syndrome (RS) a severe neurological disorder of unknown etiology limited to females. The patients (65) selected according to the clinical criteria of Hagberg were in different stages of syndrome. Sera from patients with RS stains neurons, glial cells and nerve terminals as determined by indirect immunofluorescence on frozen sections of human and rat brain, in a high percentage of cases (85% - all in stages II-III-IV), at a dilution of 1:200 or greater. Samples of CSF from 6 patients tested as above, also stained human and rat neurons at a lower dilution:1:10. No antibodies to neuronal or glial cells could be dected in sera from patients in the I stage of syndrome, in control sera (80 cases) in CSF (4) from healty patients, and in sera from children (20 cases) with several neurological disorders which must be distingueshed from RS. Immunoblot study carried out on 20 patients with RS showed that serum samples stained several bands. However sera from a group of patients recognized common bands of 68 Kd (5) and 50 Kd(7) of rat brain proteins. Immunocytochemical evidences of antibodies to neurons in the advanced stages of syndrome, directed to a variety of neuron or glial antigens suggest that a possible immunological mechanism is involved in the pathogenesis of syndrome.

50.13 APOLIPOPROTEIN E, α_2MR/LRP- AND LDL-RECEPTOR INTERACTIONS IN ALZHEIMER DISEASE . O. Heinonen*, H. Soininen, S. Ylä-Herttuala, O. Kosunen, L. Paljärvi, P. Riekkinen Sr. Depts. of Neurology and Pathology, AIV-Institute, Kuopio University and University Hospital, Kuopio, FINLAND.

Alzheimer disease (AD) is associated with an increased prevalence of apolipoprotein E (apoE) ε4. ApoE is a plasma protein that binds to low-density lipoprotein (LDL) receptor and the α_2-macroglobulin receptor/LDL receptor-related protein (α_2MR/LRP). In central nervous system, apoE is produced and secreted by astrocytes. In AD, apoE is bound to senile plaques (SPs), tangles as well as to cerebrovascular amyloid. Colocalization of apoE and α_2MR/LRP to SPs suggests that these molecules may play a role in amyloid accumulation. The aim of this study was to investigate the apoE and its receptor interactions in AD. We determined immunopositivity for the anti-apoE (Chemicon), anti-α_2MR/LRP-α and -β (detecting α and β chains of α_2MR/LRP) and anti-LDL (S. Ylä-Herttuala, AIV-Institute) in the frontal cortex and hippocampal formation of an AD patient and an aged control. Immunostainings were done for adjacent 50 µm thick free floating sections using an avidin-biotin-peroxidase system. Immunoreactivity for anti-apoE was enhanced by 90% formic acid. Immunopositivity for anti-apoE and anti-α_2MR/LRP was seen both in diffuse and neuritic SPs as well as blood vessel walls. Anti-α_2MR/LRP intensively stained astrocytes and pyramidal cells of hippocampus both in AD and control cases. Immunoreactivity for α and β chain was equal. Weak granular anti-LDL staining was detected in neurons, especially in the upper cortical layers. In contrast to anti-α_2MR/LRP, anti-LDL did not stain SPs. These results add to body of literature suggesting that α_2MR/LRP receptors may have an impact in the AD pathogenesis.

50.14 AMINOPYRIDINE-INDUCED EPILEPTIFORM ACTIVITY IN IMMATURE RATS IN VIVO. G. Heltovics* and M. Szente. Department of Comparative Physiology, Attila József University, Szeged, Középfasor 52. 6726 HUNGARY.

Electrographic seizure susceptibility was investigated on the neocortex of immature rats aged between 9 and 21 days *in vivo*. Epileptiform activity was induced by local application of 3-Aminopyridine (3Ap) to the somatosensory cortex. Three major phases were observed according to the capacity for epileptogenesis as the animals matured.

Rats aged between 9 and 13 days never showed high frequency ictal-like epileptiform activity after the application of 3Ap. Instead they developed irregular, slow interictal discharges with large amplitude on both hemisphere. These events were superimposed upon a rather simplified background activity dominated by low amplitude sinusoid oscillations of 3-5 Hz.

Rats aged between 14 and 16 days showed a pronounced susceptibility to epileptiform activity. They developed sustained (lasting for 2-3 mins) rhythmic epileptiform discharges with characteristic periodicity. Seizure potentials with gradually increasing amplitude of 3-5 Hz were alternated by spike-waves with high amplitude and lower frequencies (0.8-1.2 Hz). These immature seizure events occurred on both hemispheres in most cases.

Epileptiform activity in rats of 16-21 days old gradually became similar to those observed in adult animals. Ictal-like periods were introduced by discharges of high frequencies (9-15 Hz) which never appeared in younger rats. Ictal events were mostly restricted to the site of 3Ap application and to the homologous area of the contralateral hemisphere. The latency of the first seizure event after 3Ap application gradually decreased with the age but never reached the value observed in adult rats. Our findings coincide with the morphological changes described in developing immature rat neocortex.

50.15 CHANGES IN VOLTAGE-DEPENDENT CALCIUM CHANNEL (VDCC) α_1 SUBUNIT mRNA LEVELS DURING KINDLING EPILEPTOGENESIS. H. Hendriksen*, W. Kamphuis, F.H. Lopes da Silva. Graduate School for the Neurosciences, Institute of Neurobiology, University of Amsterdam, Kruislaan 320, 1098 SM Amsterdam, The Netherlands

The establishment of a focus of epileptiform activity in the hippocampus of the rat, using the kindling paradigm, leads to changes in the voltage-dependent calcium currents. Patch-clamp studies on dissociated CA1 pyramidal neurons showed an enhanced calcium conductance (Vreugdenhil et al.; Neuroscience 59, 105-114, 1994). We initiated studies, using semi-quantitative in situ hybridization techniques with specific oligo-nucleotides, in order to investigate whether these changes are associated with an altered expression of the genes that encode for the different subunits of the VDCCs. In rats, electrodes were chronically implanted and electrical stimulation was applied to the Schaffer collateral-commisural pathway twice daily, eventually leading to tonic/clonic convulsions. The expression of α_1 subunits was determined 24 h after the last seizure. Two groups at different stages before the appearance of generalized seizures were investigated in order to gather information on the development of changes in expression during epileptogenesis. Therefore, animals were sacrificed after 6 or 14, kindling stimulation elicited, afterdischarges. Furthermore the involvement of VDCCs in the maintenance of epileptogenesis was studied in fully kindled rats at one day and at long term (28 days) after the last seizure. The first results revealed a significant increase of the VDCCα_{1A} mRNA expression in the CA1 and CA3 neurons of the hippocampus in animals of the 6 an 14 AD groups. On average, the α_{1A} mRNA levels were significantly increased by 15% in comparison to control rats. However, no significant changes were apparent in fully kindled animals at 24 h or 28 days after the last generalised seizure. The possibility of changes in other variants of the VDCC subunits (α_{1A-E} and β_{1-4}) will be investigated and the results are discussed in relation with the electrophysiological alterations found previously.

50.16 CALCIUM CONCENTRATIONS IN SYNAPTOSOMES FROM PATIENTS WITH FOCAL EPILEPSY.

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One of the possible mechanisms underlying epileptogenesis is a disturbed balance between excitatory and inhibitory transmission. The cellular and molecular mechanisms underlying this disturbance have mainly been studied in experimental (animal) focal epilepsy models. In these models pre- and postsynaptic changes in calcium-signalling appear to be crucial. Presynaptic changes reported in stimulus-secretion coupling include increased calcium levels, neurotransmitter release and protein phosphorylation. In this study we compared presynaptic calcium levels in biopsies taken during surgical intervention from patients with chronic pharmacologically intractable forms of epilepsy.

From six patients with medically refractory temporal lobe epilepsy, a neocortex (NC) and mesiolimbic (ML) biopsy was collected. Synaptosomes (pinched-off isolated nerve terminals) were prepared (according to Dunkley et al. Brain Res. 441, 59-71; 1988) and loaded with FURA2-AM to measure basal and K^+-stimulated free calcium levels. One patient had tumor-associated epilepsy, the others temporal sclerosis associated epilepsy. The basal calcium concentration of the NC (mean±SEM: 486±29 nM, n=6) was significantly higher (p=0.018, F=12.1) than that of ML synaptosomes (320±39 nM, n=6). After depolarisation with 30 mM KCl there was no significant difference in calcium between synaptosomes of the biopsies (p=0.197, F=2.2). Supported by the Dutch National Committee for Epilepsy Research grant A91 to PNEdG.

50.17 COGNITIVE MEMORY IMPAIRMENT OF WISTAR AND LONG EVANS RATS IS PROPORTIONAL TO THE DURATION OF PILOCARPINE-INDUCED SEIZURES. J.Hort*, E.Pavlišová[1], V.Komárek, P.Mareš[3], G.Brožek[2]. Dept.Neurol., [1]Dept.Pediatric Neurol. and [2]Dept. Physiol., 2nd Med. Faculty, [3]Dept. Pathophys., 3rd Med. Faculty, Charles University, Prague, Czech Republic.

Navigation of pilocarpine-treated (PIL) and control Wistar (W) and Long Evans (LE) rats in the Morris water maze was mutually compared. Control LE rats were more efficient in place navigation learning than W rats. The effect of PIL (i.p. 320 mg/kg) was different in both strains. PIL induced in all LE rats a status epilepticus (SE) which had to be stopped after 2 hours by Clonazepam. In the W strain, only minority (30%) of rats developed SE, while majority (70%) responded by temporary seizures. During the following "silent period", SE deteriorated memory of W rats more than of LE strain. Memory of Wistar rats with temporary seizures was only slightly influenced and they could be tested immediately after seizures, whereas both strains with SE were not be able to stay on the platform during 9 days after seizures and their navigation was significantly impaired. Memory of PIL rats without seizures was intact. (Supported by grant UK 215/93/C)

50.18 EFFECT OF METABOLIC INHIBITION ON K^+ CHANNELS IN PYRAMIDAL CELLS IN RAT BRAIN SLICE. L. Hyllienmark* and T. Brismar. Dept of clinical neurophysiology, University Hospital of Linköping, S-58185 Linköping, Sweden

Metabolic inhibition or anoxia causes an inhibition of neuronal activity which in several studies have been related to an initial hyperpolarization due to an increase in membrane K^+ conductance. The aim of the present study was to analyse this mechanism in pyramidal cells *in situ*, and to elucidate the type of ion channel involved.

Brain slices (300 µm) were obtained from 10 to 19 days old rats and individual cells were visualized with infra-red differential contrast microscopy. Recordings were obtained from the CA1 field in the hippocampus. Whole-cell recordings were performed on pyramidal cells with patch-clamp technique (2-4 MOhm pipettes). The slices were continuously perfused with oxygenated CO_2 buffered Ringer solution with 10 mM glucose and 300 nM tetrodotoxin.

The resting potential of the cells (n=60) were -53.9±0.32 mV (mean, SEM). The mean slope conductance, measured from -80- to -50 mV was 4.4±0.15 pS. Addition of the metabolic inhibitor dinitrophenol (1mM) hyperpolarized 63% of the cells by on an average 5.3 mV (range: 1-12 mV). The hyperpolarization was accompanied by an increased outward current. The average change in conductance was 55% (range 2-112%). The hyperpolarization and change in conductance could be partially blocked by addition of either tolbutamid 1 mM or apamin 50 nM whereas charybdotoxin 100 nM had no such effect.

The results indicate that metabolic inhibition in a majority of pyramidal cells *in situ* activates several types of K^+ channels, leading to hyperpolarization and a decrease in excitability. This work has been supported by the Swedish Medical Research Council (project no. 14X-4255).

50.19 FREQUENTRY OPPORTUNISTIC INFECTION IN THE AGED CHRONIC NEUROLOGICAL PATIENT

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In many cases of the aged at the Chronic Neurological Disease have frequently opportunistic infective symtom in the clinical medicine. Most of these are respiratory infection. urinary tract infection. The opportunistic infection is caused by bulbar palsy and psuudobulbar palsy that can't discharged the sputum and dysphagia because of meddulla cranial nerve nuclear and cortico bulbar fiber damaged. and caused uninary ballon tube put continued becaused neurologenic bladder.

From aspect clinical data. inflammation index(WBC. CRP. ESR. IgG. IgM. IgA. C3. C4. Ch50. Lymphocyte%. T cell%. B cell%. CD. B cell IgG. B cell IgM. B cell IgA) analysis. Total case 15 cases. After the drawe blood measured at the laboratories.

Result:1)the aged compromised patient and normal range many immuno indexs go down. 2)in the aged comlpomised patient between infection state down not only T cell function but also B cell.

50.20 LOCALIZATION OF HISTONES IN THE SENILE PLAQUES OF ALZHEIMER'S DISEASE: CYTOCHEMISTRY AND ELECTRON MICROSCOPY

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An altered histone complement has been demonstrated biochemically in the brain cortex of patients with Alzheimer's disease (AD)(Lewis et al., 1984). In order to search for morphological evidence of the biochemical finding we used the ammoniacal silver reaction of Black & Ansley (1966) which visualizes color differences in the nuclear histones in Epon semithin sections. Yellow staining reveals lysine-rich histones, whereas black staining reveals arginine-rich components. Blocks of frontal cortex from 3 AD patients and 3 control subjects were fixed in sodium acetate buffered formalin and processed for electron microscopy. The study of semi-thin section of the cortex of the controls showed arginine only in the nuclei of neuronal, glial and endothelial cells. Semi-thin sections of the cortex of the AD patients, in addition to the staining of the nuclei, revealed intense staining of all senile plaques in the section, from the diffuse to the burnt-out type. The arginine-rich histones were localized in central cores and in neurites of the senile plaques, while the lysine-rich histones were more prevalent in the diffuse and the primitive plaques. These results show profuse amounts of histones abnormally localized in extranuclear sites. This finding may explain the high serum titers of antihistone antibodies reported in the AD patients (Meccoci et al., 1993). The arginine-rich histones overlap, thus, with the sites of amyloid and amyloid-precursor-protein (APP) deposition in the plaque neurites, probably indicating aberrant production and diversion from the cytoplasm to the processes instead of normal deposition in the nuclei. These findings may justify the biochemical data; however, their significance for the pathogenesis of AD remains to be determined.

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50.21 AUDIOGENIC SEIZURE AS A GENETIC ANIMAL MODEL OF EPILEPSY: MOLECULAR-GENETIC STUDIES. N.V.Ivanova A.P.Ryskov. Institute of Gene Biology Russian Academy of Sciences, Moscow, Russia.

The Krushinskii-Molodkina rat strain (KM strain) predisposed to audiogenic epilepsy can be used as a model for the investigation of the mechanisms of naturally occurring seizures. This predisposition is inherited and expressed in 98% of cases. 2% of KM rats are resistant to sound treatment. In this study we compared the kinetics of transcription of c-fos mRNA and RNAs homologous to ID and L1 repetitive elements of the rat genome in brain cells of KM rats. mRNA was monitored by Dot and Northern blot analysis before and at 0, 15, 30, 60, 120, 240 min after audiogenic seizure. A high basal level of c-fos mRNA was detected in the brain and liver of KM rats both sensitive and resistant to sound treatment. During sound treatment the basal level of c-fos mRNA decreased dramatically and then increased up to the normal level at 240 min after seizure. Kinetics of transcription of ID homologous RNA in a total brain has been found to be similar to that of c-fos mRNA, but differed significantly in cortex, medula oblongata, hippocampus and cerebellum.

50.22 LOW-THRESHOLD CALCIUM SPIKE BURSTS IN THE HUMAN THALAMUS: COMMON PHYSIOPATHOLOGY IN NEUROGENIC PAIN, DYSKINESIAS, EPILEPSY, TINNITUS AND PSYCHOSIS. D. Jeanmonod*, M. Magnin and A. Morel. Laboratory for Functional Neurosurgery, University Hospital, Ramistrasse 100, 8091 Zürich, SWITZERLAND.

Positive symptoms arise idiosyncratically after lesions of the nervous system and include neurogenic pain, abnormal movements, epilepsy, tinnitus and certain neuropsychiatric disorders (major depression, obsessive compulsive disease and psychosis). Stereotactic medial thalamotomies approved by the University Hospital ethics committee were performed on 104 patients with chronic therapy resistent positive symptoms. Microelectrode recordings revealed that most units (1994/2012) in the medial thalamus (central lateral and centre median-parafascicular nuclei, posterior complex) did not respond to motor activation or sensory stimuli as they normally do. Half of these units exhibited random or rhythmic (3-5 Hz) bursting activities with characteristics fulfilling extracellular criteria for low-threshold calcium spike (LTS) bursts. These were shown experimentally to be related to a hyperpolarized state of thalamic cells. After thalamotomy and depending on the symptom, 43 to 67% of the patients reached a 50 to 100% relief, with sparing of all neurological functions. On the basis of these clinical and electrophysiological results, we propose that positive symptoms result from a lesion-related loss of activation or increase of inhibition of the lateral thalamus and consequently of the thalamic reticular nucleus (RT). RT cells are thus hyperpolarized and in a position to produce LTS bursts that inhibit both medial and lateral thalamic nuclei. Under this inhibitory influence, medial and lateral thalamic cells can in turn generate LTS bursts which, sent back to the RT, lead to a self entertained LTS production very akin to the physiology of slow wave sleep.

50.23 BRAINSTEM AUDITORY EVOKED POTENTIALS REFLECT PERIPHERAL AND CENTRAL INVOLVEMENT IN MYASTHENIA GRAVIS?

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Myasthenia gravis (MG) is a hallmark for a disorder of neuromuscular transmission resulting from an autoimmune lesion of cholinergic receptor. Using the brainstem auditory evoked potentials (BAEP) we investigated parameters of auditory pathway in 30 patients with MG in stages II to III according to Osserman. BAEP were examined with monoaural rarefaction click stimulation of 69 dB SPL intensity and 12 Hz frequency. Data were recorded during 10 ms poststimulus intervals from M1-Cz and M2-Cz leads according to site of stimulation. Two experimental protocols were employed, in study A) in 20 patients and 10 controls, BAEP were obtained in four consecutive averages of 500 responses, and in study B) in 10 patients and 10 controls, four BAEP averages of 1000 responses were interspersed with three unrecorded sequences of 2000 stimuli. In the total number of 60 monoaural recordings of 2000 (study A) or 4000 (study B) averaged responses, BAEP abnormalities were found in 38%. Their reasons but were different. In 28%, the I-III interval was prolonged, and in 15% abnormal recordings both I-III and III-V intervals were delayed. In several recordings (17%), isolated latency increases of waves I or V were found. The mean amplitude of wave V was found higher in MG patients (study A and B) then in the control group. Comparisons between BAEP amplitudes obtained from successive averages in study B) in MG patients show: Gradual decrease of wave I amplitudes, by 18% in the 4th collection compared with the 1st one ($p<0.05$), gradual increase of wave III amplitudes, by 36% in the 4th collection compared with the 1st one ($p<0.01$). The amplitudes of wave V as well as all amplitude values obtained in the A) study did not significantly differ between separate collections. In controls, no sequential amplitude changes were found in either experimental protocol. Sequential amplitude decreases of the BAEP wave I seem to suggest a weakening of neural transmission in the cochlear segment of the auditory pathway, similar to EMG findings in MG. In turn, high mean amplitude of wave V and gradual increase of wave III amplitudes during longterm stimulation (study B) may represent a secondary involvement of central amplifying mechanisms. On the other hand, abnormal BAEP latencies found in an important proportion of MG patients may reflect focal lesions within the auditory pathway. We conclude that in MG are abnormal changes on both peripheral and central level of auditory pathway.

50.24 COMPARISON OF TOXIC DAMAGE INDUCED IN VITRO BY CISPLATIN AND CARBOPLATIN IN NON-NEURONAL CELLS OF FOETAL RAT DORSAL ROOT GANGLIA.

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Two distinct types of non-neuronal cells, fibroblasts and Schwann cells, migrating out from foetal rat dorsal root ganglia (DRG), were evaluated after cisplatin or carboplatin treatment. Chromosomal damage was estimated by quantification of micronuclei (MN). Evaluation of granular condensation of nuclear chromatin, another toxicological phenomenon, closely retaled to activation of apoptosis, was performed to compare genotoxic and cytotoxic action of the drugs. Both types of cellular damage were dependent on the concentration of the drugs (cisplatin ranged from 0.125 to 12.5 μmol/l and carboplatin from 0.5 to 400 μmol/l), as well as on the exposure time (24, 48 and 72 h).

The maximum number of micronucleated fibroblasts was similar after cisplatin and carboplatin treatment, and reached maximally 385% of control values. The formation of micronuclei in Schwann cells induced by cisplatin reached 914, 1032 and 1693% of control values after 24, 48 and 72 h exposure, resp. Maximal micronucleation of Schwann cells induced by carboplatin was different at shorter exposure times, predominantly at 24 h (366, 819 and 1667% of control values).

Our results suggest that Schwann cells are highly sensitive to platinum chemotherapeutics, especially to cisplatin. This fact can play a significant role in the development of cisplatin-induced peripheral sensory neuropathy.

50.25 EFFECT OF FIMBRIA-FORNIX TRANSECTION ON MOSSY FIBER SPROUTING IN EXPERIMENTAL STATUS EPILEPTICUS

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Administration of kainic acid (KA) induces prolonged seizures that are accompanied with a neuronal loss and mossy fiber sprouting in the dentata gyrus (DG). How the morphological changes are regulated by afferent neuronal pathways to the hippocampus, is poorly understood. In the present study, we investigated the effect of transection of the major subcortical pathway, fimbria-fornix (FF) on the neuronal loss and mossy fiber sprouting in the DG of rats with generalized seizures. Two days following KA administration (9mg/kg, i.p.), the FF was bilaterally cut by aspiration. Two months later, the rats were perfused for Timm staining. The severity of sprouting was scored from 0 (no sprouting) to 7 (most severe sprouting). Somatostatin immunohistochemistry was used to estimate the damage on hilar somatostatin neuronal loss. In the KA-treated rats, a dense sprouting of mossy fiber was seen along the septotemporal axis of the dentata gyrus (Timm score 4.72±1.09 septal end; 5.62±0.25 temporal end) accompanied with a severe loss of somatostatin neurons (42.4% in the septal end; 80.7 % in temporal end). In the KA-treated rats with FF transection, the sprouting in the septal end of the dentata gyrus was slightly less severe (3.47±0.28) than that in the KA-group. In these rats, however, there was virtually no damage of somatostatin neurons in the septal end of the hippocampus while the temporal end was severely affected (72.9 %). In the FF-transected rats without seizures, the amount of sprouting or the number of somatostatin neurons did not differ from that in normal rats. Our study suggests that in rats with generalized seizures (1) FF transection does not have any major effect on mossy fiber sprouting, (2) FF transection diminishes the loss of somatostatin neurons in the hilus, (3) mossy fiber sprouting is not necessarily associated with the loss of somatostatin neurons in the hilus.

50.26 DEVELOPMENTAL DISTRIBUTION OF CALBINDIN-D28K IN RAT CNS: IMPLICATIONS FOR HUMAN AMYOTROPHIC LATERAL SCLEROSIS.

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Calcium-binding proteins regulate neuronal calcium homeostasis, by buffering changes in intracellular free calcium concentrations. The calcium-binding protein Calbindin-D_{28k} (CAB) is present in subsets of neurons. The differential distribution of this protein may contribute to selective vulnerability in human Amyotrophic Lateral Sclerosis (ALS): CaB-immunoreactivity is absent in adult motor neurons which are selectively vulnerable in ALS. On the other hand CaB is present in virtually all neurons which are known to be spared in ALS. The aim of the present investigation was to study the CaB-distribution in the CNS of the rat during development using immunocytochemical staining techniques on cryostat cut tissue of embryonic day 15 (E15), Postnatal day 3 (P3) and adult male rats. Spinal motor neurons were only slightly CaB-immunoreactive in E15 rats. However, at P3, an intense CaB-staining was observed in motor neurons. In the adult rat CNS, CaB-immunoreactivity was relatively absent in spinal motor neurons, but clearly present in some layer V neurons in the motor cortex. Adult spinal sensory interneurons in the substantia gelatinosa and neurons in the thalamus, were also CaB-immunopositive. Our observations indicate a loss of CaB-immunoreactivity in motor neurons during postnatal development. We conclude that the CaB-distribution in the adult rat is comparable to human spinal cord.

50.27 GLUCOCORTICOID TREATMENT INFLUENCES THE CEREBRAL DAMAGE OUTCOME IN A RAT TRANSIENT HYPOXIA/ISCHEMIA MODEL.

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In vivo and in vitro studies indicate that glucocorticoids can potentiate the vulnerability of neurons to a variety of noxious stimuli. To study the effects of glucocorticoids on damage outcome in a hypoxia/ischemia rat model two experiments were conducted: I- acute pretreatment with vehicle (Cont;n=7), corticosterone(Cort;n=8) or Metyrapone (MET;n=6, a steroidgenesis inhibitor). II pretreatment for 8 days with vehicle(n=8) or corticosterone(n=4).

Methods: For all experiments halothane (1%) anaesthetized male wistar rats were used. In experiments I and II rats were perfused resp. 24 h and 6 h after hypoxia/ischemia. Degenerative changes in sections were evaluated using silver impregnation. Blood samples were taken during hypoxia/ischemia to determine plasma corticosterone levels. *) In the acute experiment rats were injected with MET (150 mg/kg,s.c.) and Cort (40 mg/kg,s.c.) respectively 4 and 1 h before 20 min of combined hypoxia and unilateral ischemia. *) In experiment II rats received daily, during 8 days an injection with vehicle or Cort. The last injection was given 24 h prior to hypoxia/ischemia.

Results indicated that in experiment I: Corticosterone levels between groups differed significantly and were highest in the Cort treated group and lowest in the MET group. Damage was significantly increased in the Cort group compared to the MET group. In Experiment II, however, the Cort treated rats had significantly less damage than the controls. This might be explained by the significantly lower corticosterone levels of the Cort group during hypoxia/ischemia.

In conclusion these results suggest that corticosterone levels during hypoxia/ischemia are important for damage outcome following hypoxia/ischemia.

50.28 SPONTANEOUS SHARP FIELD POTENTIALS IN HUMAN NEOCORTICAL SLICE PREPARATIONS FROM EPILEPTIC PATIENTS

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Human neocortical slice preparations were obtained from patients undergoing surgical treatment of refractory epilepsy. Repetitive sharp field potentials appeared spontaneously, i.e. without external manipulation (cf. Schwartzkroin and Knowles (1984) Science 223: 709-712; McCormick (1989) J. Neurophysiol. 62: 1018-1027), in these preparations. These potentials resembled epileptiform potentials in the EEG (50-300µV, 0.3-0.6Hz) and were associated with sequences of excitatory and inhibitory potentials of surrounding neurons. In this investigation, these potentials were characterized pharmacologically.

The slice preparations (n=30 of 13 patients) were superfused with artificial cerebrospinal fluid. Field potential (FP) and intracellular recordings (n=10) were done from layer III to V. The following agents were added to the superfusate: DL-2-aminophosphonovalerate (APV, 100 µM, n=11), 6-cyano-7-nitroquinoxalin-2,3-dion (CNQX, 5µM), bicuculline (10 µM), CGP 55845A (10 µM), verapamil (40 µM), phenytoin and carbamazepine (50-100 µM).

FP and postsynaptic potentials were reversibly blocked by the non-NMDA antagonist CNQX, but not by the NMDA antagonist APV. Likewise, the $GABA_A$ antagonist bicuculline reversibly suppressed spontaneous potentials but not the $GABA_B$ antagonist CGP 55845A. The organic calcium channel blocker verapamil, as well as the standard antiepileptic drugs phenytoin and carbamazepine also reversily blocked all potentials.

These findings suggest that the spontaneous activity is (1) mediated via non-NMDA receptors, (2) possibly synchronized via gabaergic interneurons, (3) generated involving calcium currents and (4) suppressed by antiepileptic drugs.

50.29 LONG-TERM MONITORING OF PENETRATION OF SPREADING DEPRESSION (SD) WAVES INTO THE ISCHEMIC CORTEX IN RATS.

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To assess predictive value of slow potential (SP) recording in ischemic region produced by middle cerebral artery (MCA) occlusion in rats, 4 capillary electrodes were chronically implanted at 2mm intervals from AP-3, L3 (E1) to AP1, L6 (E4). SPs of spontaneous or evoked SD waves were recorded during 4h after MCA occlusion and at 2-3 day intervals afterwards for 3 weeks. The initial focal ischemic depolarization (FID) was maximal at E4 while SDSPs remained high at E1, decreased at E2 and E3 and were almost lost at E4. SPSD amplitude was further reduced 3 days later and slowly increased in the following week. Cortical areas displaying initial reduction of SPSD below 10% of control amplitude can either stay low or show substantial (60%) recovery, the probability of which is inversely related to the duration of initial FID and reliably increases with distance from the focus. It is concluded that outcome of ischemia is predicted better by rate of SD recovery than by acute signs of MCA occlusion. Supported by grants GAMZCR 7141 and EBEWE 8009.

50.30 EFFECT OF SELEGILINE ON BRAIN CULTURES.

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Selegiline is a monoamine oxidase -B inhibitor reported to exert protective effects in Parkinson's disease as well as in animal models including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Cocultures of mesencephalic and striatal cells of embryonic C57Bl/6 mouse brains were used to investigate whether the neuroprotective effects of selegiline depend on the treatment scheme and whether it influences astrocytes present in the cultures. Cells were exposed to selegiline (1, 10, 100 µM) in three different schemes (i) in control cultures on the 8th day for 48 hours. (ii) pretreatment: on the 8th day for 48 hours, followed by administration of 1-methyl-4-phenylpyridinium (MPP^+, 0.5 µM) on the 9th day for 24 hours. (iii) delayed treatment: on the 9th day for 48 hours while MPP^+ was administered on the 8th day and remained in culture throughout with selegiline. In the delayed scheme selegiline (1 µM) increased dopamine content, number of tyrosine hydroxylase immunoreactive cells and astrocytes in the cultures. The data suggest that since astrocytes interact with injured neurons, agents like selegiline may have an indirect protective effect on these neuronal populations.

50.31 **THE USE OF THE RESISTIVE MRI SYSTEM IN THE PATIENTS WITH VERTEBRAL AND SPINAL METASTASES.**

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Purpose. The aim of this study was to define true possibilities of MRI in the diagnosis of metastasis of malignant tumours to the vertebrae column (vertebral bodies and the posterior elements), intradural-extramedullary space and spinal cord and to create optimum tactics of MRI carrying out in such cases.

Materials and Methods. All MRI were obtained on the whole-body resistive MR-tomograph Tomikon BMT 1100 R23 (Bruker, Germany). The techinique of examination was based on two principles - we used: 1). Both T_1-weighted (T_1W) and T_2-weighted (T_2W) MRI; 2). 3 planes: sagittal , axial and coronary. Especially for osseous metastasis identification we used T_1W IR - STIR with fat suppression. Often for patients with vertebral and spinal metastasis it is very hard to endure long MRI - so, we prefered fast T_2W SE and GRE methods or anesthesia. This report based on 2,587 cases of spinal noncontrast MRI.

Results. Tumours were found in 126 cases, metastasis - in 73 (41 - of spinal cord and spinal canal; 32 - of vertebral column). Verification of the MRI diagnosis was based on clinical and sectional data. Disjunctions were about 0.6% (disjanctions with clinical data - 78%). Anatomical spinal and spinal canal metastasis were divided into: intramedullary - 3, intraduro-extramedullary - 24, extradural - 17. Fast MRI methods were enough in 80%.

Conclusion. The differentiation diagnosis of spine metastasis involment by MRI (using our MRI tactics) was very effective in early stadies, espesially without symtoms of spinal cord or nerve root compression.

50.32 LIPID COMPOSITION IN SCRAPIE-INFECTED MOUSE BRAIN

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The neutral and phospholipid composition of mouse brain infected with scrapie prions was investigated. During the later stages of this disease the level of dolichol decreased by 30% whereas the level of dolichol phosphate increased by 30%. In terminally ill mice there was also a two and a half-fold increase of both total ubiquinone and its reduced form. Furthermore, a-tocopherol was elevated at this stage by 50%. In contrast, no changes were observed in phospholipid amount, in phospholipid composition and in phosphatidylethanolamine plasmalogen content during the entire disease process. The fatty acid and aldehyde composition of individual phospholipids remained unaltered as well. No modifications could be detected in cholesterol content. Thus, the majority of membrane lipids in scrapie-infected mouse brain are neither modified in quantity nor in structure, but specific changes occur to a few polyisoprenoid lipids. This specificity indicates that, although prions accumulate in lysosomes, the infection process is not associated with a general membrane destruction caused by lysosomal enzyme leakage.

50.33 EFFECTS OF LEAD ON BEHAVIOR AND BRAIN LEVELS OF GLIAL FIBRILLARY ACIDIC PROTEIN IN ADULT ANIMALS

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Although the sensitivity of the developing nervous system to the effects of lead exposure is well known, effects in the adult organism have not been extensively studied. The purpose of the present study was to evaluate the effects of lead in adult animals and to obtain further information on the sensitivity of behavioral and neurochemical assessment methods for detecting neurotoxicity. Four groups of rats were dosed with lead acetate at 0, 4, 8 or 12.5 mg/kg i.p., 5 days/week for 4 weeks. Neurological and behavioral changes were evaluated using a standardized functional observational battery and automated motor activity prior to exposure, at the end of the dosing period, and at 2 weeks post-exposure. In addition, concentrations of glial fibrillary acidic protein (GFAP) were measured in discrete brain areas using ELISA-based techniques 4 weeks following the termination of exposure. Results indicated that repeated lead exposure resulted in dose-related decreases both in the pattern and amount of motor activity, decreased rearing, signs of motor dysfunction, and changes in arousal. Dose-related increases in GFAP of up to 100% of control values were also found in frontal and occipital cortex, hippocampus and striatum. Taken together, these results indicate that the sensitivity of the adult nervous system to relatively low levels of lead exposure.

50.34 **THE LOSS OF EXCITABLE NEURONAL UNITS PROXIMAL TO A PERIPHERAL NERVE RECONSTRUCTION, EVALUATED WITH A NEW MAGNETIC RECORDING TECHNIQUE.**

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After peripheral nerve reconstructions functional recovery is often poor. This has been explained by 1) a large number of regenerating sprouts growing into the neuroma 2) by the reversed degeneration of the sprouts that did not reach a proper target organ and 3) the sprouts that do reach a proper target organs will most often not reach the target organ they were connected to prior to the transection. Furthermore, the number of nerve fibres in the proximal segment of a reconstructed peripheral nerve is assumed not to decrease after a nerve transection. These theories are based on histological axon counts proximal and distal to a nerve lesion. The disadvantage of this quantitative method is that a traumatised axon may spawn multiple sprouts. Each sprout will be counted as a separate regenerating neuronal unit. With our new quantitative magnetic recording technique we only count the number of regenerating neuronal units. The goal of our experiment was to evaluate the number of excitable neuronal units in the proximal segment of a transected and reconstructed peripheral. Therefore we unilaterally transected and reconstructed the common peroneal nerve of 5 rabbits. The nerve compound action signals (NCASs) were recorded magnetically when stimulating reconstructed nerves 10 mm proximal to the lesion after 8 weeks of regeneration time. The NCASs were also recorded from the contralateral nerve and from 5 control animals. The amplitudes of the signals recorded from the reconstructed nerves were at average 55% less than the signals recorded from the control group ($p<0.005$) and 45% less than those recorded from the contralateral nerve ($p< 0.005$). From these signals we calculated a decrease of approximately 50% in the number of excitable neuronal units proximal to a nerve lesion. This statistically significant decrease of 50% in the number of excitable neuronal units proximal to a nerve reconstruction, could well be the reason for much of the deficit in function recovery after a peripheral nerve reconstruction.

50.35 ASTROCYTES PROTECT DOPAMINERGIC NEURONS AGAINST HYDROGEN PEROXIDE INDUCED TOXICITY **IN VITRO**

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Reactive oxygen species, including hydrogen peroxide, are supposed to be involved in the etiology of various neurodegenerative disorders. Reportedly, cultured rat neurons are much more susceptible to hydrogen peroxide induced toxicity than cultured astrocytes. In the present study, we have used cocultures of mesencephalic rat neurons, plated on a supporting monolayer of neonatal rat astrocytes, as a model more representative for the in vivo situation. The viability in pure neuronal cultures was reduced by hydrogen peroxide at lower concentrations (IC_{50} 50 μM) than in astrocytic cultures (IC_{50} 400 μM). Uptake of [^{3}H]dopamine (DA) was used to determine the integrity of mesencephalic dopaminergic neurons in cocultures, since DA was taken up predominantly in dopaminergic neurons but hardly in astrocytes. The outgrowth of dopaminergic neurons was enhanced by striatal astrocytes, but not by cortical astrocytes, as reflected by an increase in DA uptake in cocultures of neurons and striatal astrocytes compared to cocultures containing cortical astrocytes or pure neuronal cultures. Hydrogen peroxide between 10 and 100 μM reduced the DA uptake in pure neuronal cultures. In cocultures, however, DA uptake was not affected by hydrogen peroxide at these concentrations. This neuroprotective effect was observed using either striatal or cortical astrocytes, which result suggests that neuroprotection by astrocytes is not related to a neurotrophic effect of the supporting astrocytes.

50.36 INTRAPERITONEAL INFECTION OF SCID MICE WITH THE SCRAPIE AGENT.

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Transmissible Spongiform Encephalopathies (TSE) include Creutzfeldt-Jakob disease in humans, scrapie in sheep and bovine spongiform encephalopathy. Their aetiology is still unknown and the knowledge of their pathogenesis incomplete. Infectivity and accumulation of PrPres (an abnormal, protease resistant isoform of the host encoded PrP protein) are found in the organs of the lymphoreticular system (LRS) before the involvment of the brain. Splenectomy of intraperitoneally infected mice prolongs the incubation period, and Severe Combined Immunodeficiency (SCID) mice are not infectable with the CJD agent via peripheral route. We questioned about the requirement of a LRS replication phase in the pathogenesis of the disease. SCID, immunologically reconstituted SCID and CB17 mice were intraperitoneally inoculated with the C506M3 scrapie strain. 33% of SCID mice were infected, whereas 97% of reconstituted SCID and 100% of CB17 mice developed the disease. PrPres was detectable by Western Blotting in the brains of all the diseased animals. However, in contrast to the two control groups, no PrPres was detectable in the spleen of SCID mice which developped the disease. This study directly evidences the existence of a primary replication step in the LRS in immunocompetent animals. It also strongly suggests that scrapie agent can spread directly to the central nervous system from the peritoneum, probably through autonomic visceral nerve fibres. To this point of view, the role of the peripheral replication step would not involve a processing of the agent, but would merely consist in increasing the probability for the agent to reach the central nervous system.

50.37 PROTEINE KINASE C ACTIVATION INDUCES NEURONAL TAU PHOSPHORYLATION AT SERINE 202.

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Neurofibrillary tangles observed in Alzheimer's disease brains are composed of paired helical filaments (PHF) accumulated in neurons.
Protein tau is one of the major structural proteins of PHF.
The monoclonal antibody AT8 (Innogenetics) recognize PHF-tau in a phosphorylated dependent manner (at serine 202).
Previous works showed that overactivation of protein kinase C (PKC) can induce neurodegeneration associated with antigenic changes in tau immunoreactivity.
The aim of this study is to investigate if direct activation of PKC is able to induce phosphorylation of tau protein epitope recognized by AT8 antibody. PKC activation is produced by phorbol ester (PMA) treatment.
Primary neuronal cultures were exposed for 15 min to increasing concentrations PMA (10^{-9} to 10^{-6} M) or to PMA (10^{-6} M) for 5 min to 1 hour.
AT8 immunoreactivity was analysed in exposed and in control cultures by laser confocal immunocytochemistry and by immunoblot analysis.
Our study reveals that PMA exposure induces in neuronal cultures a time-dependent and a dose-dependent increase in AT8-tau immunoreactivity compared to control cultures.
PKC activation induces directly or via an intracellular biochemical pathway (activation of MAP-kinases for exemple) an enhancement of AT8-tau immunolabelling in primary neuronal cultures and could be involved in accumulation of phosphorylated tau protein.

50.38 SYMPATHETIC SKIN RESPONSES AND R-R INTERVALS IN DIABETICS.

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The Sympathetic Skin Responses (SSR) described a century ago, have been proposed by Shahani et al. (1984) as a method for the study of sympathetic unmyelinated fibres dysfunction in polyneuropathies, and electrocardiogram R-R intervals as a method for studying the parasympathetic control of heart rate. Because these studies are attributed a great inter-individual variability, it has seemed interesting to us to test their diagnostic value on a group of diabetic subjects, by comparing them to EMG and clinical examination.

36 diabetic subjects were examined and classified into 5 groups according to the existence and importance of a polyneuropathy. They were compared to an age matched group of 32 control subjects. The SSR were recorded at the extremities of the 4 limbs, synchronized on a short electric shock, and R-R intervals were measured at rest, during 3 Valsalva manoeuvres, and one active orthostatic test. The sensitive and pain thresholds were searched for, and a standard EMG recording was performed.

The amplitude is the most reliable criterion in SSR evaluation : it significantly decreases in diabetics with polyneuropathy, and can even disappear in case of severe polyneuropathies. This amplitude is correlated to motor and sensitive conduction velocities and to the H reflex. A decrease in R-R interval variations is observed in diabetics during rest as well as Valsalva and orthostatic manoeuvres, and becomes maximum in severe polyneuropathies. R-R interval variations during Valsalva and orthostatic manoeuvres are correlated to median nerve motor and sensitive conduction velocities.

These results suggest that despite the disadvantage of a great inter-individual variability, the study of unmyelinated fibres of the autonomic nervous system by SSR and R-R intervals constitutes a complementary approach to that of large diameter fibres of the sensori-motor system by EMG.

50.39 LIPID PEROXIDATION AND PHOSPHOLIPIDS IN RABBIT SPINAL CORD AFTER ISCHEMIA/REPERFUSION INJURY.

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The effect of spinal cord ischemia (10, 20 and 40 min) and post-ischemic recirculation (10, 30 and 60 min) on lipid peroxidation (LP) and phospholipids was investigated. Spinal cord ischemia was accompanied by lipolytic processes with relatively small changes in concentration of LP products (TBA-RS). Reestablishment of the blood supply after 20 min ischemia was accompanied by significantly increased levels of TBA-RS from 30 min of recirculation, following 40 min ischemia already after 10 min of recirculation. Higher accumulation of TBA-RS during recirculation was accompanied by higher phospholipid degradation. Ischemia itself significantly reduced the concentration of phosphatidyl inositol (IP), phosphatidyl ethanolamine (EP), ethanolamine plasmalogens (Epls) and phosphatidic acid (PA). Onset of recirculation after ischemia was accompanied by diverse pattern of changes in PA,IP, Epls and phosphatidyl serine (SP), while the concentration of EP remained at the levels detected after particular ischemic intervals.

50.40 THE EFFECTS OF GINKGOLIDE B ON GUINEA PIG MEDIAL VESTIBULAR NUCLEUS NEURONS IN VITRO.

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It has been shown that ginkgolide B enhances vestibular compensation, the behavioural recovery process which occurs following the removal of the vestibular receptors in one inner ear. The present study investigated the mechanisms of action of ginkgolide B by examining its effects on medial vestibular nucleus (MVN) neurons in guinea pig brainstem slices. Ginkgolide B, 10^{-6} M, was dissolved in 25% dimethylsulphoxide (DMSO) and 75% distilled water. The action potential frequency of MVN neurons was recorded from 500µm coronal slices. After baseline firing had been recorded ginkgolide B was superfused for 4 mins followed by a return to standard artificial cerebral spinal fluid (ACSF). When the cell had returned to baseline firing DMSO was applied for 4 mins, followed by ACSF. The drug protocol was reversed after the first 10 cells. Preliminary analysis demonstrates that when DMSO was applied first 60% (6/10) of MVN neurons responded to ginkgolide B. Of these 20% showed a biphasic decrease with a mean magnitude of 100%, 30% displayed a monophasic decrease with a mean magnitude of 78% and 10% showed a 30% increase. When ginkgolide B was applied first 20% (2/10) of the cells responded. Of these 10% showed a monophasic decrease of 69% and 10% showed an increase of 20%. While it is necessary to investigate these effects further the results indicate that ginkgolide B has a direct effect on MVN neurons, at least in vitro.

50.41 DO DIFFERENCES IN DISTRIBUTIONS AND PHARMACOLOGICAL PROPERTIES OF VOLTAGE-OPERATED POTASSIUM CHANNELS CONTRIBUTE TO DIFFERENCES IN SEIZURE SUSCEPTIBILITY OF BRAIN AREAS ?

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The family of voltage-operated potassium channels contains a great number of members which have on the one hand different properties and on the other hand different distributions in brain. These differences might possibly contribute to the distinct seizure susceptibility of several brain areas. In order to shed some light on this question, we have investigated the effect of the epileptogenic drug pentylenetetrazol (PTZ) on eight cloned potassium channels (slow and fast inactivating neuronal potassium channels of the rat; expression in oocytes of Xenopus laevis; investigation with the two-electrode voltage-clamp-technique).
The investigations revealed that the potassium channels had a different sensitivity to PTZ. For example, at a potential of 0 mV there were strong current reductions for the $K_v1.1$, $K_v1.4$ and $K_v2.1$ channel, moderate for the $K_v1.3$ and $K_v1.6$ channel and small reductions for the $K_v1.2$, $K_v1.5$ and $K_v3.4$ channel. Correlating these results with the distribution of the potassium channels in rat brain (in-situ hybridization data from literature) showed that the hippocampus, a region with a high seizure susceptibility, predominantly contains the channels with the strong sensitivity to PTZ, whereas in the cerebellum, a region of low seizure susceptibility, the amount of channels with a low sensitivity is much more pronounced.
Although the relevance of the above shown results has to be further elucidated, the data lead one to speculate that the different distributions of potassium channels with different properties play a role in the development of different seizure susceptibility of the brain areas.

50.42 DISTRIBUTION OF CALCIUM BINDING PROTEIN-IMMUNOREACTIVITY IN THE EPILEPTIC HUMAN DENTATE GYRUS

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Human epileptic patients with intractable seizures originating in the temporal lobe have undergone surgery, and hippocampal sections from the biopsy tissue were immunostained with antisera against the calcium binding proteins calbindin D28k, parvalbumin and calretinin. The CA1 region of all patients was seriously injured, frequently even absent, and the hippocampus reduced to a dentate gyrus with remnants of the CA2/CA3 subfield. Numerous calbindin-containing interneurons were found in all subfields of the hippocampus, however, the granule cells of the dentate gyrus - which are normally strongly immunoreactive for calbindin - only rarely showed consistent staining. Parvalbumin-containing interneurons were found in small numbers with a regular spacing in the dentate gyrus. Based on their light microscopic features they were identified as axo-axonic cells, which was confirmed by electron microscopic demonstration of axon initial segments as postsynaptic targets.Parvalbumin-containing basket cells were absent, since somatic synapses were rare. Calretinin-containing neurons were sparse, however, calretinin-immunostained axon terminals forming both symmetric and asymmetric synapses were observed in large numbers in the entire width of the dentate molecular and granule cell layers. The high density of asymmetric calretinin-positive synaptic terminals in the outer two thirds of the molecular layer suggests a sprouting of supramammillary afferents, which are normally restricted to the inner third of the molecular layer. The changes observed here support the view of the dentate gyrus as a motor of recurrent temporal lobe seizures.

50.43 EFFICACY OF THEOPHYLLINE IN REDUCING THE TREMOR OF PATIENTS WITH ESSENTIAL TREMOR OR PARKINSON'S DISEASE.

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Although propranolol is a standard treatment for tremor in patients with essential tremor, we have previously reported that theophylline is effective in this disorder. In this presentation, we will present data which indicate that theophylline is also effective in the management of troublesome tremor in patients with Parkinson's disease. Tremor was measured using the volumetric method in a series of newly diasgnosed patients who had not yet been treated with drugs. Over a period of 2 weeks theophylline reduced significantly the extent of the tremor and greatly improved subjective assessments and general mobility. The mechanism is unclear, but at the dose levels employed it is likely that antagonism of adenosine receptors is involved, rather than inhibition of phosphodiesterase which is only achieved at much higher doses. The mechanism of action may also involve inhibitory neurones, since we have shown that chronic treatment of animals increases the sensitivity of neurones to GABA. It is suggested that theophylline may be a useful adjunct to the therapy of Parkinsonian patients.

50.44 CALCIUM-BINDING PROTEINS IN THE HIPPOCAMPUS OF TMT-TREATED RATS:AN IMMUNOCYTOCHEMICAL AND IMMUNOCHEMICAL STUDY

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Administration of the neurotoxicant TMT is known to cause severe damage to the neuronal component of the CNS,especially the hippocampus,inducing cognitive deficits comparable to those seen in Alzheimer's disease.The present study investigates by immunocytochemical and immunochemical methods the behaviour of the calcium-binding proteins S100ß and parvalbumin(PV),which label glial cells and specific neuronal subpopulations respectively,in the hippocampus of rats acutely treated with TMT.Both the concentration of S100ß in extracts and the number of S100ß-labelled cells were significantly higher in treated rats than in controls.However,in TMT-treated rats PV-containing neurons were selectively spared from the generalized neuronal reduction,especially observed in CA3,their number not being reduced.Whether the increase in S100ß merely reflects the reactive gliosis or is also related to the possible neurotrophic role of the protein remains to be elucidated.Likewise,a relationship between the possible calcium-buffering protective role of PV and the selective sparing of PV-containing cells is a matter of speculation.The behaviour of other calcium-binding proteins(calbindin,calretinin)is currently under investigation.

50.45 EFFECT OF *IN VIVO* TREATMENT WITH CABERGOLINE ON ANTIOXIDANT ENZYMES AND PHOSPHOLIPID PEROXIDATION IN HIPPOCAMPUS AND STRIATUM OF RAT BRAIN.

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The role of oxygen radicals and lipid peroxidation in the pathogenesis of Parkinson's disease (PD) is currently considered of great interest. In this context, it is interesting to note that some drugs used for the treatment of PD are able to elicit an increase in antioxidant enzymes, such as the superoxide dismutases (SOD's) in the rat striatum (pergolide, deprenyl), or reduce lipid peroxidation in the rat brain (bromocriptine).

Cabergoline is a compound that mimicks the action of dopamine at D_2 receptor sites in the central nervous system.The aim of this work was to investigate the effects of cabergoline on lipid peroxidation and antioxidant enzymes, i.e. Cu,Zn-SOD, Mn-SOD, catalase and glutathione peroxidase in rat brain hippocampus and striatum.

Cabergoline was administerd in two different doses (2.5 and 10 mg/kg per os) for 3, 6 and 10 times.

Cabergoline treatment decreased basal and stimulated lipid peroxidation both in hippocampus and striatum without markedly acting on antioxidant enzyme activities. This suggested a protective action on membrane structure rather than a specific antioxidant action.

50.46 PROTECTION OF CULTURED EMBRYONIC DOPAMINERGIC NEURONS AGAINST 6-OH-DOPAMINE-INDUCED DAMAGE BY NEUROTROPHIN-4/5, BY ACTIVATED P21RAS OR BY A PEPTIDE INHIBITOR OF THE PRO-INTERLEUKIN-1ß-CONVERTING ENZYME

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The possible neuronal function of the receptor tyrosine kinase signal-trans-ducing proto-oncogene p21ras was investigated by using transgenic mice expressing activated Ha-p21Ras under the control of the neuronal synapsin-I-promotor. We prepared primary cultures of the E14 mesencephalon of transgenic animals containing the tyrosine hydroxylase positive neurons of the substantia nigra. 74,6 % of these neurons survived the treatment with 150 µM 6-hydroxy-dopamine (6-OHDA) for 2 hours. In cultures obtained from wildtype animals only 38 % of the tyrosine hydroxylase positive neurons survived. The activated p21ras transgene replicates the protective effect against 6-OHDA damage promoted by neurotrophins: Preincubation of wildtype tyrosine hydroxylase positive neurons with NT-4/5 (50 ng/ml) showed that over 80 % of the dopaminergic neurons survived.

In order to approach the possible intracellular mechanism leading to the protective effects against 6-OHDA treatment, we used an irreversible inhibitor of the pro-interleukin-1β converting enzyme (ICE), the chloromethyl-derivative of the tetrapeptide YVAD. Preincubation with the peptide-inhibitor (150 µM) for 1 day led to a significant increase in the survival of cultured tyrosine hydroxylase positive neurons (78 % survival versus 24 % in control cultures). This protective effect of the ICE-peptide inhibitor against 6-OHDA damage was also observed in PC12 Cells (80 % survival versus 30 % in controls) and in cultured chicken sympathetic neurons (80% survival versus 30 % in controls).

50.47 ACTIVATION OF RESTRICTED CAUDAL MIDBRAIN REGIONS SUPPRESSES TONIC SEIZURES.

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Activation of an area of dorsal midbrain centred on the intercollicular nucleus suppresses tonic seizures in the maximal electroshock model of epilepsy. Integrity of ipsilateral descending projections from this area to the lateral pontine and rostroventral medullary reticular formation is critical for this effect. However, major efferent connections to these parts of the brainstem are shared by several dorsal midbrain structures including the intercollicular, PAG, cuneiform and pedunculopontine areas. The present study therefore examined whether the shared efferent anatomy in dorsal midbrain was predictive of a common ability to suppress tonic seizures in the electroshock model.

To provide a more detailed map of regional sensitivity for seizure supression, injections of the GABA antagonist bicuculline methiodide (100pmol/400nl) were made at different locations within the dorsal midbrain of chronically cannulated rats. Each animal also received control injections of an equivalent volume of saline. Following the microinjections maximal electroshock was administed via ear-clip electrodes and the duration of tonic hindlimb extension (THE) was measured.

The results showed two sensitive regions where bicuculline injections produced a greater than 50% suppression of THE compared with the saline control. The first zone was centred on the intercollicular area (22/30,73% of sites >50% suppression) and confirms findings of previous mapping studies. The second zone was located in the caudal cuneiform area and rostral parabrachial nucleus (11/14,79% of sites >50% suppression). Areas surrounding these zones were significantly less sensitive (11/48,23% of sites <50% suppression) (Chi squared =25.062; df=2; p<.0001). These data confirm previous reports of an anticonvulsant zone centered on the intercollicular nucleus; previous results have been extended by the provision of a clear caudal boundary to this region. Secondly, a completely new anticonvulsant zone centred on the caudal cuneiform/rostral parabrachial area has been identified. It would be interesting to determine the relationship between this and other anticonvulsant midbrain regions.

50.48 EEG MAPPING IN HUNTINGTON'S DISEASE.

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Study of the brain bioelectrical activity is one of the most important and valuable methods of investigations of the pathological changes in Huntington's Disease (HD).We have investigated bioelectrical activity of brain by EEG mapping in 20 patients with classical hyperkinetic type of the disease (8 males and 12 females, average age 41,8 years), as well as in their 22 clinically healthy first-degree relatives. All patients were divided into 2 groups - with moderate and severe dementia. We have found significant intensification of the δ-activity power in frontal and temporal parts, and intensification of the high-freguensy β-activity power in temporal parts of the brain. It has been estabished that more pronounced power decrease in fast region of spectrum and depression of α-rhythm in central-parietal parts correspond to the severe degree of dementia. Group of clinically healthy relatives (siblings and children of HD patients) turned out to be characterized by the power increase of biopotentials in δ-, θ-, and α-2-range. Increase of δ- and θ-activity was observed more often in frontal parts of hemisphere.

On the basis of our EEG mapping results we can suggest that there are some subsequent changes in bioelectrical activity of the brain in every stage of the disorder which perhaps reflect the degree of neurodegenerative process in Huntington's Disease.

50.49 SISTEMICALLY APPLIED PENICILLIN IN CONDITION OF DEEP HYPOTHERMIA (14-17°C) INDUCES THREE TYPES OF GENERALIZED EPILEPSY.

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In our recent studies it was shown that rats underwent artificial cooling to 14-17°C suffered from alteration of the activity of thalamocortical synapses and exhibited spike & wave discharges (SWD) in the EEG, at the body temperature (b.t.) of 25°C. The objective of the present investigation was to determine the ability of deep hypothermia to change the integrity of thalamocortical circuits after systemic penicillin (PCN) injection. At normal b.t. this agent elicited reversible generalized epileptic seizures (petit mal), consistent with SWD in the EEG. For this purpose 45 adult rats were chronically prepared with scull electrodes in bilateral symmetrical position over the frontal and parietal cortex without affecting the cortex. After 4 days of postoperative recovery, the animals were divided into three groups and were cooled to the state of deep hypothermia (14°C, 15°C and 17°C) respectively, by the means of the closed container technique. The animals of all three groups received PCN ($1.5x10^6$ IU/kg) intraperitoneally at the b.t. of 17°C, and after that they were allowed to rewarm spontaneously in the next 5 hs. Through all this period EEG and behavior were continuously monitored.

In all three groups, PCN induced appearance of SWD but not before b.t. raised to 25°C. Once established, SWD were continuously recorded in the EEG till the zone of normothermia (37.5°C). In group I (cooling to 14°C), between 30 and 40% of animals developed grand mal atac which, in some cases, tended to progress in status epilepticus. During the atac. we recorded multiple, high-voltage, 10 Hz spikes. The mortality rate of these animals were 100%. In group II (cooling to 15°C), 80% of animals suffered from development of myoclonic epilepsy, characteryzed with severe face myoclonus and clonic movements of forelimbs. Posture muscles were not affected and animals were completely recovered. EEG recordings showed multiple spikes and waves, or/and SWD. Finally, in group III (cooling to 17°C) we could registered only 4-7 Hz SWD, together with the mild facial myoclonus. In this study, we have shown very delicate physiological differencies between cooling to 14, 15 and 17°C. This results sugest that esential differencies between these three groups could be totally or partially disruption of blood-brain barrier (BBB) in the animals cooled to 14°C and 15°C. Disfunction of BBB could mediate the effects of PCN upon structures other than cortex, such is forebrain and brain steam. This event facilitate development of more severe forms of epilepsy (myoclonic and grand mal).

50.50 MOLECULAR ANALYSIS IN DIAGNOSTICS OF SPORADIC HUNTINGTON'S DISEASE.

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PCR mutation analysis of unstable CAG repeat in IT15 gene has been used for sporadic Huntington's disease (HD) in Russian patients with no family history. Direct DNA diagnostics in combination with other examinations allowed to distinguish HD from neuropsychiatric disorders commonly misdiagnosed as HD. We reported two cases with unusual clinical features atypical for HD phenotype. The first patient had choreic hyperkinesis with repetitive stereotyped behaviour. Second patient was diagnosed with the vasculitis of brain vessels. The DNA samples from this patients demonstrated the PCR fragments with normal lengths without CAG repeat expansion.

50.51 QUANTITATIVE EEG AND rCBF IN ALZHEIMER'S DISEASE

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Relationships between quantitative EEG and regional cerebral blood flow (rCBF) were analyzed in 31 patients (20 females, 11 males; mean age 68.2 years) in different stages of Alzheimer's disease. As a group the demented patients had higher delta and theta activities, lower alpha activity and lower alpha peak frequency than control subjects. rCBF was reduced in all regions studied but mainly in the temporo-parietal areas. All the rCBF values were related to EEG measures, but the relative importance of the various predictors varied from region to region. The relative powers in the theta and alpha bands were the best predictors of rCBF changes in all regions considered. Changes in the relative power of the delta and beta bands were significantly associated with changes in all but the occipital region. The peak frequency of the alpha band was significantly associated with changes in frontal, parietal and temporal rCBF. Relationship between rCBF values and absolute power spectra values showed a significant association between the absolute power of the delta and theta bands with rCBF changes. Our findings show that a significant association exists between cerebral functional activity, as measured by EEG recordings, and rCBF. This association was evident from the inverse correlation between absolute and relative power of the delta and theta band and rCBF values and from the direct correlation between peak frequency of the alpha band and rCBF values.

50.52 INHERITANCE PATTERN OF STRIATAL DOPAMINE IN AS/AGU RATS

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The AS/AGU rat is a spontaneous mutation characterised by an ungainly, wide, staggering gait, hindlimb rigidity, whole body tremor and (with age) difficulty in initiating movement; it exhibits a considerable and progressive decrease in dopaminergic cells within the substantia nigra (Clarke & Payne, Eur.J.Neurosci. 6, 885-888, 1994). A breeding programme involving Albino Swiss (AS) and AS/AGU parent rats was used to produce the F1 offspring of AS x AS/AGU matings and, subsequently, F1 x AS/AGU back crosses. When adult, the movement of all animals was assessed blind by observers on three occasions, each animal being identifiable by a subcutaneous transponder implanted before weaning. All AS/AGU and half the F1 x AS/AGU back cross animals had abnormal gait, while all AS, F1 and the remaining F1 x AS/AGU back cross animals showed normal gait, implying that the mutation is recessive. Brains of males aged 12-15 months (n = 10 per group) were sectioned transversely on a cryostat (-20°C) to produce a cut face just caudal to the anterior commissure (approx. Bregma -0.5mm) and 1mm diameter x 1mm deep micropunches were taken from three areas of the caudate-putamen. Levels of dopamine were measured in all samples by HPLC-ECD followed by protein estimation. Levels of dopamine in the dorsal and central caudate-putamen varied according to a simple inheritance pattern, being high in males from AS, F1 and F1 x AS/AGU back crosses without locomotor impairment, but lower in AS/AGU and F1 x AS/AGU back crosses with disordered gait. Dopamine levels in the ventral caudate-putamen did not show such a clear variation.

50.53 ACTION OF FELBAMATE IN STRIATUM: BEYOND ANTIEPILEPTIC EFFECTS

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We have characterized the effects of the anticonvulsant drug felbamate (FBM) on striatal neurons, recorded in vitro by using both intracellular recordings in slices and whole-cell recordings in acutely isolated neurons. FBM, at therapeutically relevant concentrations (30-300 μM), showed multiple mechanisms of action. Like other antiepileptic drugs, FBM showed a direct inhibitory action on current-evoked firing discharge of striatal neurons. A patch-clamp analysis of this effect revealed a dose-dependent reduction on voltage-dependent sodium currents (10-100 μM). We also tested whether FBM affected corticostriatal glutamatergic transmission. In control medium (1.2 mM magnesium), both AMPA-mediated extracellularly and intracellularly recorded field potentials and EPSP respectively, evoked by cortical stimulation, were not affected by 30-300 μM FBM. When magnesium was removed from the perfusing solution, a procedure which reveals an NMDA component in the corticostriatal potential, FBM (30-300 μM) produced a dose-dependent reduction in the amplitude of both field potentials and EPSPs. Furthermore, these concentrations of FBM reduced the inward current produced by either bath- or focal-application of NMDA, suggesting that the observed reduction of the NMDA-mediated component of the synaptic potentials can be caused at a postsynaptic site. Although an interaction with the NMDA receptor-channel complex has been already suggested for FBM, to our knowledge this study represents the first investigation on the effects of this drug on an identified glutamatergic pathway in the mammalian brain. The unique pharmacological profile of FBM does not only account for the antiepileptic effect, but seems to encourage its use in other neurological diseases, like neurodegenerative disorders (Huntington's Chorea, Parkinson's Disease), where the failure of energy metabolism combined with an excessive activity of excitatory transmission has been supposed to be responsible for neuronal death.

50.54 ACTIONS OF ALUMINIUM ON TEA-INDUCED POTENTIATION.

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In a previous study we have shown that aluminium (Al) blocks tetanus-induced long-term potentiation (tLTP). Since Al inhibited this NMDA-receptor dependent potentiation, we here studied another form of neuronal plasticity induced by a brief application of the K^+-channel blocker tetraethylammonium chloride (TEA). This form of potentiation is believd to be based on the activation of voltage activated calcium channels (VDCCs), which can be blocked by Al in neuronal cultures. Using the hippocampal slice preparation, excitatory postsynaptic potentials (EPSPS) were elicited by stimulating the Schaffer collateral/commissural pathway and extracellularly recorded in the stratum radiatum of the CA1 region. TEA (25 mM/7 min) induced a robust and sustained increase in synaptic transmission (TEA-LTP). Occlusion experiments revealed that a subsequent tetanus did not allow further potentiation of synaptic transmission. When TEA was applied together with 0.68 μg/ml Al, the potentiation was significantly suppressed. For 2.7 μg/ml, the inhibition of TEA-LTP was more pronounced and the remaining potentiation declined below baseline values within 45 min. Interestingly, the block of TEA-LTP by Al allowed the subsequent induction of t-LTP. Therefore we hypothesize that Al inhibits the induction of TEA-induced potentiation by a block of VDCCs. Concerning the effective concentrations the effect of Al on TEA-LTP is directly comparable to the effect of Al on t-LTP. Both, the occlusion experiments and the effective concentration range provide evidence that both forms of potentiation share common mechanisms. Furthermore, TEA-LTP has proven to be a sensitive model to investigate Al-induced alterations of neuronal plasticity.

51.01 **EFFECT OF FEEDING-INDUCING PVN NOREPINEPHRINE MICROINJECTIONS ON DOPAMINE AND ACETYLCHOLINE IN THE NUCLEUS ACCUMBENS: MICRODIALYSIS IN FREELY MOVING RATS.**

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Norepinephrine (NE) was microinjected into the paraventricular nucleus (PVN) while microdialysis was used to monitor extracellular dopamine (DA) and acetylcholine (ACh) in the nucleus accumbens (NAc). The PVN is a site where exogenously administered NE can act through alpha-2 receptors to elicit eating behavior and preference for carbohydrates. It was hypothesized that NE in the PVN acts on a behavior reinforcement system by altering DA/ACh balance in the NAc.

NE microinjections (80 nmol in 0.3 µl), which effectively elicited feeding in satiated rats in separate tests, caused a significant increase in extracellular DA (209 %) and decrease in ACh (73 %) when the same animals were tested in the absence of food. In contrast, when the food was available and ingested, extracellular ACh levels increased (151 %) instead of decreasing.

These results and others, suggest a functional link between the PVN and the NAc involved in the reinforcement of eating in which DA initiates and ACh stops appetitive behavior.

51.02 REPEATED ETHANOL ADMINISTRATION AND DEHYDRATION DIFFERENTIALLY ALTER THE LEVELS OF PARVALBUMIN AND CALBINDIN-D28k IN MOUSE BRAIN

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The Ca^{2+}-binding proteins parvalbumin (PV) and calbindin-D28k (CB-D28k) are known to mediate or regulate the effects of cytosolic, free Ca^{2+} ions on intracellular metabolism. Moreover, both ethanol and dehydration alters Ca^{2+} homeostasis of neurons. In the present study, alterations in the number of neurons expressing PV or CB-D28k were studied after repeated ethanol treatment or dehydration.

Male mice were injected i.p. with ethanol (4g/kg b.w.) for 7 days, while control animals received physiological saline. Another group of animals was dehydrated for 4 days, while matching controls were kept under normal conditions. After treatment, PV and CB-D28k immunocytochemistry was performed. The number of PV or CB-D28k immunoreactive (IR) interneurons was quantified in frontal and parietal cortices and hippocampus.

Repeated ethanol administration significantly decreased the number of PV-IR interneurons in the frontal and parietal cortices and hippocampus. In contrast, the same treatment had reversed effects on CB-D28k-IR interneurons. 4 day-long dehydration elevated the number of PV-IR and CB-D28k-IR interneurons in frontal and parietal cortices as well as in hippocampal sections.

These results provide further information on the changes of Ca^{2+} homeostasis and the role of Ca^{2+}-binding proteins in balancing cytosolic free Ca^{2+} movements under experimental conditions.

51.03 SENILE PLAQUE-LIKE FORMATIONS IN THE LOCUS COERULEUS OF YOUNG SUICIDES WITH A DIAGNOSIS OF MAJOR DEPRESSION

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A study of the locus coeruleus (LC) with the Ammoniacal Silver Reaction (ASR) for histones (Black & Ansley, 1966) in the brains of young suicides with a diagnosis of major depression revealed a high incidence of senile plaque-like formations. Observations of the resin-embedded semi-thin sections in the light microscope showed a high concentration of diffuse and primitive senile plaques (SP). In the matched controls only rare atypical black deposits were encountered. In the LC of the patients the SP were seen in contact with cell bodies and glial nuclei, around capillaries, next to dendrites and also interconnected in long assemblies. Observations of the thin sections with the electron microscope revealed a fibrillar texture with ASR deposites of the SP and granular deposits in the chromatin of the nuclei of both controls and patients. This confirms that SP contain also histones. The presence of SP in young individuals is unexpected. However, using antibodies to amyloid, SP have been found in temporal lobotomy specimen of young epileptics (Ian et al., 1994). Thus, it seems that the deposition of amyloid in the brain is not a property uniquely of the aged, but is induced by the pathology of the area. In view of the involvement of the noradrenaline pathway from the LC neurons in the pathogenesis of major depression, the presence of SP in this area is significant. It suggests that some aspect of major depression has an inducing influence on the deposition of histones in SP-like formations in young individuals.

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51.04 THE EFFECT OF TEMPORAL LOBECTOMY ON PERFORMANCE IS VERBAL AND VISUOSPATIAL MEMORY TESTS

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Our previous study demonstrated that focal lesion to the anterior part of hippocampus and/or medial part of amygdala results in memory deficit limited to visuospatial function. As the left and right side damage yielded similar effects we supposed that memory functions subserved by those structures are not lateralized. The present study was to investigate whether temporal lobectomies, involving large portions of temporal cortex in addition to hippocampus and amygdala, would produce laterality effects in the same test. Eighteen patients who has undergone unilateral temporal loboctomy and 11 control subjects participated in this study. Four experiments were run in which subject's task was to recall verbal or visuo-spatial material presented in a simultanous or sequential manner. The data showed that only the right-side lobectomy resulted in memory impairment. However, similarly to our previous study, this impairment was observed solely in visuo-spatial material (in both sequencial and simultanous versions of the tests), whereas memorazation od verbal material was not disturbed either by left or right side lesions. The results suggest that laterality effects are probably connected with the function of temporal cortex.

51.05 RETENTION AND WORKING MEMORY IN SCHIZOPHRENIA AND IN PATIENTS WITH FRONTAL LOBE PATHOLOGY.

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Background: In schizophrenic patients deficits in working memory are found, suggesting frontal lobe involvement. The present studies examine working memory in schizophrenics and patients with frontal lobe pathology using the subjective ordering paradigm and a visuospatial working memory test.

Methods: Two tasks relying on short-term retention, i.e. digit span, missing item scan, and two tasks on working memory, i.e. randomization span and self-ordered pointing were presented to schizophrenic patients (n=24), patients with frontal lobe pathology (n=12) and matched normal controls (n=24). The DOT test was administered to schizophrenic patients (n=12) and normal controls (n=12). All patients gave written consent.

Results: The schizophrenic patients performed significantly worse on the short-term retention tasks, while no significant differences were found on the working memory pointing tasks. The frontal lobe patients showed a reversed pattern. In a second study schizophrenic patients showed a significant worse performance on the visuospatial working memory test compared to normal controls.

Conclusion: The data show that the schizophrenic patients show deficits in short-term retention, in contrast to patients with frontal lobe pathology and normal controls. The results also suggest that the Subjective Ordering Tasks are vulnerable to self-organization strategies in working memory.

51.06 COGNITIVE ENHANCERS AND HUMAN AGING

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Although caffeine is widely recognized as a mild CNS stimulant drug, its consumption might lead to improvement of higher cognitive functions, particularly memory.

The scopolamine model of amnesia was used to test the memory-enhancing effects of caffeine, administered as three cups of coffee. Subjects were 16 healthy volunteers who received caffeine 250 mg (3 cups of coffee) and nicotine 2 mg separately, in a placebo-controlled, double-blind, cross-over design.Compared to placebo, caffeine and nicotine attenuated the scopolamine-induced impairment of free recall from short-term memory. Caffeine accelerated the recovery from scopolamine-induced impairment of free recall from long-term memory.

A survey conducted over 2043 people distributed over 5-year age categories ranging from 25 to 85 years showed that more than 90% of all people over 35 years of age consume coffee daily. The estimated amount of daily caffeine intake is lowest in the youngest and oldest age groups. The youngest age groups contain a lower percentage of respondents reporting daily coffee consumption whereas the oldest age groups report a lower amount of daily consumption.

On the basis of these results it was concluded that caffeine, probably the worlds most used psychoactive substance, posesses cognition enhancing properties. Caffeine could be used as a control drug in studies using the scopolamine paradigm and possibly also in other experimental studies of cognitive enhancers, as the effects of a newly developed cognition enhancing drug should at least be superior to the effects of three cups of coffee.

51.07 **HIPPOCAMPUS AS A LINEAR INTERPOLATOR.**

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Navigation towards a submerged target in classical version of the Morris water maze requires, among other things, the rat's ability to judge relative distances in a homogenous field. We designed and tested a 1D version of the task, i.e. the distances to be judged were part of a line viewed from the distance. The underwater platform was cued by a hard plastic board (60 cm wide) stemming 20 cm vertically from the water in a water tank (2 m in diam.). The platform was placed 18 cm from one of the edges in front of the board. Rats were taught to remember location of the platform relative to the edges of the board.

As we hypothesized, intact rats (n = 10) swam towards the board and learned platform position within one session. Latency on Session 1 decreased significantly (ANOVA, $F(8,72) = 9.9$, $p < .0001$, trials as repeated measure). Animals with bilateral lesion of the dorsal hippocampus (n = 10) had failed to learn at the same rate. When the number of within-limit trials (in less than 40 s) equaled that of the intact rats, navigation precision of the two groups was compared. The hippocampals were less accurate (deflection 10.9 ± 2.0 cm) than intact animals (4.0 ± 0.5 cm) in the approach to the target ($t(18) = 3.1$, $p < .01$).

We conclude that impairment of performance in classical version of the Morris water maze after a lesion of the dorsal hippocampus may be caused by the rats' inability to interpolate in a homogenous field rather than (or in addition to) the lack of processing of spatial arrangement of extramaze cues.

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51.08 ELECTROPHYSIOLOGICAL EVIDENCE OF DIFFERENT MECHANISMS OF CALLOSAL TRANSMISSION

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Interhemispheric transmission time (IHTT) was investigated by means of Visual Evoked Potentials in 16 right-handed young adults of age ranging between 20 and 28 years. The stimuli were brief 2 x 2 degree flashes generated by a VGA monitor that could appear randomly either in the right or in the left hemifield 8° lateral to the fixation point (ISI 1500-2400 ms). The luminance of the stimuli was 93 cd/m². The task required a simple manual response to the onset of the light stimulus. The electrodes were positioned according to the 10/20 International system and were referred to linked ears references. Horizontal ocular movements and ocular blinks were monitored by means of bipolar EOG. In accord with previous studies we found that the early waves (P100 and N150) had shorter latencies when recorded over the hemisphere contralateral to the field of stimulation than when recorded over the ipsilateral hemisphere. The difference in latency between ipsilateral and contralateral field stimulation (12.2 msec and 5.2 msec, respectively, for the P100 and N150 components) represents the time taken for callosal transfer. For the P100 component, but to a lesser extent also for the N150 component, IHTT was faster at central compared to lateral and posterior electrode sites.

Our data support the hypothesis that the IHTT measured at different electrode sites reflects different mechanisms of callosal transmission, and in particular a faster channel subserving transfer at premotor level and a slower channel subserving transfer at visual level.

51.09 REPRODUCTION OF THE MEMORIZED VELOCITY PROFILE OF A PASSIVE LINEAR TRAVEL.

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In order to investigate the brain mechanisms used in linear Path Integration, subjects had to reproduce the distance of the linear segment they have passively travelled. Seven normal subjects participated. A mobile robot (the Robuter™, Robosoft SA, France) transported in complete darkness the subject along 2, 4, 6, 8 or 10 m, forward on the X-axis, with a velocity profile which was either triangular, trapezoidal or square-like, randomly. Maximal velocity range was 0.06-1 m/s, and duration of the imposed travel was identical for all distances: 16 s. After this stimulus, the subject had to reproduce the distance he just travelled, in the same direction, controlling robot velocity with a joystick.

The results show that although the duration of each imposed displacement (stimulus) could not provide any information assisting its reproduction (response), the subjects reproduced correctly the imposed distance, whatever the velocity profile: the slope of the linear regression between stimulus and response distance for all three profiles was 0.92 ± 0.18 (n = 21), with a correlation coefficient r of 0.94 ± 0.05.

The most striking finding was that the subjects reproduced not only the distance, as required, but also the imposed velocity profile: response velocity had a triangular, trapezoidal, or square-like shape, according to the shape of the corresponding stimulus.

In conclusion, we report here for the first time that humans can reproduce a passive linear displacement of the whole body in darkness, and that the movement is probably stored as a dynamic process which is "replayed" by the brain during active reproduction, by retrieval of the velocity profile of the movement.

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51.10 **DEVELOPMENTAL DYSLEXIA: DIFFERENTIAL EFFECTS OF WORD FREQUENCY**

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Developmental dyslexia affects about 3.5 to 6% of all schoolchildren and is characterized by an impairment of reading and associated language skills in the absence of deficits in other cognitive domains. A number of hypotheses have been advanced regarding the etiology of this disorder. In the cognitive domain problems on sequential and word production tasks have been found while perceptual tasks appeared relatively preserved.

To further delineate the specific deficits in developmental dyslexia we used the event-related potential (ERP) approach. Aim of the study was to study ERPs in a group of otherwise unimpaired adult dyslexics and control subjects in a word repetition paradigm using words of different frequencies of usage. It has been shown that the N400 component of the ERPs can be modulated by word frequency and repetition and is typically reduced for words that can more easily be integrated into the preceding word- or sentence context.

The two groups of subjects viewed words of high and low frequency of usage which were repeated after some intervening words and they distinguished between first and second presentations of a word.

In the range from 350 to 550 ms post stimulus the amplitude of the N400 component was found to be reduced for high frequency words. This effect was more pronounced in the dyslexic group. The effects of word repetition also tended to be reduced in the dyslexic group for high frequency words. These findings show that there are differences in the processing of frequently and infrequently used words between dyslexics and controls and it is discussed that these differences are due to cognitive strategies which are other in dyslexics than in controls.

51.11 THE FEAR-POTENTIATED STARTLE RESPONSE AND PLASMA CORTICOSTERONE LEVELS IN THE RAT.

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The startle response can be potentiated by presenting the startle-eliciting stimulus in the presence of a visual stimulus previously paired with an electric shock. Potentiation of the startle response is considered to be a measure of anxiety. As anxiety is often accompanied by an increased corticosterone (CS) secretion, we investigated the relationship between startle potentiation and plasma CS levels.

Three groups of rats (n=16) were trained during two days. One group received the standard paired light-shock training, one group received a random light-shock training and one control group was placed in the startle device without presentation of any light or shock. Half of the animals were sacrificed directly after the second training session. The remaining animals were exposed to startle-eliciting stimuli on the next day in order to measure startle potentiation, and were subsequently sacrificed. Trunk blood was collected for all animals.

After training, CS levels were elevated in the paired light-shock and random light-shock training groups as compared to the control group, while CS levels were equally elevated in all groups after testing on day three as compared to the CS level of the control group on the second training day. On the other hand, potentiation of the startle response was observed as expected in the paired light-shock group only.

Plasma corticosterone levels increase during anxiety as measured by the fear-potentiated startle paradigm. However, this effect is not specific.

51.12 THE INFLUENCE OF FOOD AND WATER DEPRIVATION ON PERIPHERAL NATURAL KILLER CYTOTOXICITY IN RATS.

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The influence of fasting or dietary restrictions which are regarded as stress procedure, on the defence system, including natural killer cytotoxicity (NKC), seem to be far from the definitive explanation. In the present study, peripheral NK cytotoxicity of Wistar rats maintained on ad libitum diet (controls; n=6) versus food and water deprivation (FWD group; n=10) was compared using an 4 hour ^{51}Cr-release assay, against YAC-1 target cells at four different effector (E):target (T) cell ratio of 50:1, 25:1, 12:1, and 6:1. Blood samples from FWD group were taken 7 days before ingestive restrictions were imposed, after reduction of body weight by about 20% (213.72 ± 12.73g vs. 267.41 ± 10.91g; mean ± SD) over a period of 4 days and after stabilization of body weight at approximately 90% of the initial weight (247.97 ± 16.42g) on the 21st day of deprivation conditions. The results indicate that no significant effect on NK cytotoxicity was induced by acute (20% body weight decrease) food and water deprivation as compared to both predeprivation value (29.13 ± 10.91% vs. 36.75 ± 3.17%; $P > 0.3272$) and controls (45.40 ± 17.92% vs. 37.94 ± 10.79%; $P > 0.4543$; E:T=25:1; mean ± SD). Prolongation of FWD into 21 days (10% body weight decrease) similarly did not significantly change NK cytotoxicity as compared to the predeprivation value (34.17 ± 3.17%) and with the ad libitum controls (46.10 ± 16.99; $P > 0.0568$). The results revealed failure of both acute and prolonged food and water deprivation to influence blood NKC. This suggests that this kind of stress does not influence in a decisive way peripheral NKC in rats.

51.13 SELF-PACED DELAYED ALTERNATION (DA) DURING WEEK-LONG EXPOSURE OF RATS TO AN AUTOMATED APPARATUS. Yu. Kaminsky*, L. Zinyuk and J. Bures, Inst. Physiol., Acad. Sci., Prague, Czech Republic

Conventional DA studies are often made under conditions far from natural performance optima. To examine self-paced DA 10 male rats were placed for one week into an automated device, consisting of start, runway and goal chamber with 2 drinking spouts. The goal had collapsible floor connecting it to a lower runway, providing a return path to the start. Alternating visits of the two spouts were rewarded by 5s drinking whereas repeated visit of the same spout caused an immediate opening of the floor. Naive rats (n=10) attained more than 50% DA already on day 1 and learned the task during 3-4 days. The visits had a circadian distribution with minimum between 11-15 h and two maxima after onset of darkness and before down. DA incidence was the same during activity maxima and minima, but was inversely related to intertrial interval (ITI): it dropped from 90% at 10s to 65 % at 5 min. When no DA was required and all visits were rewarded, mean ITI increased to 30s. It is concluded that DA performance is not modulated by circadian rhythm and that rats tend to emit ITIs yielding the highest DA success. Supporting grants: IGAAVCR 711401 and JSMF 92-57.

51.14 EPISODIC MEMORY IN A CATEGORY-SPECIFIC VISUAL AGNOSIC. Kitchner, E.G.*, McCarthy, R.A. Dept. of Experimental Psychology, University of Cambridge, UK.

In this study, we describe our investigations of episodic memory function in a patient previously documented as having a category-specific impairment of semantic memory, following a severe closed-head injury. MRI scan indicates diffuse cerebral damage, with focal abnormality in the left temporal and parietal regions. Previous work has established that PHD is very gravely impaired in deriving information about animals from pictures and models. By contrast, Knowledge of foods and objects is near control levels and his ability to define the spoken names of animals, albeit not fully intact, is also relatively preserved. Since most patients with category-specific semantic deficits have also suffered from grave impairments of their autobiographical and event memories, little is known about the impact of their disorders of semantic knowledge upon episodic memory. PHD is not amnesic and has access to a considerable number of autobiographical episodes in both the anterograde and retrograde domains. He was, However, found to be impaied on those tests of episodic memory which required the delayed recognition or recall of animal stimuli. Results are discussed in terms of theories of the realtionship between episodic and semantic memory function.

51.15 HIPPOCAMPAL EVOKED POTENTIALS TO PITCH-DEVIANT AND TIME-DEVIANT TONES IN THE TRAIN OF AUDITORY STIMULI IN THE CAT: MISMATCH-LIKE NEGATIVITY (MMN) AND ITS CONNECTIONS TO THE NEURAL BASIS OF LEARNING AND MEMORY. K.Kivirikko*, T.Korhonen, T.Ruusuvirta, J.Arikoski and P.Astikainen. Dept. of Psychol., Univ. of Jyvaskyla, P.O.Box 35, 40351 Jyvaskyla, Finland.

Hippocampal auditory evoked potentials elicited by pitch-deviant or time-deviant tones were recorded during a passive oddball situation in the cat. Experiment 1 showed that the hippocampal N130d recorded in the cat can be evoked by the presentation of a pitch-deviant tone (2500 Hz) in the sequence of repeated standard tones (2000 Hz) despite the lack of behavioral orientation to the stimuli. The recordings in CA1, CA3 and dentate fascia of the hippocampal formation showed that the main deflection in response to the deviant tone appeared in the latency range of 100-170 ms (N130d). The only similarity to the hippocampal MMN-like potentials previously reported in the cat, was N40d. No N130d was observed to the standard tones preceding the deviant tones. The stimulus parameters eliciting the N130 and its latency range support an assumption according to which the N130 may reflect the hippocampal neural orienting response. Consistent with the results obtained in the human cortical MMN studies concerning delayed noise bursts we could detect no N40 or N130 to the time-deviant tones following the pre-standard tones. The deviant event was a doubled interstimulus interval (ISI=1000 ms, p=.05) which occurred randomly in a sequence where the regular ISI was 500 ms. High selectivity of the hippocampal N130, to be elicited only in response to the deviant tone, is consistent with an assumption that the hippocampal novelty detectors are responsible for the response to the deviant tone in the sequence of standard tones.

In experiment 2 our purpose is to examine whether a shortened (250 ms) or a doubled (1000 ms) ISI used as a deviance in a sequence of tones where the regular ISI is 500 ms produces hippocampal or cerebellar MMN in the rabbit.

51.16 UNILATERAL VTA LESION SENSITISES LOCOMOTOR RESPONSE TO CONTRALATERAL VTA STIMULATION. I. Klejbor*, W. Trojniar, J. Tokarski Dept. Animal Physiology, University of Gdańsk, 80-822 Gdańsk, Poland.

We found previously that unilateral electrocoagulation of the ventral tegmental area (VTA) facilited feeding evoked by electrical stimulation of the homologous VTA tissue across the midline. Such "contralateral facilitation" of function may constitute important, not yet explored mechanism of recovery of function after acute brain injury. In the present experiment we studied whereas our previous results could be replicated on other functional models. We choose forward locomotion, one of the most commonly observed responses to stimulation of VTA.

In 12 male Wistar rats implanted with bilateral VTA electrodes latency to initiate locomotion was measured as a function of stimulation frequency. Then, unilateral electrocoagulation of VTA (n=5) or the tissue above VTA (n=7) was performed in the hemisphere contralateral to the stimulating electrode, and latency-frequency functions were determined daily for 5-14 days postlesion. It was found that lesion sensitised locomotor response to VTA stimulation which manifested as decrease of frequency threshold (up to 43% of the prelesion baseline), and a leftward shift of the latency-frequency function. On the other hand control lesions localised above VTA (hypothalamus, thalamus) impaired locomotor reactions. The results provide further evidence for anatomically specific sensitisation of function of the intact hemisphere after acute unilateral brain injury.

51.17 EFFECT OF AMPHETAMINE ADMINISTRATION INTO THE DORSAL STRIATUM ON LATENT INHIBITION IN THE CONDITIONED TASTE AVERSION PARADIGM

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Repeatedly presenting a non-reinforced stimulus normally retards conditioning to this stimulus when it is coupled to a reinforcer. This phenomenon is called latent inhibition (LI) and can be demonstrated in several different conditioning procedures, including conditioned taste aversion. Systemic amphetamine administration has been shown to disrupt LI. Until now the literature does not agree about the brain structure(s) involved in this disruption. Most studies ascribe this disruption to a higher dopaminergic transmission in the nucleus accumbens, others have suggested the involvement of the dorsal striatum. This study examined the effects of local administration of amphetamine (10 μg/0.5 μl, bilaterally) into the dorsal striatum on LI in the conditioned taste aversion paradigm in the rat. Amphetamine was administered in the preexposed and conditioned phases, but not in the test phase. The preexposed phase consisted of 3 days preexposure (PE) to a fixed amount of sucrose solution (5%), the nonpreexposed (NPE) group received an equal amount of water. On the fourth day (conditioning phase) both the PE and NPE groups received sucrose followed by a LiCl injection (75 ml/kg i.p.). On day 5 (test phase) the rats were given a two-bottle choice. LI was measured as the difference in percentage sucrose drunk on the test day between the PE and NPE group. The results of this study showed a disruption of LI after amphetamine administration into the dorsal striatum. This finding indicates an important role for the nigrostriatal dopamine system in disrupting LI in the conditioned taste aversion paradigm.

51.18 MUTUAL INHIBITION OF NEURAL PATHWAY SYSTEMS DURING FORWARD AND BACKWARD CONDITIONING SUGGESTS SYMMETRICAL ATTENUATING MECHANISM DURING ASSOCIATIVE LEARNING. T.Korhonen*, T.Ruusuvirta and J.Arikoski, Dept.of Psychol.,Univ.of Jyvaskyla, P.O. Box 35, 40351 Jyvaskyla, Finland.

Forward and backward conditioning procedures were used for an evaluation of the order effect of the conditioned (CS) and unconditioned stimulus (UCS) presentation. Six cats were first classically conditioned using tone-CS (1500 ms) delay paradigm in which a rewarding electrical stimulation train (500 ms) of the lateral hypothalamus served as the UCS. Both behavioral (head movements) and evoked neural responses were recorded in hippocampal areas (CA1, dendate fascia and subiculum) in freely moving cats. The result showed that during the forward pairing both the head movements and unconditioned evoked responses were significantly attenuated compared to to the UCS-alone presentations. Correspondingly, the responses to the CS (short latency, alpha responses) were significantly attenuated during the backward sessions compared to the CS-alone presentations. These findings suggest that the preceding stimulus leaves a temporal trace the effect of which temporally overlaps the subsequent stimulus. An assumption of the local postsynaptic interaction might explain the mutual inhibition effect of the converging CS and UCS pathways found in the present study. This conclusion was also supported by an observation of the specific modifying effect the UCS pathway on the CS pathway and vice versa.

51.19 DOES MELATONIN HAVE AN EFFECT ON COGNITIVE PERFORMANCE?
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Oral melatonin doses cause phase shifts of circadian rhythms, reduce body core temperature, induce drowsiness, and may possibly reduce cognitive performance. The hormone's putative effect on cognitive tasks is controversial due to differences in methods used to manipulate melatonin levels (oral doses at daytime and light suppression at night) and time of testing after ingestion, and by averaging data from untrained subjects. Using a N=1 double-blind alternating treatments design, we measured daytime (1500-1600 h) performance on four cognitive tasks (Walter Reed performance assessment battery) and subjective alertness (Stanford sleepiness scale) after oral doses of placebo or melatonin (1.6 mg). Serum melatonin and body core temperature were also recorded. Alertness and performance data were obtained for both treatments during time intervals corresponding to the serum melatonin peak (45-105 min) and the temperature trough (240-300 min), respectively, following melatonin administration.

Main findings were: (a) After melatonin ingestion alertness was slightly depressed during the early phase (melatonin peak) and significantly depressed during the late phase (temperature trough); (b) No difference in performance on the cognitive tasks was observed between treatment conditions during the early phase; (c) During the late phase, a significant performance reduction was found on a visual-spatial task (Manikin), whereas no differences appeared between treatment conditions on logical reasoning, serial add/subtract, and four-choice reaction time tasks. These results suggest that ingested melatonin has little if any direct effect on cognitive performance during its peak serum level, but may have an indirect and slightly delayed effect mediated through its thermoregulatory properties. Our findings are consistent with research showing that melatonin binding sites are present in hypothalamic nuclei but absent in cerebral cortex.

51.20 SOCIAL INTERACTIONS IN CATS: REGIONAL BRAIN MONOAMINES DISTRIBUTION IN DOMINANT AND SUBMISSIVE CATS.
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Regional brain concentration of monoamines (NA, DA and 5-HT) and their metabolites (MHPG, DOPAC, HVA and 5-HIAA) were measured (Hewlett-Packard HPLC-ED) in dominant and submissive cats in predatory competition test and in predatory test of single cats. A submissive position in predatory hierarchy produced increased concentration of NA in the hypothalamus in comparison with dominant cats. Simultaneously, a dominant position of cats was accompanied by elevation of hippocampal DA, 5-HT and MHPG contents and MHPG/NA ratio compared to submissive cats. The social situation increased DA and its metabolites concentration of dominant and submissive animals in the hypothalamus in the submissive and dominant cats compared to single cats in predatory test. Additionally, a diminution of NA and MHPG concentration in the midbrain in dominant cats compared to single animals in predatory situation was observed. The data obtained demonstrate a considerable differentiation in the effects of predatory aggression and predatory behavior in social situation on monoamines brain distribution. The results indicate that predatory behavior in single and paired cats are regulated by different catecholamine mechanisms.

51.21 CHILDREN COMPARED TO ADULTS IN A VISUO-MOTOR TASK INVOLVING COGNITIVE STRATEGIES AND MEMORY REPRESENTATIONS.
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In a recent cognitive study (Ballard et al. Cognitive Neurosci 1995), adults were required to copy, via a visual motor task, an eight block configuration. During the copy task, the subjects appeared reluctant to use short term memory capacity preferring instead to utilize strategies that involved serial information processing. In the adult, task accomplishment with repetitive visual scanning strategies proved more efficient than strategies dependent upon short term memory. In the present study, we investigated whether children followed an adult-like serializing strategy or rather were more dependent upon a global and holistic representation of spatial material. Adults and children were tested in the present study; the age range of the children was 6 to 14 years. The task involved copying, accurately, a pattern consisting of six Duplo Lego blocks. Copying variables included block position as well as block colour; three colours were employed. The task required hand-eye coordination and memory with subjects voluntarily selecting their own task steps and accomplishment strategy. To identify the particular copy strategy, eye and hand movements were monitored. Eye movements were recorded with an infrared reflection oculography technique; head movements were stabilized with a bite bar. Hand movements at the display were simultaneously video monitored. The block pattern to be copied was either a random configuration of 6 blocks as one Gestalt or two Gestalt patterns of three blocks each. The block display was divided into three areas after Ballard et al. (1995), as model, source and workspace. The results show that children, at least from 6 years of age, effect more eye movement fixations during copy tasks than adults. However, rather than depending upon short term memory, the children employ serializing visual scanning strategies comparable to adults.

51.22 OLFACTORY CUES HAVE TO BE LINKED TO A SPATIAL FRAME OF REFERENCE TO BE USED IN A CONFIGURAL WAY.
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Spatial orientation and olfactory information processing are largely used to study rats' cognitive capabilities. We have already shown that rats remembered the relative positions of olfactory cues, but were unable to use these cues efficiently for spatial orientation when vision was allowed.

The aim of this study was to determine if rats could rely on a configuration of olfactory cues independently of an external spatial frame of reference. Rats were trained in darkness in an eight-arm radial maze with supplementary olfactory cues, distributed so that they could not be used as a list of independent items characterising each arm. The configuration of the olfactory cues was stable within the maze, but the maze was either fixed or rotated between each session.

In both conditions, rats' performance was slightly lower than that of control animals trained with a different olfactory cue characterising each arm. However, the organisation of movements of the rats trained with a fixed maze was similar to that of control animals. Whereas rats trained with a rotated maze were similar to rats trained in the absence of olfactory cues. Animals trained with a fixed maze were further tested with an interruption procedure, during which the maze could be manipulated. Rats relied on the configuration of the olfactory cues when it was coherent with an external spatial frame, but they were unable to use the configuration of the olfactory cues when the maze was rotated during the interruption.

This series of experiments showed that the representation of the configuration of the olfactory cues was not established within the maze itself, but was linked to an external spatial frame of reference even in total darkness. This reference did not seem to be linked to any non controlled cues from outside the maze, but might rely on a single point of reference to which the configuration of the olfactory cues could be connected through the integration of animal's movements.

51.23 WORKING MEMORY DEFICIT AND EFFECTS OF THA IN AGED C57BL/6 MICE.
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Working memory is the recall of recent events of transient usefulness. It is vulnerable to interference and influenced by aging process. Our study was aimed at comparing working memory performance of young and aged C57BL/6 mice in an alternation paradigm using an opened Y-maze. Young (4 months) and aged (21-22 months) mice were trained with either an intertrial interval (ITI) of 40 sec. or an ITI of 2 min. 30. All animals were trained during 4 consecutive days with one session of 11 trials each day. On each trial, excepted for the first, food was always found in the arm opposite to the one previously visited . The results indicated that whereas no significant age-related difference was observed with 40 sec. ITI, a significant decrease in alternation scores was recorded in aged mice trained with 2 min. 30 ITI (at the end of training 68% vs 50% in young and aged respectively) . However, with a 40 sec ITI, a comparison between alternation scores on the 5 first choices and the last 5 choices revealed a significant decrease in intra session performance. No such effect was observed in young mice at any delay tested. In view of the age-related deficit in the 2 min. 30 ITI paradigm, the effects of THA (1 and 3 mg/kg ip) was investigated in aged animals. A significant improvement in memory performance was observed with a 1 mg/kg dosage on the 3rd (69% vs 46% in THA and control respectively) and 4th days of testing (66% vs 55% in THA and control respectively).

Taken together, these results indicated that aged mice are much more sensitive than young mice to the effects of proactive interferences. They also demonstrated a rapid forgetting in aged animals as the delay of retention increased. This deficit in learning abilities might be reversed by facilitation of the cholinergic neurotransmission.

51.24 NAVIGATION IN THE WATER MAZE WITH SIMULTANEOUS OR SUCCESSIVE PRESENTATION OF DISTANT CUES.
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Navigation in Morris water maze is impaired when landmark sighting is limited by flickering illumination. In order to simplify the complexity of the scene, rats were trained for five days in a minimum cue situation using two dimly back-lit shapes A and B as distant landmarks in darkness (Exp. 1). Acquisition proceeded in the control group (n=10) with permanent visibility of A and B at the same rate as with whole room illumination (mean latencies 20.6, 13.6 and 8s on Days 1 to 3, respectively). Learning was slightly slower (24, 15 and 10s) when A and B were simultaneously flashed (300ms A+B, 700ms darkness; n=10) and was significantly impaired (30, 19 and 16s) when A and B alternated (300ms A, 200ms darkness, 300ms B, 200ms darkness; n=10). In Exp. 2, 10 rats trained with two permanent cues were equally successful when navigating to a new goal with simultaneous (19s) or alternating (15s) exposure of landmarks. The results suggest that navigation depends both on memory of goal-landmark distances and of between-landmark angles (the estimation of which requires simultaneous landmark sighting).
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51.25 COMPARISON OF EXCITOTOXIC HIPPOCAMPAL LESIONS AND MID-LINE ISCHAEMIC DAMAGE ON DELAYED NON-MATCHING PERFORMANCE IN THE RAT.

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The relative contribution of the hippocampus in the mediation of short term memory function is the subject of much current debate. In this study neurotoxic lesions limited to the hippocampus were compared to the effects of the anterior cerebral artery occlusion (ACAO). The later procedure producing ischemic damage limited primarily to the cingulate and retrosplenial cortices and to medial aspects of the septal complex.

24 animals were trained to perform an operant delayed non-matching to place procedure (DNMP). Once asymptotic performance had been reached the animals were randomly allocated to one of four groups. One group received ibotenic acid infusions at fourteen sites in the hippocampal formation bilaterally. ACAO was acheived in the second group by stereotaxic application of endothelin-1 as it arises from the circle of Willis. The control groups underwent appropriate sham procedures.

Analysis of data collected during post-operative reassessment revealed delay dependent impairments in the performance of both lesion groups ($p<0.001$). Hippocampal performance was attenuated at delays in excess of 10 sec., while ACAO accuracy was reduced at delays as short as three seconds. There were no changes in response latency or the number of trials completed. However, the ACAO group did exhibit a tendency to adopt a position bias.

The study demonstrates for the first time a) the behavioural consequence, of a novel ACAO model, and b) the effects of this type of hippocampal lesion on DNMP performance. Taken together the results suggest that componentsof the limbic cortical circuit, other than the hippocampus, are of equal, if not greater, importance for nomal mnemonic function in the rat.

51.26 **BLOCKADE AND DISINHIBITION OF A BEHAVIOURAL 5-HT$_{1A}$ RECEPTOR MEDIATED-RESPONSE BY DIFFERENT DOSES OF CORTICOSTERONE.**

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Corticosterone (B) blocks the 5-HT$_{1A}$ receptor-mediated hyperpolarisation of CA1 pyramidal cells in vitro and in vivo via the mineralocorticoid receptor (MR). Combined MR + glucocorticoid receptor (GR) occupation by B restores the electrophysiological response. We studied whether the effect of 1A agonist 8-OH-DPAT in the Morris water maze depends on MR/GR occupation in a similar way.

Adrenalectomized (ADX) male Wistar rats were implanted with 20% B pellet to obtain a constant MR occupation. One week after the operation the animals were trained for 4 days to find a submerged platform in a pool. On the 5th day the platform was removed and the behaviour of the animals was monitored during a 1-min swim session. 90 Min before this free swim trial, a s.c injection of 1 mg/kg B or vehicle was given; 30 min before the trial 0, 100 or 300 μg/kg 8-OH-DPAT was administered i.p. 8-OH-DPAT had a stimulatory effect on the distance swum by the animals; therefore the number of crossings of the former platform location per meter ('crossings') was taken as the main measure of the drug effect on hippocampal processes. 100 μg/kg 8-OH-DPAT lead to a decrease in crossings in B-treated animals, but not in vehicle-treated animals. 300 μg/kg 8-OH-DPAT lead to a decrease in crossings in both groups. There were no differences in distance swum between B and vehicle-treated animals.

These results suggest that predominant MR activation by B suppresses 5-HT$_{1A}$ receptor-mediated responses in the hippocampus in vivo, and that subsequent occupation of the GR sites can override this effect. They also provide a striking parallel between the hormonal dependency of the activity of a single CA1 neuron and a parameter in a spatial memory task in response to 5-HT$_{1A}$ receptor stimulation with 8-OH-DPAT.

51.27 RETRIEVAL OF PROPER NAMES IS DISPROPORTIONABLY SLOWED AFTER TRAUMATIC BRAIN INJURY.

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According to the IAC model of person recognition by Burton and Bruce (1992), proper name retrieval is more sensitive to brain injury than retrieval of other semantic information about a person, because of the relative small number of connections to the name representations in memory. As a result, the amount of activation spreading to the names is relatively small and a general reduction of activation, for instance after brain injury, would most strongly affect the retrieval of proper names. It is known that for patients with traumatic brain injuries access to semantic information is slower than for healthy controls, suggesting a reduced level of activation. The IAC model would predict that for these patients retrieval of people's names is disproportionably slowed. Comparing categorization and naming latencies for famous faces from 13 head injured patients and 14 controls indeed confirmed this. On both tasks the patients' latencies were significantly longer, but the increase in latencies from categorization to naming was significantly larger in the patient group. In addition, in both groups the latencies for naming famous buildings were exactly the same as those for the faces.

51.28 DIFFERENT EXTRACELLULAR DOMAINS OF THE NEURAL CELL ADHESION MOLECULE L1 ARE INVOLVED IN DIFFERENT TIME WINDOWS OF MEMORY FORMATION.

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Long term synaptic remodeling appears to be a crucial step in the cellular cascade which subserves long term memory formation. Structural elements which play a key role in this remodeling are synaptic membrane glycoproteins whose carbohydrate moiety extends into the synaptic cleft. Long-term memory for a one trial passive avoidance task in chicks requires two waves of glycoprotein synthesis: the first wave occurs in the hour following training, the second in the period 5.5 - 8 h after training.

The neural cell adhesion molecule L1 is a multidomain protein that plays important roles in cell adhesion, migration and neurith outgrowth. Its extracellular part consist of six Ig-like domains and five fibronectin type III homologous repeats. Intracranial injection of polyclonal antibodies directed against L1 resulted in amnesia for passive avoidance training in day old chicks only when administered at one of two time windows: 30 min pre-training and 5.5 to 8 hr post-training. To investigate the functional properties of the different structural domains of L1 we tested these protein fragments for their capacity to influence memory formation. Intracranial injection of Ig-like domain I-VI resulted in amnesia for the passive avoidance task only when injected 30 min prior to training. No amnesia was apparent when injections were made 5.5 hr after training. When the Ig-like domains I-II, III-IV or V-VI were tested individually, only injection of domain V-VI resulted in amnesia while the others were ineffective. In contrast to Ig-like domains, fibronectin type III homologous repeats 1-2 resulted in amnesia only when injected 5.5 hr after training procedure. These findings indicate that L1 uses different domains for the two time-windows analyzed here.

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51.29 IMPAIRED INTERHEMISPHERIC TRANSMISSION IN PATIENTS WITH UNILATERAL VISUAL EXTINCTION

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Early components of visually evoked potentials (VEP) elicited by unilateral (left or right hemifield) or bilateral visual stimulation were recorded in right brain-damaged patients with left visual extinction as well as in normal subjects while performing a simple manual reaction time (RT) task. The electrodes were positioned according to the 10/20 International system. In normals, right or left unilateral stimuli yield a longer RT than bilateral stimuli. On the contrary, in patients RT to bilateral stimuli did not differ from that to right unilateral stimuli, but both were significantly shorter than RT to left unilateral stimuli. These behavioural results indicate an impaired visual processing in the contralesional hemifield of patients with extinction and a lack of interfield summation, which is instead present in normals. In patients parietal and occipital recording sites in both hemispheres showed a clear N150 wave in response to bilateral and contralateral hemifield stimulation while such waveform was absent or very weak following ipsilateral stimulation. The lack in both hemispheres of a clear N150 response to stimuli presented to the ipsilateral hemifield is in keeping with an impaired interhemispheric transmission in these patients. Moreover, the asymmetry in speed of manual response to contralesional vs. ipsilesional stimuli correlates well with the pattern of electrophysiological responses recorded in the two hemispheres. Taken together, these results suggest that extinction may result from a deficit of commissural input to the undamaged left hemisphere.

51.30 ASCENDING REAL AND VIRTUAL HILLS IN DARKNESS: A TEST OF VESTIBULAR NAVIGATION IN RATS.

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Vestibular assessment of the slope of terrain can detect orienting gradients the importance of which increases in darkness. In Exp. 1 vestibular klinotaxis was studied in 10 hooded rats trained to search in darkness in a large (2m dia) arena a 2cm feeder placed in center of a circular (1m dia) plastic sheet or on the top of a 4cm high cone. The rat's movement was monitored with a computerized infrared tracking system. Finding the feeder was slower on the flat surface (4.7s) than on top of 2 or 4cm high cones (3.8 or 2.6s), directing the rat's search. In Exp. 2, 3 feeders were placed 35 cm from the center of a styrofoam disk (1m dia). Raising a 5cm rod below one feeder inclined the disk in a plane passing through the feeder and the rat's center of gravity. Multitude of such planes generated by the rat's movements forms the surface of an asymmetric virtual cone. After the rat finds the feeder, the disk returns to horizontal. Raising another feeder starts a new search the efficiency of which improves with slope steepness. Participation of hippocampus in vestibular klinotaxis is discussed. Supported by grants IGA AVCR 711401 and BMFT 01VJ 9200215/26.

51.31 RITANSERIN POTENTIATES THE EFFECTS OF RACLOPRIDE ON SUCROSE INTAKE AMJ. Montgomery* and A. Suri, Psychology Dept, London Guildhall University, Old Castle Street, London, E1 7NT, UK.

Taking due care to minimise discomfort we examined the effects of a dopamine (DA) D2 antagonist, (raclopride RAC; 0–0.3 mg/kg); a serotonin 5-HT2 antagonist (ritanserin RIT; 0–0.4mg/kg); RAC (0.15 mg/kg) with RIT (0–0.4 mg/kg) and an atypical neuroleptic (clozapine, 0 & 6mg/kg) on consumption of different concentrations of sucrose (SUC; 0.7%, 7%, & 34%). In drug-free rats, 7% SUC supported the highest intake. RAC (0.3 mg/kg) inhibited intake of 7% SUC, but its effect on 0.7% SUC fell short of significance and intake of 34% SUC was unchanged. RIT had no effect on SUC intake, but when combined with an ineffective dose of RAC (0.15 mg/kg), led to an inhibition of 7% SUC intake and an increase in comsumption of 34% SUC (cf Phillips et al (1991) Psychopharmacol 105: 355). Clozapine inhibited intake of 0.7% and 7% SUC, whilst sparing 34% SUC. These data suggest that 5-HT2 antagonism potentiates D2 antagonism in the mesolimbic DA system and this interaction might contribute to the efficacy of clo zapine as an antischizophrenic drug.

51.32 THE MODULATORY EFFECTS OF THE BRAIN PROLYL ENDOPEPTIDASE INHIBITORS ON MONOAMINERGIC- AND CHOLINERGIC-MEDIATED BEHAVIOR IN RODENTS

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Various behavioral effects of thyroliberin (TRH), the main prolyl endopeptidase (PEP) endogenous substrate prompted us to study psychopharmacological profile of some dipeptide PEP inhibitors of general structure Z-X-Pro-OH, where Z is carbobenzoxyl group and X is Ala, Gly, Cys and Ile amino acid residues. The substances studied (10 mg/kg, i.p.) were shown to reveal antidepressant effect reducing the duration of immobility of mice in forced-swimming test and potentiating apomorphine induced stereotyped behavior in mice. PEP inhibitors were demonstrated to antagonize catalepsy in rats induced by haloperidol (2 mg/kg, i.p.) or trifluoperazine (5 mg/kg, i.p.). The dramatic increase of PEP activity in brain cortex and subcortical structures following treatment with neuroleptics was observed. This increased enzyme activity was abolished by the administration of PEP inhibitors. The present data make possible to suggest an involvement of dopaminergic link in the psychotropic effects of PEP inhibitors. It was also shown that PEP inhibitors were able to potentiate arecoline-induced tremor in mice that might indicate the possible involvement of the brain cholinergic system in the mechanism of action of the latters. In a similar manner, dipeptides suppressed head twitches in mice induced by 5-hydroxytryptophan which might be considered as an evidence of the involvement of central 5-HT- ergic system in the pharmacological mode of action of dipeptide PEP inhibitors. It might be concluded that dipeptide PEP inhibitors strongly affect dopamine-, seroton- and muscarinic cholinergic-mediated behavior in rats and mice.

51.33 ANOTHER "SPATIAL" STRUCTURE REVEALED BY THE WATER MAZE? A CRITICAL VIEW.

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The Morris water maze has been used extensively for many years as a task testing navigational performance and spatial memory in rats. Lesion studies have shown that destruction of septo-hippocampal system, mammillary bodies, striatum, and cingular, parietal, insular, and perirhinal cortices, impairs performance in the water maze.

Here I report a performance deficit in the water maze after bilateral excitotoxic lesions in the posterior insular cortex (at AP-0.3 and AP-2.3 mm). Nine rats in either group were trained for two days (9 trials per day) one week after surgery and their latency to reach the platform, total distance swum, speed of swimming, periphery dwelling, percent of time spent and percent of path swum in target quadrant were compared with 16 intact and 2x7 sham operated animals. Both lesion groups had longer latencies ($F(4,86)=4.3$. $p=.005$) and smaller percentage of time spent in the target quadrant ($t(23)=3.5$, $p<.005$ for AP-0.3, and $t(23)=2.8$, $p<.01$ for AP-2.3) than the intact animals on Block 2 of Day 1. The performance of sham injected animals was not significantly different from either the intact or the lesion groups.

In order to succeed in the water maze task, rats should have not only their spatial processors intact but their motivational, attentional, general mnemonic, and perhaps other cognitive capabilities must be unimpaired too. It is concluded that due to its multi-factor sensitivity and the relative difficulty in controlling for the non-spatial effects, this experimental paradigm presents big problems when a structure is to be related with spatial processing.

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51.34 LOCALIZATION OF THE NERVE NET OF TENTACLE REFLEXES IN *HELIX POMATIA*.

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In *Helix* intracellular stimulation of identified giant cells in the CNS induce contractions in muscles involved in certain reflexes; these giant cells are therefore assumed to be part of the reflexes. However, time delays from neuron activation to the onset of muscle movement often outlast the natural response delays by several seconds; a screening study for faster connexions from the CNS to the muscles of the posterior tentacles in *Helix pomatia* was therefore performed.

Local extracellular electric stimulation was given to the CNS, which was isolated with the posterior tentacles still connected. Hereof one tentacle was suspended in a mechanoelectric transducer system, measuring isometric tension in both periferal (PM) and central tentacular muscle (CM). The timelag from near-threshold stimulus to onset of contractions was measured.

The delay from stimulus to the onset of contraction was shortest with stimuli given upon the periferal part of the tentacle (delay: 20 ms in PM, 30 ms in CM); with stimuli on the ipsilateral cerebral ganglion the delay increased (60 ms in PM, 40 ms in CM), and more from more distant ganglia, but in no case to more than 500 ms.

All parts of the CNS thus seem able to induce tentacle contractions; the actual nerve net of the reflexes may therefore depend upon the specific sensory inputs that elicite them under natural conditions. The role of the giant cells still awaits clarification.

51.35 IS THE 5-HT$_3$ RECEPTOR INVOLVED IN STRESS RESPONSES?

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In a number of animal paradigms, 5-HT$_3$ receptor antagonists display anxiolytic activity. When animals are placed in situations which evoke anxiety or stress, this is often accompanied by increases in stress hormones, like ACTH, corticosterone and prolactin. Several anxiolytics, like the benzodiazepines, decrease, besides anxiety, also the plasma levels of stress hormones. The question then is whether 5-HT$_3$ antagonists are able to reduce stress hormone levels. Moreover, it is interesting to study the effects of 5-HT$_3$ agonists on hormonal parameters.

In order to judge the intrinsic effects of 5-HT$_3$ ligands on ACTH, corticosterone, prolactin and glucose we injected (s.c.) the 5-HT$_3$ receptor agonist metachlorobiphenylguanide (mCBPG) and the 5-HT$_3$ receptor antagonist ondansetron in rats (s.c.) and collected trunk blood 45 min later. mCPBG dose-dependently (3-10 mg/kg) enhanced corticosterone levels, but not ACTH, prolactin and glucose. Ondansetron (0.01, 0.1 and 1 mg/kg) had no intrinsic effects on ACTH, corticosterone and glucose. Ondansetron (0.1 and 1 mg/kg) was not able to antagonize the MCPBG (10 mg/kg) induced rise in corticosterone, neither did it affect ACTH, prolactin and glucose levels. These results suggest that the rise in corticosterone plasma levels after mCPBG is not caused by activation of 5-HT$_3$ receptors. It is as yet unclear whether 5-HT$_3$ receptors modulate stress-induced hormonal and behavioural responses.

51.36 REPEATED COCAINE, BUT NOT APOMORPHINE, INCREASES GLUCOSE UTILIZATION IN THE SHELL OF THE ACCUMBENS.

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Repeated administration of psychostimulants induces progressive increase of locomotion upon rechallenge with the drug. Dopamine transmission within the mesolimbocortical system and, in particular, within the Nucleus Accumbens has a prominent role in accompanying neuroadaptation which underlies the behavioral changes. A question is whether the Nucleus Accumbens is implicated in incentive motivational processes or merely in their locomotor concomitants. In order to address this issue we employed the 2-[^{14}C]deoxyglucose method for measuring local rates of glucose utilization. The study was carried out in adult rats administered daily for 8 days with apomorphine (0.5 mg/kg, sc., n=6) or cocaine (15 mg/kg, i.p., n=5). Cocaine is a powerful reinforcing drug and it is readily self-administered by humans, monkeys, and rats. Apomorphine has locomotor effects similar to those induced by cocaine but it lacks incentive motivational properties. A third group (n=5) of rats injected with saline served as control. The 2-[^{14}C]deoxyglucose procedure was initiated 5 or 10 minutes following the last injection of drug or saline. Repeated administration of both drugs progressively increased locomotion. Both apomorphine and cocaine increased glucose utilization in extrapyramidal areas including the Nucleus Accumbens. However, the pattern of altered glucose utilization within the Accumbens differed between the two drugs. The core was affected both by apomorphine and cocaine, while the shell was affected by cocaine, but not by apomorphine. The data suggest that the metabolic change of the shell reflects a functional activation associated with incentive motivational properties of cocaine.

51.37 THE SELF-ORGANIZATION OF LANGUAGE: A NEUROBIOLOGICAL MODEL AND ITS APPLICATIONS

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The focus of this paper is set on two phenomena observed in the organization of living systems: the search for coherence and the increasing complexity characterized by differing degrees of persistent order. Data from various instances of language acquisition will illustrate the non-linear processes of pattern generation, i.e. the dynamic experience-dependent shaping of an incipient system into a highly-specialized network of interacting modules. As our data suggest children's preferences in the selection of input data are in accordance with the principles of neuronal group selection, i.e. saliency, frequency and repeated occurrence in a comparable configuration play a dominant role in sorting out the patterns of the input. Samples of child-directed speech (CDS) give evidence of the variety of cues parents/caretakers employ to stimulate inborn dispositions and to ease the search for coherence. The impact of sensory deprivation in deaf and blind children on the development of computational and lexical systems might answer some of the pending questions in the long-standing nature-nurture debate.

51.38 EFFECTS OF PASSIVE LENGTHENING OF THE POSTERIOR NECK MUSCLES ON THE POSITION OF THE EGOCENTRIC REFERENCE

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Goal directed actions, such as grasping at objects, require that sensory informations from the external world would be calibrated in spatial coordinates, i.e.with respect to a body reference. The latter can be conceived as the internal representation of the midsagittal plan resulting normally from the symmetrical activity of a group of structures involved in sensorimotor integration.

In the present study we have investigated the role of the proprioceptive informations from the neck muscles on the position of the egocentric reference. Passive rotations (15°) of the trunk or head were performed in a group of 8 normal subjects. They were asked to point with the hand straight ahead in the dark. In a first experiment they had to adjust their responses in front of their trunk axis and in a second one in front of their head axis.

Significant shifts of pointing were observed in both experiments, although they were larger in the first one. Displacements produced by the rotation of the trunk or of the head were of similar amplitudes but opposite directions. Pointing responses were displaced in the same direction as trunk rotation, and in the direction opposite to head rotation. However a maximal effect was obtained when the subjects were rotated to the left and had to point in front of their trunk.

One patient with a left hemineglect participated in the first experiment. His subjective straight ahead in the control condition (no rotation) was displaced by 7° to the right. Interestingly, he was significantly improved only by rotation of the trunk on the left.

These data stress the role of the proprioceptive informations from the neck muscles in building and up-dating the internal representation of egocentric space. In

51.39 BIOCHEMICAL NEURO-ANATOMY OF LEARNED HELPLESSNESS.

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The learned helplessness animal model of depression has proved useful to decipher the mechanisms of action of antidepressant drugs. We are using in vivo microdialysis to study neuronal networks involve in the development and maintenance of learned helplessness, and in its dissipation with time. Also, we are looking at how anxiolytic and thymoleptic agents impact on the brain chemistry of this model, to prevent development of adverse reactions to stress. From this research has developed a multi-transmitter, multi-region map of learned helplessness. Briefly, development of helplessness follows the acute stress response of biogenic amines in medial prefrontal cortex , modulated by GABA and glutamate. Cortical transmission is propagated to entorhinal cortex, where GABA gates the perforant path into hippocampus. Here, stress becomes depression, as painful memories are consolidated into future maladaptive responses, using norepinephrine and GABA. From hippocampus, depression becomes a serotonergic phenomenon in lateral septum, and finally the vegetative responses emerge from hypothalamus, mostly regulated by norepinephrine. Data will also be presented on n. accumbens and amygdala. Helplessness, and depression, can no longer be conceptualized as mono-transmitter phenomena.

51.40 **ISOLATING VISUAL IMAGERY COMPONENTS: A COGNITIVE-ANATOMICAL ANALYSIS OF THREE CLINICAL CASES**

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According to the model of visual imagery put forward by Kosslyn and Farah (Kosslyn, 1980; Farah, 1984) three main components are involved during the evocation of a mental image: the first is the *long-term visual memory* which contains the representations used for building visual images, the second is the *visual buffer* that acts as a temporary store of visual information drawn from long term memory, and the third is the *image generation process* which translate the deep representations of the long term memory into surface images in the visual buffer.

Recent experimental and clinical investigations have provided evidence supporting the functional and anatomical independence of these components.

The aim of the present work was to add new evidence to these observations reporting three cases of different visual imagery disorders. Results of visual imagery tests, plus other additional tests, strongly suggest that the first of these patients suffered from a deficit at the long term visual memory level, the second from an inability to generate visual images, while the third had a deficit into the visual buffer. Besides, the analysis of available anatomical data about our patients strengthens the assumption that these three components are subserved by different portions of the cerebral cortex.

51.41 SPATIAL REASONING AND PROBLEM-SOLVING IN THE RHESUS MONKEY

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The experimental data show that a Rhesus monkey (macaca mulatta) can perform complex spatial tasks. It is able, for instance, to memorize the order of illumination of 3 fixed spatial targets and, after a delay, to press them in the same order. This task entails complex neural processes such as the capacity to integrate the spatio-temporal information given by the environment (the order of the targets) into a spatial plan. It needs also to store this plan, and later, during the target-press phase, to update it continuously, with the location of the targets that have been already pressed. The present report analyses the behavioural data obtained in two rhesus monkeys in a problem-solving situation derived from the spatial task described above. The task consisted in finding, by trial and error, the order (that the animal ignores) of touching 2 or 3 targets in a set of 3 or 4 fixed spatial targets. Whenever an order had been discovered and practised several times, a signal was sent to the animal indicating that a new order had to be discovered in the same set of targets, under the condition that two successive sequences never had the same first target. The data show that monkeys are capable of conducting a methodic research of the hidden order and of finding the solution in a **minimal** number of trials. When the first target is found, it is kept in ongoing trials until the second target is found and so on, until the whole sequence is discovered. This optimal research seems to be guided by an integration of the location and rank of the successful and erroneous target-touches, i.e. by manipulations of internal representations of the environment.

We conclude that the monkey brain is able, in a spatial problem solving task of this type, to construct complex cognitive structures which mimic a spatial reasoning. Our working hypothesis is that prefrontal cortex organizes those cognitive structures and that prefrontal neural activities observed during this spatial experiment would give a model of neural activities during spatial reasoning.

51.42 NEW ASPECTS OF CHLORPROMAZINE EFFECT ON INTRACELLULAR BIOCHEMICA. ACTIVITY

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Chlorpromazine (CPZ) is antipsychotic drug commonly used in chronic treatment of hard psychotic disorders, realising its basic effects by blocking D_2 receptors. However, the clinical application of CPZ may be limited due to its hepatotoxicity. In searching for a more sensitive method for the detection of an early intracellular biochemical damage, probably still in reversible phase, the CPZ-induced change in target enzyme carboxylesterase (CarbEs) (EC 3.1.1.1.) localised inside live and morphologically intact polymorphonuclear neutrophils, hepatocytes and neuronal brain cells of mouse was measured by Method for Intracellular Measurement of Drug-Enzyme-Cell Interaction (MIMDECI). The advantage of MIMDECI is providing two markers (enzyme activity and cell morphology) for measuring the effect of drug before the specific damage of cell occurs.

Our studies established a clear relationship between the increasing concentrations of CPZ and the extent of inhibition of CarbEs. The impact of CPZ on cells ranged from no effect to death, with intermediary effects of decreased CarbEs activities without either morphological changes or structural changes. Our results indicate that intracellular CarbEs activity inhibition by CPZ is dose-dependent, though drug concentration required to bring about 50% inhibition of the initial activity (ID-50) varies between the cell types of mouse. The correlation of inhibitory effect in all the cell types, has been demonstrated whereby the polymorphonuclear neutrophils were proved to be the most sensitive and the hepatocytes most resistant to CPZ effect. CPZ concentrations was ranging from 0.5 to 5.0 mg/ml (1.4 to 14.08 mmol/l).

51.43 BEHAVIOURAL, PHARMACOLOGICAL AND PHYSIOLOGICAL STUDIES ON THE VALIDATION OF A NEW ANIMAL MODEL FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

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Childhood hyperactivity (attention deficit hyperactivity disorder, ADHD) is a common behaviour disorder among grade-school children. The characteristic symptoms are attentional problems and hyperkinesia. The main purpose of the present research was to develop a new animal model of ADHD, which includes attention deficit, hyperactivity and alleviation of these symptoms by treatment with a psychostimulant. We used rats trained for a 5-choice serial reaction time task which assessed sustained attention. In this behavioural paradigm rats are required to discriminate spatially a short visual stimulus that will occur randomly in one of 5 locations and maintain a sufficient activity level. The ability of a rat to maintain its attention on the task can be measured by counting choice accuracy (percent correct responses) and percentage of premature responses indicates the level of activity. According to the present results, rats performing poorly in the task have lower choice accuracy and they make more premature responses than normally behaving individuals i.e. a clear correlation was observed between these parameters ($r = -0.5917$, $p < 0.001$). Furthermore, methylphenidate hydrochloride at doses of 100 µg/kg and 1000 µg/kg improved the attentional performance of poorly performing animals. At a dose 100 µg/kg, methylphenidate slightly decreased the hyperactivity in these rats. This data indicates that rats showing poor performance when trained and tested in a 5-choice serial reaction time task may be a model for ADHD.

51.44 CHOLINERGIC CONTROL OF CONDITIONED ODOUR AVERSION IN NEONATAL MICE

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Conditioned aversion to a novel odour (lemon) was tested in CD-1 11-day old mice. The behavioural paradigm used consisted of 6 repeated 15s-odour exposures, each paired to a mild footshock. Acquisition of the odour aversion was assayed 1hr or 24hrs following conditioning in a odour preference test, in which time spent in the lemon - or mint - scented area of a Plexiglas arena was recorded. Results evidenced a marked ontogenetic disassociation between the onset of short- and long-term memory. Indeed, one hour after the conditioning session, a clear aversion to the lemon odour was displayed by the conditioned animals as compared to control pups (CS-only and CS-US unpaired). When the odour preference test was carried out 24hrs later, no aversion to the odour previously paired with footshock was evident in conditioned mice. Interestingly, control pups exposed only to the lemon odour (CS Only group) showed a preference for that odour both 1h and 24h after the conditioning session.

Much evidence indicates that functional maturation of cholinergic basal forebrain neurones depends largely on Nerve Growth Factor (NGF) trophic activity in the CNS. Since the olfactory bulbs receive an important cholinergic innervation from the septal area, and have high NGF content, we are currently investigating the effects of neonatal manipulation of endogenous NGF levels on the establishment of early olfactory memories.

51.45 SEROTONIN DEPLETION DECREASES THE THERAPEUTIC EFFECT OF NICOTINE, BUT NOT THA, IN AGED RATS.

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The present study was designed to investigate the hypothesis that the degeneration of serotonergic system may decrease the therapeutic effects of cholinergic drugs on cognitive functioning in Alzheimer dementia. Therefore, we compared the effects of systemic pretraining injections of a cholinesterase inhibitor, tetrahydroaminoacridine (THA, 3 mg/kg, i.p.) and nicotine (0.1 and 0.3 mg/kg, i.p.) on spatial navigation water maze (WM) performance in aged control rats and in aged rats following p-chlorophenylalanine (PCPA, a serotonin synthesis inhibitor) treatment. Aged rats were impaired in WM task compared with young controls. PCPA treatment did not aggravate the WM failure of aged or young rats. THA (3 mg/kg) and nicotine (0.3 mg/kg) promoted significantly WM navigation of aged rats. THA (3 mg/kg) improved WM performance of PCPA-lesioned aged rats, but nicotine (0.3 mg/kg) did not promote test performance of aged rats after PCPA treatment. This result demonstrates that serotonergic pathology may decrease the therapeutic effect of nicotine in aged rats. The present results suggest that, in Alzheimer's disease, the degeneration of serotonergic system decreases the therapeutic effect of nicotine, but not that of THA.

51.46 DOPAMINE AGONISTS INHIBIT PROLACTIN (PRL) RELEASE VIA D_2 RECEPTORS AND DECREASE CORE TEMPERATURE (CT) AND DOPAMINE SYNTHESIS PRIMARILY VIA D_3 RECEPTORS

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In this study, we examined the relationship between the affinity at cloned human D_2 and D_3 receptors (transfected into CHO cells) of several agonists (PD 128,907, bromocriptine, apomorphine, quinpirole, (+)-3-PPP, (+)-7-OH-DPAT, piribedil, N-0434, CGS 15855A and quinerolane) versus their influence upon PRL secretion, CT and nucleus accumbens turnover of dopamine (DA). In male Wistar rats, CT was measured rectally and DA synthesis was determined as ratios of DOPAC to DA levels by HPLC. Measures were made 30 min after injection of vehicle or agonist. Doses in mg/kg, s.c., are the lowest different ($P < 0.05$) to vehicle. The most preferential D_2 agonist was bromocriptine (pK_is = 8.5 vs 8.1) and the most preferential D_3 agonist was PD 128,907 (pK_is = 8.6 vs 6.3). Bromocriptine (0.00016) more potently decreased PRL than PD 128,907 (0.16), whereas PD 128,907 more potently decreased CT (0.16) and suppressed DA synthesis (0.16) than bromocriptine (10.0 and 10.0). Potency for suppressing PRL correlated poorly to potency for reducing CT ($r = 0.02$) and synthesis (0.06) whereas these measures correlated highly (0.96). Potency for decreasing PRL correlated more highly to D_2 affinity (0.82) than D_3 affinity (0.42) whereas potency for decreasing CT and DA synthesis correlated better to affinity at D_3 (0.68 and 0.65) than D_2 sites (0.12 and 0.21). Further, we calculated correlation coefficients to a model of cellular activity; inhibition of [^{3}H]-thymidine incorportion (TI) into cells transfected with human D_2 and D_3 receptors (Sautel *et al.*, Neuroreport 6, 329 - 332, 1995). For PRL, coefficients were higher for D_2 (0.87) than D_3 (0.58) transfected cells. Conversely, for hypothermia and synthesis, correlations were superior to TI controlled by D_3 (0.99 and 0.95) than D_2 (0.38 and 0.31) sites. In conclusion, inhibition of PRL secretion by DA agonists is mediated primarily by D_2 sites, whereas actions at D_3 sites predominate in the modulation of CT and DA synthesis.

51.47 EFFECTS OF PRENATAL HARMINE EXPOSURE ON MONOAMINE METABOLISM IN BRAIN REGIONS OF MALE AND FEMALE NEONATE RATS.

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Alterations in MAO activity have been implicated in some developmental neuropsychiatric disorders. The indole tremorogen harmine, a reversible MAO-A inhibitor, has been shown to modify cerebral serotoninergic and dopaminergic function.

We have studied the effects of chronic prenatal harmine on monoamine metabolism in different brain regions of two days old male and female rats. Pregnant Sprague-Dawley rats were s.c. injected daily with two different doses of harmine (2 and 25 mg/Kg) or vehicle solution. Injections were started on E10 and given for eleven days.

Only the lower dose of harmine induced a significant reduction of 5-hydroxytryptamine (5-HT) and 5-HIAA levels, which was very marked in hippocampus. Moreover, noradrenaline and dopamine levels remained unaltered with the treatment.

Our results suggest that developing serotoninergic neurons innervating the hippocampus are specially sensitive to the prenatal harmine.

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52.01 TOWARDS AN UNDERSTANDING OF THE PHYSIOLOGICAL SIGNIFICANCE OF NEUROSTEROIDS: an electrophysiological and neuropharmacological approach.
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In vitro recordings have demonstrated that neurosteroids are potent and selective modulators of amino-acid mediated inhibitory and excitatory transmission in the mammalian CNS. Thus, neurosteroid-mediated actions may constitute an important mechanism in regulating neurotransmission. At present, however, the functional and pathophysiological significance of these findings remains to be elucidated in relation to *in vivo* CNS functioning. Therefore, the current study comprises an electrophysiological analysis of the effects of various neurosteroids on the functional state of a neuronal network recorded from the hippocampus of free-moving rats.

Rats were implanted with a pair of wires in the dorsal hippocampus to stimulate the Schäffer collaterals. A second electrode was implanted in the CA1 stratum radiatum to record dendritic population EPSPs. Following a 1-wk recovery period, input-output curves of single pulse responses were recorded at different intensities (range 20-400 μA). Subsequently, paired-pulse stimulation was given at 0.1 Hz with varying interpulse intervals (IPI; range 10-3200 ms). Analysis of I/O- and IPI-curves reveals the functional state of the neuronal network and thereby the effect of neurosteroid modulation.

Application of 5α-DHPROG (10 mg/kg i.p.), a neurosteroid with GABA-agonistic and NMDA-antagonistic activity, had no significant effect on single and paired-pulse responses. However, DHEAS (10 mg/kg i.p.), a neurosteroid with GABA-antagonistic and NMDA-agonistic activity, increased pEPSP amplitude and suppressed paired-pulse inhibition. These findings suggest a role of neurosteroids in modulating neuronal excitability *in vivo*.

52.02 BACKGROUND ADAPTATION AND SYNAPSE PLASTICITY IN THE PARS INTERMEDIA OF *XENOPUS LAEVIS*
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The process of background adaptation of the clawed toad *Xenopus laevis* is regulated by the melanotrope cells in the pars intermedia of the pituitary gland, which produce and release the pro-opiomelanocortin (POMC)-peptide αMSH. Suprachiasmatic neurons are responsible for the inhibitory control of the melanotropes. Immunoelectron microscopy, using freeze- substituted material, shows that their axon varicosities in the pars intermedia contain GABA, NPY and dopamine. GABA is present in electron-lucent vesicles, whereas NPY and dopamine coexist in dense granules. Morphologically specialised synaptic contacts between the varicosities and melanotrope cells show clustering of exclusively lucent vesicles to the presynaptic membrane, indicating release of GABA. Ultrastructural morphometry reveals a strong plasticity of the varicosities and their synapses, in relation to background adaptation: transferring animals from a black to a white background leads to a significant increase in the number and size of the varicosities and their active zones. These structural data indicate that the inhibitory control mechanism of the melanotropes is more active in white- adapted animals than in black-adapted ones. This morphological plasticity of the varicosities is reflected in a plasticity of the neurotransmitter contents: biochemical studies demonstrate effects of background on the storage and release of dopamine, GABA and NPY.

52.03 DIFFERENTIAL DISTRIBUTION OF SYNAPTOPHYSIN AND SNAP-25 IN RETINAL RIBBON SYNAPSES

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The synaptic v-SNARE synaptophysin and t-SNARE SNAP-25 are implicated in the mechanisms of docking and membrane fusion during exocytosis. However, little is known about the distribution of the docking/fusion proteins in terminals of selected neurons.

The retina, besides conventional synapses, contains the characteristic ribbon synapses. In the present study we were interested to know whether ribbon synapses are endowed with the same exocytosis machinery as conventional synapses. We analyzed the distribution of synaptophysin and SNAP-25 in the mouse and rat retina.

Immunohistochemical observations revealed that synaptophysin is present both in conventional and ribbon synapses of the retinal plexiform layers. Interestingly SNAP-25, found in conventional synapses, was ultrastructurally absent from the ribbon synapses.

Our data indicate the absence of SNAP-25 from photoreceptor and bipolar neuron terminals, suggesting different mechanisms in transmitter exo-endocytosis in these terminals.

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52.04 γ-HYDROXYBUTYRIC ACID (GHB) DOES NOT STIMULATE PRE-SYNAPTIC $GABA_B$ AUTO-RECEPTORS.
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GHB is a metabolite of GABA which induces generalized absence seizures when given to animals. This effect of GHB is blocked by $GABA_B$ antagonists. We investigated whether presynaptic $GABA_B$-mediated mechanisms are operative in the GHB model of generalized seizures. The affinity of $GABA_B$ receptors for GHB was determined in the agonist receptor assay using [^{3}H] baclofen or [^{3}H] CGP 27492 as radioligands, the IC_{50} in several brain structures were 110 μM. Hill factor was 0.85. Using the antagonist radioligand [^{3}H] CGP 54626, the IC_{50} was 5.5 mM in the absence and 25mM in the presence of 300 μM Gpp(NH)p ($p < 0.05$). Like the $GABA_B$ agonist (-)-baclofen, GHB induced a dose-related decrease in cerebellar cGMP which was antagonized by $GABA_B$ antagonists. Taken together, these results indicate that GHB acts as an agonist at $GABA_B$ receptors. The effects of GHB on the electrically stimulated release of [^{3}H] GABA from rat cerebral cortex, striatum and hippocampus slices were also examined. Waldmeier and Baumann (Ann N.Y. Acad. Sci., **604**, 136-151, 1990) have shown that the Ca^{2+} -dependent release of [^{3}H]GABA from cortical slices evoked by low frequency (0.125-2 Hz) electrical stimulation was inhibited by (-)-baclofen (IC_{50} = 370 nM as compared to 35 nM in the agonist binding assay). The effect of (-)baclofen was more marked at lower than at higher frequencies (0.125 - 4Hz). These data are compatible with the existence of $GABA_B$-type presynaptic auto-receptors modulating the release of this amino acid. GHB (0.1 to 3 mM), however, had no significant effect on the basal and electrically (0.125-16Hz) evoked release of [^{3}H]GABA from cortical, striatal and hippocampal slices. GHB (0.1-3 mM) also did not alter [^{3}H]DA, [^{3}H]NA and [^{3}H]5HT release.

These results do not support the hypothesis that a presynaptic mechanism mediated by $GABA_B$ auto-receptors is directly involved in the mechanism of GHB-induced absence seizures.

52.05 SELECTIVE IMPAIRMENT OF LTP WITHOUT DEFECTIVE SPATIAL LEARNING IN MICE LACKING THE NEURONAL CELL SURFACE GLYCOPROTEIN THY-1.
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Thy-1 is a major cell adhesion molecule found on the surface of mature neurons. We have compared long-term potentiation (LTP) in genetically engineered mice lacking the Thy-1 gene and in wild-type litter-mates. Four different conditioning protocols (including theta-burst, 100Hz and 250 Hz) all of which gave robust LTP in the dentate gyrus of anaesthetized wild-type animals, produced neither short-term potentiation (STP) nor LTP in mutant animals; a fifth protocol (6 trains of 6 pulses at 400Hz, inter-train interval 20 sec, intensity twice that of test stimuli) yielded LTP that was significantly less than that seen in wild-type animals using the same protocol. However, in area CA1, LTP was similar in wild-type and mutant animals, both *in vivo* and *in vitro*. The gross morphology of the hippocampus, and the distribution of the neuronal cell fields was qualitatively similar in the two groups, and no difference was seen in hippocampal NMDA receptor binding properties. Acquisition and retention of spatial information in the watermaze was indistinguishable between the wildtype and mutant animals, even with minimal training regimes. These results indicate that Thy-1 modulates LTP to different extents in the dentate gyrus and area CA1, and that certain types of learning are not affected by impaired synaptic plasticity in the dentate gyrus.

52.06 ARACHIDONIC ACID INCREASES THE EXTRACELLULAR LEVELS OF GLUTAMATE AND GABA IN RAT HIPPOCAMPUS BY INHIBITION OF THEIR PRESYNAPTIC UPTAKE
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The effects of the fatty acid arachidonic acid (AA) on the release of both excitatory (glutamate and aspartate) and inhibitory (GABA) amino acids were investigated in purified nerve terminals (synaptosomes) from rat hippocampus. AA dose-dependently increased the extracellular levels of glutamate, aspartate and also of GABA, in the absence of depolarizing agents.This effect was not due to nonspecific disturbances in the energetic balance (ATP/ADP ratio) or membrane integrity (LDH leakage) by AA. The AA-induced effect could be induced by either enhancing the spontaneous release or inhibiting the re-uptake of these neurotransmitters. The effect of 25 μM AA was completely independent of extracellular Ca^{2+}, suggesting that exocytotic release was not affected by this AA concentration. Absence of effects of the PKC inhibitors H-7 and sphingosine (10 μM) on the AA enhanced extracellular amino acid levels exclude involvement of this enzyme. Possible effects of AA on re-uptake of spontaneously released amino acids were investigated by labelling them with traces of 3H-GABA or 3H-D-aspartate and measuring their uptake in synaptosomes. Under these conditions AA inhibited the net Na-dependent uptake of 3H-GABA by 20% and of 3H-D-aspartate by 30%. We conclude that in addition to the reported PKC-mediated action of AA on exocytotic glutamate release (Herrero et al, Nature vol. 360 1992), this fatty acid enhances extracellular levels of amino acids in the rat hippocampus by inhibition of their recycling.

52.07 A POSTSYNAPTIC MECHANISM FOR DEPRESSION OF GABAergic SYNAPSES BY OXYTOCIN IN THE HYPOTHALAMUS OF THE RAT

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Oxytocin, involved in neuropeptidergic autoexitation, gives rise to an IP3 mediated release of calcium from intracellular store(s) within supraoptic nucleus (SON) neurons (Moos and Richard, 1994). It is also known that the $GABA_A$ receptor channel functioning may depend directly (or indirectly) on the intracellular free calcium concentration. Therefore the effect of oxytocin on the GABAergic synaptic input in the SON was analyzed. Under visual control I have performed *in situ* patch clamp recordings from individual neurons of the SON. Spontaneously occurring, bicucullin sensitive GABAergic inhibitory synaptic currents (IPSCs) were pharmacologically isolated from the excitatory synaptic input. It was a spontaneously active, chloride conducting, tonic synaptic input, both arising from somatic as well as from dendritic synaptic contacts. Application of oxytocin during such recordings, strongly reduced the amplitude of spontaneous IPSCs in 60 % of the recording. This reduction was (i) completely reversed by washing, (ii) blocked by an oxytocin receptor antagonist and (iii) observed in slices both from females as well as from male animals. In cells that were *not* sensitive to oxytocin, vasopressin gave a similar response. The effect of oxytocin was maintained in presence of TTX, it was blocked after perfusion of βS GDP within the recorded cell, and it was mimicked by thapsigargin application. Therefore the oxytocin induced depression of $GABA_A$ receptor functioning is mediated through a postsynaptic mechanism involving a rise in the intracellular calcium concentration. The resulting *disinhibition* of magnocellular neurons may explain why a neuropeptide like oxytocin facilitates it own release.

52.08 EFFECT OF AMISULPRIDE IN BIOCHEMICAL MODELS PREDICTIVE OF A BLOCKADE OF PRE-AND POST-SYNAPTIC DOPAMINERGIC RECEPTORS.

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The substituted benzamide, amisulpride, is a novel antipsychotic agent which shows a high affinity and selectivity for D_3 and D_2 receptors. It displays a pharmacological profile distinct from that of classical neuroleptics, which could be related to a preferential blockade of presynaptic dopaminergic receptors. The aim of the present study was to evaluate the effect of amisulpride in biochemical models predictive of a blockade of presynaptic (synthesis of dopamine (DA) in the presence of γ-hydroxybutyrate (γOH) in limbic areas and striatum) and postsynaptic (acetylcholine (ACh) levels in the striatum) dopaminergic receptors.
Experiments were performed on male Sprague Dawley rats. L-DOPA and ACh levels were measured by HPLC with electrochemical detection.
Amisulpride increased the synthesis of DA, as measured by the accumulation of L-DOPA after administration of the decarboxylase inhibitor NSD 1015 (100 mg/kg ip), with a relative selectivity for the limbic regions (nucleus accumbens + olfactory tubercle) versus striatum (ED_{50} = 19 and 44 mg/kg ip, respectively). In the presence of γOH (750 mg/kg ip), the preferential D_3 agonist, 7-OH-DPAT decreased DA synthesis without any regional selectivity (ED_{50} = 39 and 43 µg/kg sc, in the limbic and striatal structures, respectively) and amisulpride antagonized the effect of 7-OH-DPAT (82 µg/kg sc) with the same potency in the two structures (ID_{50} = 10 and 11 mg/kg ip, respectively).
In the striatum, amisulpride decreased ACh levels with an ED_{50} of ≈ 60 mg/kg ip.
In conclusion, the present results confirm that amisulpride preferentially blocks presynaptic versus postsynaptic dopaminergic receptors.

52.09 ANTI-CALMODULIN ANTIBODIES DECREASE CALCIUM-INDUCED NORADRENALINE RELEASE FROM PERMEATED SYNAPTOSOMES.

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Introduction of several antibodies (IgGs) against the nervous tissue-specific protein B-50 (GAP-43) into permeated synaptosomes has indicated that the calmodulin (CaM)-binding properties of B-50 are important in the mechanism of Ca^{2+}-induced neurotransmitter release (Hens et al. (1995) *J. Neurochem.* **64**, 1127-1136). Therefore, we investigated the rolë of CaM in Ca^{2+}-induced noradrenaline (NA) release by the introduction of polyclonal anti-CaM IgGs, exogenous CaM and several CaM antagonists into permeated synaptosomes. Affinity-purified anti-CaM IgGs were specific for CaM and inhibited Ca^{2+}/CaM-dependent protein kinase II autophosphorylation in synaptosomal plasma membranes and in vitro B-50 dephosphorylation by Ca^{2+}/CaM-dependent phosphatase 2B. Moreover, anti-CaM IgGs decreased Ca^{2+}-induced NA release from permeated syaptosomes in a concentration-dependent manner, whereas control IgGs were without effect. Addition of exogenous CaM (≤ 6 µM) failed to stimulate Ca^{2+}-induced NA release from permeated synaptosomes, indicating that if CaM is required for the induction of NA release it is still present in sufficient amounts in permeated synaptosomes. Of the tested CaM antagonists trifluoperazine (at 10^{-4} M), W-7 (at 10^{-4} M), calmidazolium (at 10^{-4} M) and polymyxin B (at 200 IU/ml), only the latter potently inhibited Ca^{2+}-induced NA release. Interestingly, polymyxin B was also the only antagonist affecting the interaction between B-50 and CaM, thus lending further support for the hypothesis that B-50 serves as a local Ca^{2+}-sensitive CaM store underneath the plasma membrane in the mechanism of neurotransmitter release. We conclude that CaM plays an important role in vesicular NA release, probably by activating Ca^{2+}/CaM-dependent enzymes that are involved in regulating one or more steps of the molecular mechanism of NA release after the Ca^{2+} trigger.

52.10 LONG-TERM DEPRESSION (LTD) AND REVERSAL OF LONG-TERM POTENTIATION (LTP) IN AREA CA1 AND THE DENTATE GYRUS IN THE AWAKE RAT.

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We have examined the ability of several stimulation protocols to induce long-term depression (LTD) or to reverse a previously established long-term potentiation (LTP) in area CA1 of the hippocampus and in the dentate gyrus (DG) of the awake rat. Synaptic potentials evoked in DG by activation of the lateral and/or medial perforant paths, or in stratum radiatum of CA1 by activation of the Schaffer collaterals /commissural system (SCC) were recorded in the freely-moving rat.

Homosynaptic LTD: (1) Low-frequency trains (900 pulses at 1-5 Hz) failed to produce LTD in DG or in CA1; the same trains given 30 min (CA1 and DG) or 10 min (CA1) after LTP-inducing stimulation, did not reverse LTP. (2) Pairs of pulses (200 pairs, ISI 25msec) at 0.5 Hz induced LTD (lasting at least 2 days) and were able to reverse LTP in CA1, when the intensity was sufficiently high to produce paired-pulse depression at 25msec ISI; depotentiation can also be reversed by a further LTP-inducing stimulation. (3) The paired-pulse protocol was not effective in inducing LTD or depotentiation in the DG.

Heterosynaptic LTD: (1) Tetanic stimulation (400Hz) of the lateral perforant path produced a lasting depression (4 days) and was able to depotentiate the medial pathway; no LTD or depotentiation could be obtained on the lateral perforant path. (2) Reversal of LTP in the medial pathway was obtained when heterosynaptic trains were applied 30 min or 1 day after LTP induction. (3) After saturation of LTP and depotentiation, LTP could be reinstated by tetanization.

These experiments suggest that only certain patterns of activity are capable of inducing LTD in the hippocampus of the awake adult rat, and show pathway-specificity in the ability of different protocols to induce LTD. In all cases, protocols for inducing LTD are also able to reverse a pre-established LTP, suggesting that LTP and LTD mechanisms compete in the regulation of synaptic plasticity.

52.11 LOW FREQUENCY TRAINS FAIL TO INDUCE HOMOSYNAPTIC LONG-TERM DEPRESSION (LTD) OR DEPOTENTIATION IN AWAKE OR ANAESTHETIZED ADULT RATS

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In experiments performed at Orsay on awake adult rats and Mill Hill on anaesthetized young rats (10 days-3 months), we have examined the ability of low frequency trains (900 pulses at 1-5Hz) to induce LTD or depotentiation. In the dentate gyrus and area CA1 of both anaesthetized and awake adult rats we found no evidence that LTD or depotentiation could be induced by low frequency stimulation. Furthermore in young anaesthetized rats, from 10 days to 3 months, low-frequency stimulation failed to produce depotentiation or LTD in the dentate gyrus. Only in area CA1 of anaesthetized rats aged 10-11 days was reliable LTD or depotentiation seen, by 16 days this plasticity was lost. These experiments suggest that repetitive low-frequency stimulation evokes a developmentally-regulated form of LTD which in the hippocampus is seen only in specific pathways in the young animal. Our results leave open the question of whether alternative patterns of activity are capable of inducing LTD and/or depotentiation in the adult rat.

52.12 Melatonin stimulates calcium- dependent chloride- currents in mRNA- injected Xenopus oocytes

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Melatonin (MEL) is a hormon synthesized in the pineal gland. Receptors of this hormon have been detected in different areas of the mammalian brain. The present study analyzed membrane currents elicited by application of MEL in Xenopus oocytes after injection of mRNA from rat brain.
MEL (0.1- 100 µmol/l) was administered to the oocytes for 150 sec. Membrane currents of the oocytes were recorded 3 to 7 days after injection of mRNA using a two- electrode voltage- clamp technique; holding potential: -20 to -80 mV.
The MEL- induced membrane currents showed the following characteristics: **1.** MEL elicited oscillatory inward currents with amplitudes up to 80 nA. **2.** Responses to MEL were dose- dependent with a threshold concentration of about 0.1 µmol/l. **3.** The membrane currents occured 40-90 sec after onset of the MEL-application and persisted for 1.5- 15 min after end of application. **4.** The equilibrium potential of the inward currents was about -25 mV. **5.** The MEL- induced membrane currents were completly blocked by the chlorid-channel-blocker 9-anthracencarbonacid (200 µmol/l). **6.** Native oocytes were not sensitive to MEL.
This experiments showed that MEL- sensitive receptors, expressed in oocytes after injection of mRNA from rat brain, stimulates Ca^{2+}-dependent Cl^-- currents.

52.13 DIVERSE PATHWAYS OF REGULATING NEUROTRANSMITTER RELEASE. STUDIES WITH PURIFIED NERVE TERMINALS.

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Regulation of presynaptic neurotransmitter release is decisive for fine-tuning of neurotransmission. It seems more rule than exception that in CNS different transmitter types, such as aminoacids and peptides are co-localized inside the same nerve terminal. Rapid K-induced depolarization showed different kinetics in regulating exocytotic release of aminoacids ($t_{1/2}$=100 msec) and Cholecystokinin (CCK) ($t_{1/2}$=1 sec) from purified synaptosomes. Fast exocytotic aminoacid release was primarily induced via Agatoxin IVA-sensitive P-type channels, but also other HVS Ca-channels (N and L) were involved. In contrast, CCK release was triggered only by Agatoxin IVA-sensitive channels.
Aminoacid release appeared to be regulated by both metabotropic and ionotropic receptors, depending on the brain region studied. In hippocampus, Ca-dependent release of excitatory aminoacids was stimulated by CCK in a L365,260-sensitive (CCK_B-antagonist) way. Arachidonic acid evoked extracellular aminoacid levels by distinct pathways. It enhanced glutamate exocytosis by synergistic stimulation of PKC with the phorbolester PDBu. In addition, arachidonic acid inhibited presynaptic Na-gradient driven glutamate and GABA uptake carrier activity in a PKC-independent way. In hippocampus synaptosomes, NMDA elevated aminoacid release at low dose (50 µM) in a MK801- and Mg- sensitive way. Evidently, a variety of signals act on nerve terminals to regulate (differential) transmitter release.

52.14 THE CELLULAR AND SUBCELLULAR LOCALIZATION OF METABOTROPIC GLUTAMATE RECEPTORS 1a AND 5a IN THE RAT NIGROSTRIATAL SYSTEM.

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The cellular and subcellular localization of two metabotropic glutamate receptors (mGluR) mGluR1a and mGluR5a, both linked to inositol phosphate (IP) second messenger was studied in the rat nigrostriatal system. The mGluR immunoreactivities (ir) were detected both with preembedding immunoperoxidase and immunogold methods for light and electron microscopic studies.

At the light microscopic level an abundant mGluR1a immunoreactivity (ir) was accompanied with a light labeling for mGluR5a in the substancia nigra. Conversely, in the striatum a strong mGluR5a immunolabeling was associated with a light immunostaining for mGluR1a.

At the ultrastructural level both mGluR immunoreactivities were present in perikarya and dendrites, while axons were always devoid of mGluR ir. When studied with preembedding immunogold labeling, mGluR1a and mGluR5a-ir-s were in association with intracellular and plasma membranes, both at the periphery of the postsynaptic specializations, as well as extrasynaptically. As previously shown, subsynaptic specializations were always devoid of ir. Combining preembedding mGluR immunogold labeling with tyrosine hydroxylase immunohistochemistry the morphological relationship of neurons expressing the different mGluRs to tyrosine hydroxylase immunopositive neuronal elements is also analysed.

These findings provide morphological evidence for the differential involvement of IP-linked mGluR1s in the nigrostriatal system. (Supported in part by OTKA grants 1107, T 016164, 2617 and ETT grant T-04 491/93.)

52.15 TEMPORAL CONSTRAINTS ON ASSOCIATIVE PLASTICITY (AP) OF RAT NEOCORTICAL NEURONS UNDER REPEATED COMBINED ACTION OF L-GLUTAMATE AND ACETYLCHOLINE.

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Timing relations of analogs of conditioned and reinforcing stimuli (CS,RS) in neuronal models of learning under which AP occurs frequently don't reflect pattern of activity of neuronal inputs in the course of acquisition of conditioning [1,2]. The study of the temporal relations of single neurons excitatory reactions (ER) in sensorimotor cortex of untotal anethetized rats to repeated paired microiontophoretic 0.5-1 s applications of L-Glu (as CS) and ACh (as RS) showed that AP occurs as enhancement of Glu-ER (190±48% of control) in the case when Glu-ER and ACh-ER onsets are coincident (5(71%) units) or when ACh-ER develops at the fall of Glu-ER (172±58% of control, 1.6±1.7 s of overlap, 5(46%) units). Significantly lesser (6(14%)) number of neurons increases Glu-ER if Glu- and ACh-ER are separated by 1.7±1.1 s period of background activity or inhibitory reaction. Isolated ACh applications don't influence on Clu-ER as compared with changes of Glu-ER during isolated applications of L-Glu (19 and 96 units respectively). Modifications of both Glu- and ACh-ER don't depend on relation of number of spikes in original responses to transmitters (coefficient of rank correlation are 0.069, $P>0.5$ for Glu-ER plasticity and 0.097, $P>0.2$ for ACh-ER). It is concluded that mechanisms of AP induced under presentations of CS and US analogs in accordance with the pattern of afferent activity during conditioning acquisition (delayed ACh applications in paires) may cause potentiation of neuronal responsiveness observed during behaviour modifications. It is important that temporal overlap of Glu- and ACh-ER but not their magnitude is the critical factor for AP induction. (1) Rasmusson, Dykes, Exp.Brain Res, 70: 276, 1988; (2) Schreurs, Alkon, Soc.Neurosci. Abstr., 18:337, 1992.

52.17 NEURONAL CONNEXINS IN THE RETINA

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Connexins represent a family of widely distributed integral membrane proteins forming channels (gap junctions) that render a direct intercellular communication and are regarded as important elements for the regulation of signal transduction in the nervous system. The permeability of these channels can be modulated by a variety of second messengers which in turn are regulated through the activity of neurotransmitters.

In the present study, we used the fish retina, where many subclasses of neurons form gap junctions, and three different anti-connexin antisera to identify neuronal connexins and to characterize their distribution. We further analyzed the effect of dopamine and forskolin/IBMX on the endogenous phosphorylation of potential horizontal cell (HC) connexins. Immunoblotting revealed the presence of specific Cx32- and Cx43-immunoreactivity in retinal membrane and cell fractions. Immunocytochemistry showed (i) substantial anti-Cx43-ELII-immunoreactivity in one class of ON-bipolar cells and subclasses of amacrine and ganglion cells; (ii) the presence of Cx43-CT-immunoreactivity in Mueller cells and (iii) a strong labeling of HCs and their axon terminals with anti-Cx32α. The treatment of isolated HCs with dopamine or forskolin/IBMX, both known to modulate HC gap junctions via cAMP-dependent phosphorylation, resulted in an increase in the endogenous phosphorylation of several proteins in the range of 25-50 kDa.

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52.18 THE ACTION OF α-LATROTOXIN ON INTRACELLULAR CA^{2+} DYNAMICS AND α-MELANOPHORE STIMULATING HORMONE (α-MSH) SECRETION IN MELANOTROPE CELLS OF *XENOPUS LAEVIS*

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The spider protein α-latrotoxin binds to the presynaptic protein neurexin and, through interaction with either the Ca^{2+} binding protein synaptotagmin or interaction with N-type Ca^{2+} channels, stimulates transmitter release. The purpose of the present study was to determine if α-latrotoxin would affect Ca^{2+} dynamics or hormone release from the neuroendocrine melanotrope cell of *Xenopus laevis*. This cell displays intracellular Ca^{2+} oscillations, generated through the action of N-type Ca^{2+} channels, which drive α-MSH secretion. $[Ca^{2+}]_i$ was imaged using confocal laserscanning microscopy and secretion was assessed by prelabelling the cells with ^{3}H-lysine and following release of radiolabelled peptides during the Ca^{2+} imaging experiments. The results showed that α-latrotoxin induced broad intracellular Ca^{2+} transients in the majority of cells imaged. The toxin stimulated secretion with a time-course similar to time-course of its action on $[Ca^{2+}]_i$. To determine if the effects of α-latrotoxin on secretion are Ca^{2+}-dependent Ni was used to block Ca^{2+} channels. Ni quickly blocked Ca^{2+} oscillations in all imaged cells and led to a rapid inhibition of secretion; α-latrotoxin had no effect on $[Ca^{2+}]_i$ nor on secretion from Ni-treated melanotropes. Similarly, the action of α-latrotoxin on $[Ca^{2+}]_i$ and secretion could be blocked by ω-conotoxin, a specific N-type Ca^{2+} channel blocker. Our results indicate that the action of α-latrotoxin on the secretory process of *Xenopus* melanotropes is Ca^{2+}-dependent, possibly involving action of the toxin through its neurexin receptor directly on the Ca^{2+} channel. The melanotrope cell of *X. laevis*, because of the ease with which it can be imaged and secretion measured, will make a good model to further study the function of the neurexin-N-type Ca^{2+} channel-synaptotagmin complex in secretory processes.

52.19 SUBUNIT-SPECIFIC REGULATION OF NMDA RECEPTOR CHANNELS BY THE TYROSINE KINASE $pp60^{c\text{-}src}$.

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Tyrosine kinases are expressed at high levels in neurons, growth cones and synapses, and have thus been proposed to have important neuronal signaling functions. The well characterized tyrosine kinase src is particularly enriched in postsynaptic densities (Sugrue et al., 1990), where the NR2B subunit of the NMDA receptor was found to be the major tyrosine-phosphorylated protein (Soo Moon et al., 1994). In dorsal horn and hippocampal neurons the NMDA receptor conductance was increased by injection of $pp60^{c\text{-}src}$ (Wang und Salter, 1994).

We now examined heteromeric NR1-NR2A, NR1-NR2B, NR1-NR2C and NR1-NR2D receptor channels transiently expressed in HEK 293 cells. Glutamate (100 µM) was applied in the presence of glycine (10 µM) in Mg^{2+}-free solutions at -60 mV every 20 s while purified recombinant human $pp60^{c\text{-}src}$ diffused from the patch pipette into the cell. Four to five minutes after establishing the whole-cell configuration the glutamate activated currents steadily increased about 1.7-fold in NR1-NR2A but not in the other three receptor channels. The maximal effect was reached after 9 to 10 min and persisted during the subsequent recording period without changing the kinetics of the whole-cell currents.

Although our study cannot exclude a possible tyrosine phosphorylation of other NMDA receptor subunits than NR2A, the functional consequence of the NR1-NR2A phosphorylation by $pp60^{c\text{-}src}$ indicates a mechanism by which the current flux through NMDA channels can be controled in a subtype-specific manner.

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52.20 KINETICS OF AMPA RECEPTOR CHANNELS DURING LONG-TERM DEPRESSION IN CEREBELLAR PURKINJE CELLS IN RAT.

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Kinetics of AMPA receptor(AMPAR) channels were examined during long-term depression at the synapse between parallel fibers and Purkinje cells in cerebellum induced by the conjunctive stimulation of them with climbing fibers. The current recording was done by whole cell and cell-attached patch clamp methods. Data collection and analysis were conducted with the use of pClamp system and S. Traynelis' N05 software. The single channel currents recorded from soma of the Purkinje cells in slice preparation suggest that four shut & one or two open states are involved in the kinetics of AMPAR channel. The single channel currents obtained from the soma of the cultured Purkinje cell were also analyzed and compared with those recorded from Purkinje cells in slice preparations. Long-term depression of the amplitudes of EPSCs was examined with respect to the change in kinetics of AMPAR channels in the postsynaptic membrane. The time course of EPSCs recorded from Purkinje cell was well fitted by two exponential functions. The deactivation of AMPAR channels mainly contributed to the decay phase of the EPSC. No change in time curse of EPSCs was observed, as determined by comparing time constants before and after the conjunctive stimulation.

It is concluded from the present experiments that (1)no difference was observed in the properties of AMPA receptor channels between cultured Purkinje cell and natural Purkinje cell in slice preparatons and that (2)the decreased amplitude of EPSCs after a conjunctive stimulation is explained by decreased number of active AMPAR channels, which enter into the reaction with agonists without changing the kinetics.

52.21 A_1 ADENOSINE RECEPTORS: Ca^{2+} DEPENDENT SWITCH TO THE LATENT NMDA RECEPTOR-MEDIATED COUPLING BETWEEN RAT HIPPOCAMPAL NEURONS.

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Inhibition of A_1 adenosine receptors on the background of increased external Ca^{2+}/Mg^{2+} ratio leads to a dramatic and irreversible change in the EPSC recorded by *in situ* patch clamp in CA1 pyramidal neurons. The kinetics of EPSC becomes stimulus-dependent and markedly slows down with the increase in the stimulus strength. The stimulus-dependent fraction of EPSC is carried through NMDA receptor-operated channels, but disappears under either NMDA antagonist, APV, or nonNMDA antagonist, CNQX. This indicates at the polysynaptic nature of acquired stimulus-dependence of the kinetics of EPSC: predominantly nonNMDA receptor-mediated stimulation of CA1 neurons via Schaffer collaterals is followed by the activation of previously silent NMDA receptor-mediated connections between CA1 neurons. These connections become operational on a long-term basis.

52.22 FAST EXOCYTOTIC RELEASE OF DIFFERENT NEUROTRANSMITTERS: DIFFERENCES IN KINETICS AND REGULATION BY Ca^{2+}-CHANNELS

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Calcium influx through presynaptic high voltage sensitive Ca^{2+}-channels serves as the trigger for neurotransmitter release. Our aim was to determine the timecourse and Ca^{2+}-channel regulation of rapid exocytosis of aminoacid- and neuropeptide-transmitters from rat cortex synaptosomes. For that purpose we developed a method by which synaptosomes are shortly (milliseconds) depolarised by high K^+(40mM) in the presence or absence of extracellular Ca^{2+}(2mM), so that exocytosis of endogenous transmitters can be measured. Ca^{2+}-dependent release of the aminoacids Glutamate(GLU) and GABA can be detected after a 50 millisecond depolarisation, whereas for Ca^{2+}-dependent release of the neuropeptide CCK a depolarisation of 250 milliseconds is required. For GLU and GABA release a fast phase(< 1sec) and a second slower phase can be distinguished. CCK release shows a continuous increase. The Ca^{2+}-dependent release of GLU, GABA and CCK is dose-dependently inhibited by the P-type Ca^{2+}-channel antagonist ω-Agatoxin-IVA, and is completly blocked at 200nM. 70% of the GLU and 30% of the GABA release is inhibited by ω-Conotoxin-GVIA(1μM). About 50% inhibition of release of both aminoacids is seen with ω-Conotoxin-MVIIC(1μM). Release of GLU(40%), but not GABA, is inhibited by 1μM of the L-type Ca^{2+}-channel blocker Nimodipine. No effect of ω-Conotoxin-GVIA and Nimodipine is found on CCK release. In conclusion : Ca^{2+}-dependent (exocytotic) release of GLU and GABA shows at least two kinetic components. Ca^{2+}-dependent release of CCK is slower and is propably monophasic. The P-type Ca^{2+}-channel mediates fast exocytosis of both the aminoacids and of the neuropeptide CCK. Unlike CCK, aminoacid release can be mediated by multiple, pharmacologically distinct, Ca^{2+}-channels, which probably cooperate with each other to regulate exocytosis.

52.23 CALCIUM OSCILLATIONS IN MELANOTROPE CELLS OF *XENOPUS LAEVIS* ARE REGULATED BY A cAMP-DEPENDENT AND A cAMP-INDEPENDENT MECHANISM

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Ca^{2+} oscillations may be important in the induction of α-MSH release from melanotrope cells of *Xenopus laevis*. Oscillatory, secretory and adenylyl cyclase activity are all inhibited by three receptor systems, namely the dopamine D_2 receptor, the NPY Y_1 receptor and the $GABA_B$ receptor. In the present study we focus on the actions of 8-Br-cAMP and sauvagine (which stimulates cAMP production) on cells inhibited by dopamine, NPY, and baclofen. $[Ca^{2+}]_i$ was measured in melanotropes loaded with fura-2 using digital video-imaging microscopy. 8-Br-cAMP or sauvagine increased the frequency of the Ca^{2+} oscillations and induced oscillations in non-oscillating cells. The cAMP-dependent protein kinase (PKA) inhibitor H89 blocks Ca^{2+} oscillations as well as actions of 8-Br-cAMP and sauvagine. Treatment with either 8-Br-cAMP or sauvagine under baclofen-inhibited conditions leads to a reappearance of Ca^{2+} oscillations. Neither 8-Br-cAMP nor sauvagine treatment induce Ca^{2+} oscillations during dopamine-inhibition. Cell membrane depolarization with 20 mM K^+ during dopamine-inhibition also fails to induce oscillations. However, a combination of 8-Br-cAMP with membrane depolarization restores Ca^{2+} oscillations under dopamine-inhibition. It appears that NPY-inhibition of oscillations involves a cAMP-dependent pathway, although a minor population of cells failed to respond to 8-Br-cAMP or sauvagine. Altogether we conclude that a cAMP/PKA pathway is involved in the regulation of Ca^{2+} oscillations by sauvagine, baclofen, NPY and dopamine, and that dopamine inhibits oscillations also by a cAMP-independent mechanism probably involving membrane hyperpolarization.

52.24 PHARMACOLOGICAL CHARACTERIZATION OF THE HETEROGENOUS CALCIUM CHANNEL POPULATION IN RAT MELANOTROPES.

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The melanotropes of the rat intermediate pituitary display a heterogenous population of calcium channels: a Low Voltage-Activated, rapidly inactivating T-type channel and at least two types of High Voltage-Activated (HVA) channels. One HVA channel is non-inactivating, whereas the other inactivates with a timeconstant of 70-120 ms at +20 mV holding potential. In whole cell currents, there is much variation in inactivation characteristics of the HVA current, suggesting that HVA channel sub-types are present in different ratios in different cells. It has been established previously that the HVA current is sensitive to the dihydropyridines (DHP) nifedipine and Bay K 8644. We examined the pharmacological profile of the HVA current more closely, by using nitrendipine and the potent L-channel blocker calcisceptin. Nitrendipine (10 μM) blocked the HVA current by 84.0 ± 5.8% (n=6), whereas calciseptin (10 μM) reduced the current only by 39.4 ± 13.1% (n=4). In addition, the O, P, and Q-type calcium channel blocker ω-AgaTx IVA also reduced the HVA current reversibly by 24.2 ± 5.8% (n=4). Whether this indicates that a non-T, -N, or -L type is present or that the toxin has an affinity for L-type of channels is currently under investigation. In our melanotrope culture ω-CgTx GVIA (1 μM) irreversibly blocked the HVA current by 21.7 ± 8.1 % (n=4), suggesting that a pharmacological distinct HVA N-type channel is present in these cells, which is probably the inactivating HVA channel. In addition to sensitivity to classical blockers, the HVA current of melanotropes appeared to be sensitive to new conus toxins that we isolated from *C. textile* and *C. pennaceus*.

52.25 HIGH AFFINITY BLOCK OF A PERSISTENT CALCIUM CURRENT BY NIMODIPINE IN CEREBELLAR GRANULE NEURONS

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Neuronal survival in absence of specific trophic factors is significantly enhanced by membrane depolarization. This effect is thought to be mediated by a depolarization-induced internal calcium elevation. The nature of the voltage-dependent calcium channel responsible for this persistent elevation was investigated in dispersed cerebellar granule neurons from 8-day old rats by measurements of the internal calcium concentration in Fura2-loaded cells. The cultures were routinely maintained in 25 mM KCl to enhance neuronal survival and were incubated with Fura2 either in 25 (chronic depolarization) or 5.4 mM KCl (control solution). In 25 mM KCl, the internal calcium concentration was between 100 and 150 nM, and quickly decreased to ≈ 40 nM when the external KCl was lowered to 5.4 mM. Treatment with nimodipine resulted in a decrease of calcium to the *same level* as that attained with control solution. The IC_{50} of this effect was close to 0.3 nM. In contrast, agatoxin IVA (200-500 nM) was ineffective. In 5.4 mM KCl the basal calcium level was 36±15 nM (n=95). When neurons were challenged with 15-75 mM potassium, nimodipine strongly antagonized the internal calcium rise due to depolarization. The dose-dependence of this depression was best approximated by a two site curve with $IC_{50}(1)$= 0.27 nM and $IC_{50}(2)$ = 65 nM. In agreement with previous findings in different tissues, these two constants might represent the affinities of the drug for two different states of the channel, namely closed (or resting) and open state. In chronic depolarizations, the nimodipine-sensitive current appears to be the main current responsible of maintaining the internal calcium level necessary for depolarization-induced neuronal survival.

52.26 NMDA SYNAPTIC CURRENTS MODULATION BY POSTSYNAPTIC INCREASE OF $[Ca^{2+}]_i$.
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The activity of the NMDA currents may be regulated by increase of the intracellular calcium ($[Ca^{2+}]_i$), however the physiologycal role of this modulation is not clear. In the present study we describe the Ca^{2+}-dependent regulation of the evoked NMDA receptor mediated EPSCs ($EPSC_{NMDA}$) using double-patch clamp whole-cell recordings from two synaptically connected hippocampal neurones in culture. Presynaptic neurons were activated by brief (5 ms) depolarizing pulses and the NMDA component of the evoked postsynaptic current was recorded in the presence of 10 μM CNQX and 20 μM bicucculine. $[Ca^{2+}]_i$ was estimated using confocal scanning microscopy with Fluo-3. Regular (every 8 s) stimulation of the presynaptic neuron evoked currents in the postsynaptic neuron whose amplitude was stable during 10-15 min of recording, and were inhibited by 50 μM AP-5. Trains of depolarizing pulses applied to postsynaptic neuron induced increase of $[Ca^{2+}]_i$ in dendrites and a decrease by about 50% in the amplitude of the $EPSC_{NMDA}$. The time for recovery from inactivation was in the range 10 to 50 s, and was closely coincident with the time for recovery of Ca^{2+}-dependent fluorescence in dendrites after depolarizing pulses. Analysis of the evoked $EPSC_{NMDA}$ properties showed that increased $[Ca^{2+}]_i$ changes the amplitude, but not the kinetics of $EPSC_{NMDA}$. The amplitude of the AMPA component of EPSCs as well as the amplitude of miniature AMPA EPSCs was not modulated by $[Ca^{2+}]_i$.

Our results shows that calcium influx in dendrites through voltage-gated calcium channels transiently decreases the $EPSC_{NMDA}$ without modulation the non-NMDA component. This mechanisms can play an important role in the synaptic plasticity processes in the brain.

52.27 INHIBITION OF TRANSIENT POTASSIUM CURRENT BY AN INTRACELLULAR CALCIUM MEDIATED PROCESS IN CULTURED CHICK TELENCEPHALIC NEURONS.
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The effect of intracellular calcium concentration on the transient outward current of cultured chick neurons was investigated by whole cell- and nystatine-perforated configurations of the patch clamp technique. The calcium ionophore ionomycin caused a depression in the amplitude of the transient outward potassium current. The activation and inactivation curves were not altered, neither were the time constants of activation and inactivation. The depression of transient outward currents was also reproduced by the elevation of extracellular calcium concentration, and in 65% of the cells by the glutamatergic agonists NMDA and kainate as well. In these cases however the depression of currents was reversible, and the depression caused by kainate was prevented by the non-competitive non-NMDA receptor antagonist GYKI 53784. In itself the antagonist did not cause a depression of potassium currents. This intracellular calcium-mediated effect of excitatory amino acid agonists on the transient potassium current may play a role in the excitotoxic process.

52.29 DEVELOPMENT OF AN INWARDLY RECTIFYING POTASSIUM CURRENT IN RAT VENTRAL MIDBRAIN CULTURES.
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The baclofen-induced inwardly rectifying potassium conductance in rat ventral midbrain culture has previously been demonstrated to develop with time *in vitro*[1]. In contrast, baclofen reduced calcium currents in young and old cultures, suggesting that receptor expression and G-protein coupling occurs at all ages *in vitro*. Whole cell voltage-clamp recordings were used to investigate the properties of the inward rectifier (Kir) in ventral midbrain cultures. Comparison of the magnitude of the inwardly rectifying current at different times in culture revealed a development of this current between days 10 and 12 *in vitro*. Cell capacitance remained constant during this time period. Subsequent increases in Kir currents with time *in vitro* paralleled increases in cell capacitance. In contrast to the inward rectifier, voltage-dependent sodium, calcium and other voltage-dependent K conductances (e.g. the A-current) were evident from the earliest times of recording (day 7 *in vitro*). As observed for other inward rectifiers, increasing the extracellular potassium concentration from control levels (5mM K) to 15mM or 60mM in the presence of blockers of synaptic transmission (TTX, Bicuculline, CNQX) was associated with a large increase in inward conductance. The inwardly rectifying current was blocked in a concentration dependent manner by both Ba^{2+} (IC_{50} 30μM) and Cs^+ (IC_{50} 300μM at -100mV). The block by barium did not show a marked voltage dependence, in contrast to blockade by Cs^+, which increased markedly as the membrane was hyperpolarised. We suggest that the developmental increase in the baclofen-gated K conductance may be due to delayed expression of the K channel since the Kir channel, which belongs to the same K channel superfamily, shows a similar developmental profile.

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52.30 COMMON AND DISTINCT SNARES FOR AXONAL GROWTH AND TRANSMITTER RELEASE.
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Fusion of vesicles with the plasmalemma is essential for membrane expansion and transmitter release in neurons and thereby contributes to both morphological and functional changes of mature synapses. Involvement of the same mechanism in these two major synaptic adaptations raises the important question of whether neurons can regulate one independently of the other. Here, we have used botulinum and tetanus neurotoxins (BoNT, TeNT) to cleave three different SNARE proteins in developing cortical and hippocampal primary neurons in vitro: SNAP-25, VAMP/synaptobrevin and syntaxin. All toxins showed the expected specificity with the notable exception that, in addition to syntaxin, BoNT/C cleaved SNAP-25 and induced rapid neuronal death. We report that cleavage of SNAP-25 inhibits transmitter release, axonal growth and synapse formation, while cleavage of VAMP inhibits transmitter release but has no effect on axonal growth and synapse formation. These data provide functional evidence for the SNARE hypothesis as well as a framework to understand the selective regulation of membrane fusions during morphological and functional synaptic plasticity.

52.31 DIFFERENTIAL ACTIVATION OF PRE- AND POSTSYNAPTIC PKC SUBSTRATES AFTER DEPOLARIZATION OR GLUTAMATE STIMULATION OF HIPPOCAMPAL SLICES.
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Pre- and postsynaptic PKC have been implicated in the molecular mechanisms underlying long-term potentiation (LTP). Two identified PKC substrates, which share an 18 amino acid sequence containing the phosphorylation site, the presynaptic protein B-50 (a.k.a. GAP-43, F1, neuromodulin) and the postsynaptic neurogranin (a.k.a. RC3, BICKS), have been implicated in LTP. In this study we monitored the effect of depolarization (30 mM K^+ or 100 μM 4-aminopyridine) or glutamate treatment on in situ B-50 and neurogranin phosphorylation in hippocampal slices. Slices (450 µm) were labelled with 32Pi and in situ B-50 and neurogranin phosphorylation was determined after immunoprecipitation by phosphorimaging.

K^+ and 4-AP induced a time-dependent increase in B-50 phosphorylation, whereas neurogranin phosphorylation in the same slices was unaffected. Glutamate induced a concentration-and time-dependent increase in the phosphorylation state of both proteins. The K^+-induced increase in B-50 phosphorylation was confirmed to be at ser41 by digesting in immunoprecipitates with α-chymotrypsin. This technique revealed other phosphosite(s) in B-50, not affected by membrane depolarization.

Our data show that stimuli which are relevant to the mechanism of LTP, differentially affect pre- and postsynatic PKC substrates.(supported by an ENP grant of ESF).

52.32 A NEW APPROACH FOR MODELS AND COMPUTER SIMULATIONS OF SINGLE ION CHANNEL CONDUCTIVITY.
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We present a new approach within the framework of the equivalent circuit model for simulating single channel conductivity behaviour. Common kinetic single channel models exclusively use first order state transitions and therefore need the assumption of many experimentally indistinguishable states. We use a *time variant* approach, were state transitions may be related to channel event memories and may be time consuming.

State transitions are supposed to be triggered by the absolute magnitude or the relative change of typical variables (e.g. voltage, transmitter concentration *and* time). The critical trigger values of individual channels are supposed to fluctuate, i.e. they are distributed. In our model these distributions form characteristic features of transitions. They can be defined arbitrarily and, furthermore may undergo dynamic transformations in dependency on environmental variables.

According to this approach a computer program for simulating channel conductivity models was developed. An *interval segmentation* according to channel events and stimulus variables is used. In each interval an appropriate — numerical or analytical — method for solving the differential equation defining the equivalent circuit is choosen automatically.

Using transitions that are voltage dependent and time consuming, realistic channel conductivity models with only very few states were constructed for Na- and K-channels. With these models we simulated single channel properties, like fast discrete oscillations of conductivity and voltage dependent latencies after membrane potential jumps. Moreover, we did simulations with great numbers and different types of channels, that revealed realistitic properties of membrane areas, like action potentials with stochastic thresholds, spontaneous action potentials, oscillations of the resting membrane potential and adaptive spike trains.

52.33 BIOCHEMICAL CHARACTERISTICS OF THE AMYGDALA IN RATS TRAINED TO PERFORM FOOD REACHING MOVEMENTS

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The activity of acetylcholine esterase (AChE), adenylate cyclase (AC), 5'-nucleotidase (NT) as well as the content of phospholipids (PL) and gangliosides (G) were studied in the amygdala of rats trained to perform modified food reaching movements with prolonged pushing. The animals were divided into two groups with high (H) and low (L) ability to learn the experimental task during several successive trials of training. It was found that basal activities of the enzymes as well as PL content, found in the control group, undergo significant changes, specific for both experimental groups after learning. These changes are characterized by an increase in AChE activity in H and a decrease in AC and NT activity and PL content both in H and L groups of rats. It seems to be possible that the character of changes in the amygdala depends on the ability of rats to learn the experimental task.

52.34 *IN VIVO* VOLTAGE CLAMP RECORDINGS FROM RESPIRATORY NEURONS IN CATS

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Respiratory neurons in the lower brainstem of mammals reveal rhythmic membrane potential fluctuations in phase with phrenic nerve activity. These changes in membrane potential fluctuations originate from inhibitory and excitatory processes during silent and active phases of the neuron. An attempt was made to analyze the underlying currents with the time-sharing single electrode voltage clamp method using high resistance sharp microelectrodes and suction electrodes in the whole cell configuration. Neurons of expiratory, late-inspiratory, and post-inspiratory types were recorded in the respiratory areas of anesthetized, vagotomized, paralyzed, and artificially ventilated cats.

Intracellular and whole cell recordings were performed with an SEC05L amplifier (npi electronic) at switching frequencies between 15-40 kHz and duty cycles of 25 or 50%. Currents underlying spontaneous EPSPs and IPSPs were investigated using intracellular injections of chloride or K-ATP channel antagonists and hyperventilation of the animal.

Artifacts which compromise single electrode clamp recordings *in vivo* were analyzed with active single and multicompartment cell models with independent monitor outputs from each compartment. With the cell models it was possible to simulate the in vivo recording situation and to analyze the capability of the amplifier system to perform accurate VC and CC recordings under circumstances comparable to the *in vivo* conditions.

We conclude that voltage-clamp measurements of respiratory cells *in vivo* are a useful tool to study the pharmacological nature of currents underlying spontaneous membrane potential fluctuations.

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52.35 INTRINSIC NON-GLUTAMATERGIC EXCITATION IN RAT NEOSTRIATUM.

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Intracellular recording from presumed medium spiny neurons of rat neostriatal slices revealed different types of postsynaptic potentials in response to intrastriatal stimulation. Electrical stimulation of the neostriatal network evoked a compound postsynaptic potential consisting of non-NMDA, NMDA and $GABA_A$ receptor mediated components. In the presence of the non-NMDA-antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 10-50µM), the NMDA-antagonist CGP37849 (1-5µM) and the $GABA_A$ receptor-antagonists bicuculline (50µM) and picrotoxin (50µM) a residual EPSP could be evoked. The amplitude of the residual EPSP did not change in a voltage range between -100 and -60mV. This was in contrast to the NMDA receptor mediated component that displayed its typical voltage dependence and the $GABA_A$ receptor mediated component that reversed in sign around -60mV. A linear relationship was found between residual EPSP amplitude and the amplitude of an extracellularly recorded population spike representing direct synchronous activation of neostriatal neurons.

Unitary postsynaptic potentials defined by their appearance in an all or none manner were evoked by stimulation presumably of single fibres or neurons. IPSPs recorded in the presence of CNQX and CGP37849 were identified due to their blockade by low concentrations of bicuculline. Glutamatergic EPSPs were blocked by low concentrations of CNQX. A non-glutamatergic unitary EPSP was evoked despite the presence of high concentrations of CNQX, CGP37849 and bicuculline. This non-glutamatergic EPSP was characterized by a slow time course in comparison to the glutamatergic EPSP.

In conclusion, w e suggest the existence of a non-glutamatergic EPSP in rat neostriatum which can be evoked by activation of intrastriatal neurons.

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52.36 IMPAIRED PPF IN THE CA1 REGION OF THE HIPPOCAMPUS OF COGNITIVE DEFICIENT MICROENCEPHALIC RATS.

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Recently we have shown that in the CA1 region of the hippocampus of cognitive deficient microencephalic rats LTP is disturbed. This defect could be restored by D-Serine, an agonist for the glycine-site of the NMDA receptor (Ramakers et al., Neuroscience *54*, 49-61, 1993). In the present study we have investigated paired pulse facilitation (PPF) in slices from these rats. Microencephaly was induced by injection of methylazoxy methanol (MAM, 25 mg/kg) to pregnant rats on day 15 of gestation (G15). Field EPSPs were recorded in the radiate layer of the CA1 field by stimulating (at 0.1 Hz and 1/2 maximum intensity) orthodromically. Glass-electrodes filled with artificial cerebrospinal fluid (ACSF) were used for the recording. In addition, paired pulse stimulation with interstimulus interval (ISI) of 50 and 200 ms failed to induce PPF in slices from microencephalic rats. In contrast, a depression of the second respons was observed. This depression depended on the stimulus strength, as weak stimulation showed less depression than strong stimulation. D-Serine corrected the defect in PPF with an ISI of 200 ms, but not the defect with ISI of 50 ms. The corrective effect of D-Serine could be antagonized by 7-Cl-Kyn and D-APV. The absence of PPF and the finding of PPD suggests that the defects in plasticity of glutamatergic synapses in MAM-treated rats involves both pre- and postsynaptic mechanisms and is in line with the observed increase in B-50 phosphorylation in these rats and the increased basal release of glutamate from synaptosomes prepared from microencephalic rats.

52.37 LONG-TERM POTENTIATION FAILED TO OCCLUDE THE FACILITATION OF TRANSMISSION BY VASOPRESSIN.

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Picomolar concentrations of vasopressin (VP) induce a long-lasting facilitation of excitatory postsynaptic potentials (EPSPs) in the CA1/subiculum field of the rat ventral hippocampus. In brain slices from the ventral hippocampus we have studied whether saturation of long-term potentiation (LTP) in the CA1/subiculum field of the ventral hippocampus, elicited by high frequency stimulation (100 Hz; HFS) of the stratum radiatum, occludes the facilitatory effect of 0.1 nM VP on EPSPs. The slices were superfused with the medium of the following composition (mM): NaCl (124), KCl (3.3), KH2PO4 (1.2), MgSO4 (1.3), CaCl2 (2.5), NaHCO3 (20) and glucose (10). EPSPs were evoked by stimulating the stratum radiatum at 0.05 Hz, and recorded with microelectrode filled with potassium acetate (4 M; 60-125 MΩ). LTP was induced by 3 trains (1 sec) of HFS, applied with an interval of 1 min. LTP in EPSPs was followed for 30 min after the HFS, and it was considered as saturated if an additional HFS produced no further LTP increase. VP (0.1 Nm) was bath applied for 15 min, and EPSPs were recorded during and for 60 min thereafter. Data from several neurons showed that LTP saturation does not occlude the long-lasting facilitattion of EPSPs by VP. These results, if confirmed in a larger population of neurons, demonstrates that the mechanism of the LTP increase in EPSPs was different from the EPSPs increase elicited by VP. The finding of the peptide effect in neurons that show no LTP after repeated HFS of afferent fibers support this.

52.38 NMDA-INDUCED RELEASE OF CYCLOOXYGENASE PRODUCTS IN RABBIT HIPPOCAMPUS IN VIVO: RELATION TO CHANGES IN EXTRACELLULAR CALCIUM CONCENTRATION

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In this in vivo study a microdialysis of the rabbit hippocampus combined with radioimmunoassay of 6-keto prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$) and thromboxane B_2 (Tx B_2) and with indirect, ^{45}Ca-utilising detection of changes in extracellular calcium concentration ($[Ca^{2+}]e$) was utilised to analyse relations between NMDA receptor-mediated release of cyclooxygenase products and calcium influx to neurones. Application of 1 mM NMDA to dialysis medium for 20 min evoked 500 and 800% increase in Tx B_2 and 6-keto $PGF_{1\alpha}$ concentrations in dialysates. This effect, prevented by 10 µM indomethacin, was partially inhibited by quinacrine and Ca^{2+}-free medium, indicating involvement of Ca^{2+}-dependent activation of phospholipase A_2. Furagrelate, inhibitor of thromboxane synthase reduced Tx B_2 release by 80% and doubled 6-keto $PGF_{1\alpha}$ production. Eicosanoid production evoked by 1 mM NMDA was not enhanced further by increase in NMDA concentration and was inhibited by MK-801 by only 50%, whereas NMDA over a range of 0.5 mM to 5 mM induced a dose-dependent decrease in $[Ca^{2+}]e$, that was completely prevented by 10 µM MK-801. Thus our data point to different pharmacological profiles of NMDA-induced calcium influx to neurones and eicosanoid release. It is possible that intracellular calcium mobilised upon NMDA receptor activation may participate in NMDA-induced lipolysis. Moreover these data demonstrate that $[Ca^{2+}]e$ is not a precise enough indicator of NMDA receptor activity in the hippocampus in vivo.

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52.39 NOOTROPIL AND DELTA-SLEEP INDUCING PEPTIDE COOPERATIVE EFFECT ON THE STRUCTURE AND FUNCTIONS OF RAT BRAIN MEMBRANES UNDER HYPOXIA

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The adaptational possibilities of organism are determined by adequate relationships between information and energetic processes in central nervous system.Effectivety of these processes is determined by myelin, mitochondrial and synaptosomal membranes state. We studed cooperative effect of nootropil (30 mg/kg) and delta-sleep inducing peptide (DSIP, 12 µg/100 g body weight) on rat brain membranes state under hypoxia (0,029 MPa, 3 hours in duration). Prophylactic introduction of DSIP, nootropil and their combination prevented the hypoxia-induced changes in diene conjugates and Shiff's bases level in all of tested membranes. Moreover, cooperative injection of tested substances lead to new functional state formation due to optimal ratio between inhibitory and exitatory amino acidic neuromediators: a dramatic increase in GABA content and dacrease in glutamate content in synaptic fraction..

This data offer new possibilities in cooperative using of DSIP and nootropil for functional shifts correction in central nervous system under morbid conditions. Electron microscopic evidence of membranes stabilization have been also obtained.

52.40 A SODIUM DEPENDENT POTASSIUM CURRENT IN IMMATURE AND MATURE RAT CA1 NEURONES

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Sub-slices of the mid-third CA1 hippocampal region were prepared from rats P4-6 (post-natal days) and older than P24. Cells were isolated by enzymatic (trypsin 1mg/ml) and gentle mechanical dispersion. 2-3 Mohm pipettes were used for whole-cell recording in the presence of 1.5µM TTX.

The presence of a sodium sensitive potassium current (I_{KNa}) was shown by sodium removal (N-Methyl-Glucamine or Lithium) from the perfusate. In either younger or older cells, I_{KNa} is a voltage-dependent non-inactivating current, that can be demonstrated in cells as early as post-natal day 4. Results from younger neurones showed that I_{KNa} corresponds to a comparatively bigger fraction of the total potassium currents.

As a sustained non-inactivating current, I_{KNa} should play a relevant role in firing modulation.

52.41 TIME COURSE OF FORMATION OF SYNAPTIC LONG-TERM DEPRESSION IN NEURONS OF *HELIX POMATIA*.

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The onset and early time course of formation of long-term depression (LTD) was analysed in giant neurons of *Helix pomatia*. The results indicated, that the *de-novo* protein synthesis necessary for the formation of LTD took place outside the cell nucleus.

EPSPs were monitored from neuron LPa1 and RPa3 and were activated from *nervus pallialis dexter*. The nerve was cut, separating its CNS-afferent axons from the periferally located somata. Each experiment began with a series of 30 EPSPs (1/10 Hz) displaying short-term depression. Following that, the recovery from depression was analysed by test-EPSPs obtained after an interval that was varied from one experiment to the next.

The results showed a recovery which was dominated by a monoexponential time course (time constant approx. 6.5 min.) up until 6 min. after the series of 30 EPSPs. After 6 min. a period of "inverse recovery" appeared, rendering test EPSPs at 10-, 20- and 60 min. progressively smaller than at 6 min. The "inverse recovery" was abolished by the presence of puromycin (50µg/ml), which resulted in a full, monoexponentially proceeding recovery. It is concluded from these results, that the "inverse recovery" represented the onset of LTD, which depended on *de novo* synthesis of proteins.

Two inhibitors of RNA translation: puromycin and anisomycin were capable of inhibiting the LTD. In contrast, the transcriptional inhibitor, actinomycin D had no effect on LTD, even after more than three hours of cell exposure to the compound.

In conclusion, the results provide three indications that the protein synthesis leading to LTD was initiated and took place outside the cell nuclei: 1) LTD began only 6-10 min. after the inducing EPSPs, a period considered too short for nuclear synthesis and ensuing transport of proteins to synaptic locations. 2) Only inhibitors of translation and not of transcription affected LTD. 3) The axons of the afferent nerve were separated from the somata. Cytosolic polyribosomes might synthesize the involved proteins.

52.42 CLONING OF FOUR INWARDLY RECTIFYING POTASSIUM CHANNELS FROM HUMAN BRAIN.

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Inwardly rectifying potassium channels participate in maintaining the membrane potential and controlling excitability of many different cell types. In order to obtain cDNAs coding for members of this class of ion channels, a human cerebellar cDNA library was hybridized under low stringency with the rat GIRK1/KGA1 and mouse brain GIRK2 cDNAs as probes. Several positively hybridizing plaques were purified and the inserts cloned in pBluescript. Sequencing of these clones showed that the human homologues of rat GIRK1/KGA1 and mouse GIRK2, as well as two other clones with homology to inwardly rectifying potassium channels were isolated. The amino acid sequences indicate that a core of approximately 300 amino acids is highly conserved among these inwardly rectifying potassium channels. However, the flanking amino and carboxy termini are less conserved and variable in size. Tissue distribution of the mRNAs of the four channels were studied by northern blot analysis.

52.43 MODULATION OF AMPA RECEPTORS BY COMPONENTS AND SYNTHETIC PRECURSORS OF EVANS BLUE IN RAT HIPPOCAMPAL CULTURES,

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The anionic dye Evans Blue modulates the kinetics and amplitudes of glutamate-activated non-NMDA receptor mediated ion currents in thalamic neurons (Leßmann at al., Neurosci. Lett. 146, 13, 1992). Since the commercially available dye (EB) contains only about 80% pure dye we investigated whether different components separated from the mixture exert distinct effects on glutamate-activated ion currents. Cultured hippocampal neurons obtained from rat at E18 - P5 were investigated in the whole cell patch clamp configuration with a fast perfusion system under conditions isolating AMPA/kainate receptor mediated currents. Similarly to thalamic neurons preincubation with 10 µM EB reduced peak amplitudes of glutamate - activated (1 mM) currents in all cells tested. In contrast to thalamic neurons, only 25% of the hippocampal neurons showed an increase in the time constant of desensitization. Evans Blue was chromatographically separated into 4 components and spectroscopically characterized. From 12 cells tested for the effect of the *purified* EB (10µM) 6 cells showed only a reduction in the amplitude to about 50%, 4 cells displayed a reduction in the amplitude to about 5% of initial values and 2 cells showed a delayed activation, an increased amplitude and an abolished desensitization. A putative oligomeric form of EB ("10 µM") showed a reduction of peak current amplitudes without an effect on the kinetics in all 6 cells tested. 18 cells investigated with the synthesis educt "Chicago acid SS" (100 µM) showed a reduced desensitization without an influence on activation and peak amplitudes. Our data suggest differential effects of the EB components on AMPA/kainate receptors which might reflect GluR-subunit specific modulation of these channels (see also Keller et al., PNAS 90, 605, 1993).

52.45 SYNAPTIC PLASTICITY IN HELIX NEURONS DURING LEARNING.

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Neural activity of the L-RPal neurons during sensitization (S) or food aversion conditioning was studied in Helix lucorum. Signal-specific and general effects were observed in neurons by inducing S. Signal-specific effects of S are characterized by site-specificity (more profound synaptic facilitation of neural responses to testing stimuli addressed to site of S) and by modality-specificity (more prominent synaptic facilitation of neural responses to testing stimuli having the same modality as sensitizing those). General effects of S included neural membrane depolarization, increased excitability of cell membrane and facilitation of neuronal responses to the different stimuli. During conditioning both conditioned responses and signal-specific as well general effects of S were seen.

The selective regulation of synaptic inputs in the neurons by specific proteins with short life time is assumed. This regulation seem to underlie synaptic plasticity in Helix neurons during learning.

52.46 POSTSYNAPTIC CURRENTS OF HIPPOCAMPAL NEURONS ARE ENHANCED IN LOW OSMOTIC PRESSURE.

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Hyponatraemia and low osmotic pressure of extracellular fluid (π_o) can trigger clinical seizures. The mechanism of the enhanced excitability is not clear. Earlier, we found π_o-dependent marked increase of extracellular EPSPs during hypotonia and, to a lesser degree, in low [NaCl] isosmotic condition as well. Moreover, interstitial Ca^{2+} concentration became markedly lower, indicating entry of Ca^{2+} into cells (Chebabo et al., Soc.Neurosci.Abst. 20: 1510, 1994; J.Physiol., in press). We have now recorded excitatory synaptic currents (EPSCs) in whole-cell voltage clamped from CA1 neurons in hippocampal slices. Lowering π_o to an average of 232 mosm/kg by deleting NaCl resulted in reversible increase of the maximal amplitude of EPSCs to a mean of 195% of control (range 111-297%) in 11 trials in 9 cells. For 2 additional cells in π_o of 198 mosm/kg the increase was 175 and 438%; in 2 others at π_o of 268 mosm/kg, the change was marginal; in one cell in mannitol-substituted isosmotic low-NaCl solution EPSC increased to almost 200%. The input resistance of cells reversibly increased in 8 trials and was unchanged or slightly decreased in others. The increase of EPSC was independent of input resistance and of the patch pipette solution (K- or Cs-gluconate, K-acetate, or KF, with or without the Na^+ channel blocker QX-314). We conclude that synaptic currents are enhanced in low Na^+ low π_o, perhaps by raising presynaptic Ca^{2+} leading to increased transmitter release.

52.47 MOLECULAR AND FUNCTIONAL DIVERSITY OF INDIVIDUAL NERVE TERMINALS OF ISOLATED CORTICAL NEURONS.

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Learning is associated with changes in the strength of connections between neurons which can occur independently in individual synapses of the same cell. While the molecular mechanisms of functional synaptic plasticity are still subject to debate, it is clear that both pre- and post-synaptic components are involved. A possible presynaptic component of these adaptive changes is suggested by the differential expression, in vivo, of nerve terminal proteins (NTPs) involved at various stages of membrane fusion and transmitter exocytosis. Here we show that single cortical neurons cultured in isolation are capable of differential expression of NTPs at different synapses. Using the dye FM1-43 in mixed neuronal cultures, we also show that the intensity of uptake and release of the dye following K^+ stimulation at each synapse correlate with the levels of synaptophysin, synapsin I and SV2 but not of synapsin II. These data demostrate that differential expression of NTPs is predictive of synaptic strength. They also show that physiological variations of the levels of expression of synaptophysin, synapsin I and SV2 correlate with synaptic efficacy.

52.48 MUTATIONAL ANALYSIS OF THE MAJOR HUMAN SKELETAL MUSCLE CHLORIDE CHANNEL CLC-1

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The muscle chloride channel ClC-1 regulates the electric excitability of the skeletal muscle membrane and mutations in its gene are responsible for myotonia, an inheritable disease of humans and animals. In humans, mutations in ClC-1 lead to either a recessive or a dominant mode of inheritance, and all mutations that have been functionally analysed so far lead to non-functional ClC-1 channels. Previously, we have shown that functional ClC-1 chloride channel proteins most likely consist of four identical subunits and that incorporation of a single mutated subunit carrying a dominant mutation can inactivate the whole channel complex.

We have now identified a different mutation in the ClC-1 gene of patients having the dominant disease. Expression of the mutant in *Xenopus* oocytes yields functional ClC-1 chloride channels. However, the mutant channels show a large shift in voltage-dependence of gating, and are closed within the physiological voltage range. In addition, when coexpressed with normal subunits, the resulting ClC-1 channels show similar altered properties. To further investigate the structural requirements for voltage-dependence of ClC-1 gating, additional mutations that have been generated at the same site within the channel protein are currently analysed.

52.49 MODULATORY EFFECTS OF IMMUNOMESSENGERS ON THE VOLTAGE-ACTIVATED Ca-CURRENTS OF MOLLUSCAN NEURONS

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Recently various cytokines have been shown to modulate neuronal activity through voltage- and ligand-gated ionic currents both in mammalian and molluscan neurons. Many of the interleukins behaves similarly in the immuno-endocrine system and there is an apparent redundancy in their actions. However, there are interleukins, which act on different cell types and their effects can be opposite, too. The aim of our examinations was to compare the effects of two cytokines, interleukin-2 and interleukin-4 on the voltage-activated Ca-currents of *Lymnaea* neurons.

Ionic currents were recorded in two-microelectrode voltage clamp experiments. Identified neurons of pond snail *Lymnaea stagnalis* L. were used. Interleukins were applied extracellularly and voltage-activated Ca-currents at various command levels were monitored and characterized.

It was shown that IL-4 increased, while IL-2 reduced high-voltage-activated Ca-currents in dose-dependent manner. IL-4 at low concentrations (1-100 U/ml) caused rapid and reversible potentiation of Ca-currents. The kinetics of the currents was not significantly altered.

The results showed that these cytokines are involved in the regulation of the excitability of neurons by modulation of voltage-activated channels and alterations of intracellular Ca-level.

52.50 FAST AND SLOW SODIUM CURRENTS IN CULTURED DORSAL ROOT GANGLION NEURONS

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Neurons were dissociated from neonatal rat dorsal root ganglion and cultured for 1 day in a medium enriched with horse serum. Whole cell patch-clamping was used to study pharmacologically isolated Na currents. Both TTX sensitive (fast: $I_{Na,F}$) and TTX resistant (slow: $I_{Na,S}$) Na currents were present. Using variable prepulses (V_{pp}), followed by a test pulse to -10 mV, the inactivation of the peak current was studied as function of voltage. The $I_{Na,F}$ inactivated completely at voltages, where $I_{Na,S}$ is not inactivated yet, allowing to determine separate inactivation curves by subtracting the $I_{Na,S}$ from the total current. The relation between the peak of $I_{Na,F}$ and of $I_{Na,S}$ and V_{pp} could not be described by a single Boltzmann function. The fast current needed the superposition of 3 Boltzmann relations, characterized by midpoint potentials of -127, -83 and -54 mV. The slow currents were characterized by the sum of 2 Boltzmann functions with midpoint potentials of -32 and -18 mV. The most simple interpretation is the existence of 3 types of fast TTX sensitive Na-currents and 2 types of slow TTX resistant Na currents. Our data suggest that spinal neurons may exhibit a rich variety of Na-channel subtypes.

52.51 INTERACTION OF CALCIUM L-CHANNEL ANTAGONISTS AND MELATONIN IN THE STRIATAL PROJECTION AREA OF MOTOR CORTEX IN THE RAT.

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Studies carried out in our laboratory have shown that melatonin inhibits the activity of striatal neurons and also reduces dopamine release. This effects may be calcium-dependent. Thus, the effects of melatonin and calcium channel antagonists have been studied using electrophysiological techniques and microiontophoresis. Striatal neurons whith excitatory response to motor cortex stimulation (50-100 μA) were selected. Melatonin and the calcium L channel antagonists amlodipine and diltiazem were microiontophorized. The effects of the three substances were predominantly inhibitories. Diltiazem iontophoresis produced a significant decrease of the excitatory response in 70% of the recorded neurons. On the same way, amlodipine produced a decrease in 86.6% of the neurons. Iontophoresis of melatonin also reduced the excitatory response in 85.2% of the recorded neurons.

When melatonin were iontophorized toghether with diltiazem or amlodipine, a potentiation of the inhibition was found. Nevertheless, the big difference in the latency of the response to melatonin and calcium L-channel antagonists suggest that these substances act by different mechanims (intracellular vs membrane).

52.52 NOVEL SYNAPTIC PROTEINS FROM RAT BRAIN

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Antisera against a rat synaptic protein preparation were used to screen a rat brain expression library. More than 300 cDNA clones encoding potential synapse-associated proteins (SAPs) were analyzed. Identified known proteins include i) cytoskeletal and motor elements, ii) regulatory enzymes and their substrates, iii) cell surface and extracellular matrix proteins, iv) vesicle proteins and proteins involved in exocytosis as well as various other proteins.

More than 50 cDNAs encode previously unknown proteins. Among these are new isoforms of known proteins, such as a new myosin heavy chain, a brain-specific calmodulin-like protein, and two isoforms of an aggrecan-like protein.

Another unknown protein without any correlates in public databases is represented by the clone SAP7f. Northern analysis of rat tissue revealed a brain-specific transcript (11.5kb) in cortex, cerebellum and hippocampus. Antibodies against a bacterially expressed SAP7f fusion protein recognize a diffuse signal with a molecular weight between 150 and 250 kd and a distinct band of 75 kd on Western blots of rat brain protein preparations. The diffuse high molecular weight material is enriched in the PSD fraction. SAP7f protein displays an interesting distribution as revealed by immunohistochemical studies on rat brain sections. Strong immunoreactivity is detectable in the neuropil regions. Studies at the electronmicroscopic level gave clear evidence for a presynaptic localization of the SAP7f protein, for instance in mossy fiber terminals of the CA3 and CA4 regions of the hippocampus, parallel fiber terminals in the molecular layer of the cerebellum and mossy fiber terminals in the stratum granulare of cerebellum. All these synapses are known to be glutamatergic.

52.53 **Bayesian Analysis Directly Reveals Heterogeneity between Synaptic Sites in Paired-Pulse Plasticity in the Hippocampus.**

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Dynamic changes in synaptic release probability and post-synaptic amplitude are critical aspects of neural plasticity but are typically estimated indirectly assuming a particular statistical model. We have developed a Bayesian statistical method which directly predicts both the likely number of activated synapses and inferences for synaptic parameters without assuming a restrictive model. Excitatory synapses onto CA1 hippocampal neurons were activated using a paired-pulse stimulus protocol and low noise whole-cell recording. These synapses exhibited a wide range of values for release probability (0.03-0.99) and synaptic amplitude (1.09-19.4 pA). Furthermore, they showed greater amplitude variability between synaptic sites (coefficient of variation = 77%) than that found at the same site over time (6.5%). Paired-pulse plasticity included alterations in the number of activated synapses and their release probabilities. The considerable heterogeneity between synaptic sites and their responses to short-term potentiation suggests that a wide array of mechanisms contribute to synaptic plasticity in the CNS.

52.54 β SUBUNITS MODULATE TWO ACTIONS OF NICKEL ON NEURONAL CA CHANNELS: BLOCK AND INHIBITION OF ACTIVATION-GATING

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Nickel ions have been reported to exhibit differential effects on voltage-activated calcium channels. To obtain a more precise characterization of nickel action and subtype specificity, we have investigated the effects of nickel on four major classes of cloned neuronal calcium channels (α_{1A}, α_{1B}, α_{1C} and α_{1E}) transiently expressed in *Xenopus* oocytes. Nickel caused two major effects: 1) block of macroscopic currents and 2) a shift in the current-voltage relation towards more depolarized potentials which was paralleled by a decrease in the apparent number of gating charges. In 10 mM Ba, block followed 1:1 kinetics and was most pronounced for α_{1C}, followed by α_{1E}, α_{1A}, and α_{1B} channels. In contrast, the change in activation-gating was most dramatic with α_{1E}, with the remaining channel subtypes being less affected. The current-voltage shift was well described by a simple model in which nickel binding to a saturable site resulted in altered gating behaviour. Both the affinity for block and the shift in current-voltage were reduced upon increasing the external permeant ion concentration. Replacement of Ba with Ca reduced both the degree of nickel block and the effect on gating for α_{1A} and α_{1C} channels, but increased the nickel blocking affinity for α_{1E} channels. The coexpression of Ca channel β subunits was found to differentially influence nickel effects on α_{1A} as coexpression with β_{2a} or with β_4 resulted in larger current-voltage shifts than those observed in the presence of β_{1b}, while elimination of the β subunit almost completely abolished the gating shifts. In contrast, block was similar for the three β subunits, while complete removal of the β subunit resulted in an increase in blocking affinity. Qualitative and quantitative differences in the dependence of the effects of nickel concentration on gating and block suggest two distinct nickel binding sites on neuronal calcium channels.

52.55 MODULATION OF NMDA RECEPTORS BY EXTRACELLULAR CALCIUM IN IMMATURE AND ADULT HIPPOCAMPAL SLICES.

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Lowering extracellular calcium concentration $[Ca^{2+}]_o$ in rat hippocampal slices can lead to an induction of epileptiform activity. It has been shown that this effect is more pronounced in slices of neonatal rats (postnatal day, PND 8-19) than in mature slices (>PND40) and it has been suggested that unique NMDA receptor properties of immature rat hippocampal pyramidal cells contribute to this developmental effect. In a voltage clamp experiment we tested NMDA receptor properties in hippocampal pyramidal cells by measuring NMDA receptor mediated currents evoked by iontophoretic applied NMDA in the basal dendrites of CA3 pyramidal neurons. We found that lowering extracellular calcium from 2 to 1 mM, increases NMDA evoked inward current in pyramidal cells around the resting membrane potential. However this effect is observed in slices of neonatal as well as in slices of mature rats, suggesting that there is no difference in NMDA receptor sensitivity to extracellular Ca^{2+} between these two age groups. The modulation of the NMDA receptor by extracellular calcium at physiological concentrations can have important consequences in pathological conditions during which extracellular calcium reaches low levels. Because this "hypocalcemic" condition induces a larger current influx via the NMDA receptor channel at resting membrane potentials it can further enhance cellular excitability and contribute to sustain epileptiform activity.

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53. Poster Session: Other systems II

53.01 EFFECTS OF LESIONS IN THE TUBEROMAMMILLARY NUCLEUS REGION ON LEARNING, MEMORY, AND BRAIN HISTAMINE.

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The tuberomammillary nuclei (TM) are located in the posterior part of the hypothalamus and provide the main source of neural histamine (HA) in the brain. Our experiments performed with bilateral lesions of the TM region revealed a role of the TM system in learning and memory processes. These lesions facilitated inhibitory avoidance performance and improved long-term retention in a spatial discrimination test in both adult and aged rats. However, since dc-lesions were performed, it was not possible to point at the TM neurons as responsible for the observed effects on learning and memory. Thus, the objectives of a follow-up study were two-fold. In order to determine whether the facilitation of learning was due to the destruction of intrinsic TM neurons a bilateral ibotenic acid lesions of the TM was performed and the rats were tested along with sham-lesioned controls on the Morris water maze task. Furthermore, in order to determine whether the behavioral effects revealed upon destruction of the TM neurons involve histaminergic mechanisms concentrations of HA and HDC were determined in different brain regions using immunohistochemical methods. The main finding of this study was that rats with neurotoxic lesions of the TM showed an accelerated acquisition rate in the course of place learning and an improved ability to locate the platform site during a spatial probe trial. The behavioral effects were accompanied by changes in HA and HDC concentrations in several brain regions, including the site of lesion in the TM, basal forebrain nuclei and hippocampus. The results indicate that the facilitatory effects on learning following TM lesion are based on the destruction of intrinsic TM neurons and suggest that this facilitation is related to the function of the histamine system.

53.02 ACTIVITY OF RETICULAR NEURONS REFLECTS THE MOTIVATIONAL SIGNIFICANCE OF CONDITIONED REACTION IN RABBIT.

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Extracellular single-neuron activity was recorded from midbrain reticular formation (nucleus cuneiformis) of freely moving rabbits during conditioned transswitching of motivational significance of conditioned motor response to tone (CS). In the first situation the animals were trained to avoid the electrical shock by means of motor reaction of the ears, in the second situation the rabbit had to perform the same reaction to obtain the food. Among 26 neurons recorded 23 changed their discharge rates in relation to CS. It was shown that during the conditioned transswitching 42% of neurons examined displayed significant differences of background activity in avoidance and food conditioning. 58% of neurons exhibited significantly different firing rates to CS in two conditions considered, 84% of these differences were determined by level of background discharge rate. 60% of neurons recorded showed differences in firing rate in poststimulus period, only 50% of poststimulus differences resulted from background discharge level in avoidance and food conditioning, the others were determined by increase of firing rate in food conditioning that was interpreted as expectancy of reward. It is concluded that the change of the reticular neurons activity to CS is the result of learning and the differences of background and evoked activity of neurons under the transswitching are related to the change of the motivational state.

53.03 MEDIAL SEPTAL CONTROL OF THETA-CORRELATED UNIT FIRING IN THE ENTORHINAL CORTEX OF FREELY-MOVING RATS. K.Jeffery*, J. Donnett and J. O'Keefe. Dept. of Anatomy and Developmental Biology, University College London, Gower St., London WC1E 6BT, UK.

The hippocampal formation is important in learning and memory, particularly memory for spatial location. A prominent feature of its physiology in rodents is the occurrence of a sinusoidal EEG pattern, the theta rhythm, which appears when the animals moves. Although the generators of hippocampal (HC) theta are in the dentate gyrus and CA1 subfields, its frequency and amplitude are modulated via the medial septum (MS).

Theta is also seen in the cortical input to the hippocampus, the entorhinal cortex (EC) – it is almost invariably in phase with HC theta and is similarly abolished by inactivation of the MS. Some entorhinal cells show periodic firing which is tightly coupled to theta while others are aperiodic. The present study investigated the hypothesis that periodic firing may be controlled by the MS and non-periodic firing may have its origins elsewhere (e.g., neocortex). Single cells were recorded from the EC of freely moving rats before, during and after a lignocaine injection to the MS. Theta-correlated firing was temporarily abolished by the MS inactivation while aperiodic firing was preserved. This finding suggests that EC is a site for convergence of neocortical sensory and subcortical motor information.

53.04 PHYLOGENETIC TRENDS IN THE PROJECTIONS OF THE CORTICAL TONGUE AREA WITHIN PRIMATES.
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Lingual articulation is crucial for speech but seems to be almost absent in subhuman mammalian vocal communication. One reason for this could be a difference in the neuroanatomical connections of the higher lingual motor control structures between man and subhuman mammals. In order to find out whether there is a phylogenetic trend within the primates in the connections of higher lingual motor control structures, we compared the projections of the tongue area of the primary motor cortex between the tree shrew (*Tupaia belangeri*), red-bellied tamarin (*Saguinus labiatus*) and rhesus monkey (*Macaca mulatta*). The study was made with two different anterograde tracers, tritiated leucine and Phaseolus vulgaris-leucoagglutinin. Injection sites were determined by exploring the exposed motor cortex for sites yielding tongue movements when electrically stimulated. The results show that the tree shrew lacks a direct connection between motor cortex and hypoglossal nucleus. The terminal field closest to the hypoglossal nucleus lies in the parvocellular reticular formation of the medulla, an area which, in turn, projects to the hypoglossal nucleus. In the tamarin, no terminal fields could be detected in the hypoglossal nucleus after cortical leucine injections. Phaseolus injections, in contrast, yielded a very few labeled fibres in this nucleus. In the rhesus monkey, marked terminal labeling was found. It is concluded that there is a phylogenetic trend from lower to higher primates strengthening the cortico-hypoglossal connections.

53.05 ORGANIZATION OF THE MEDIAL SEPTAL REGION IN THE RAT BRAIN: TOPOGRAPHIC DISTRIBUTION AND CONNECTIONS OF CALRETININ-CONTAINING CELLS.
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Calretinin (CR) a member of the calmodulin superfamily has been found to be in a variety of cell-types in various brain region of the rat. Even though, Jacobowitz and Winsky (1991) and Resibois and Rogers (1992) have provided a general description of CR-immunoreactive (CR-ir) neuronal elements throughout the rat brain, it is important to provide a more accurate description of the distribution, connections and co-localization of transmitters and/or other calcium-binding proteins in this cell population of the medial septum - diagonal band complex. The present study provides a detailed description of the topographic distribution of CR-ir neurons in the entire rostrocaudal extent of the septum compared to that of cells immunoreactive for choline acetyltransferase (ChAT), parvalbumin (PV) or calbindin D 28k (CaBP). CR-ir cells were localized along the lateral subdivision of the medial septal nucleus. They were found not to project to the hippocampus, but anterograde and retrograde transport studies provide evidence for projection to the supramamillary nucleus. It is evidenced by double-label experiments that CR does not colocalize within cells immunoreactive for ChAT, PV or CaBP. Based on these comparative mapping results it can be concluded that the medial septum is organized in neuronal lamellae forming a dorsoventrally oriented onion-shaped structure. This work was supported by OTKA grants T6372 and T5532.

53.06 TRANSIENT REDUCTION OF PAIRED-PULSE FACILITATION (PPF) REVEALS AN EARLIER PHASE OF LONG-TERM POTENTIATION (LTP) WITH PRESYNAPTIC INVOLVEMENT.
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LTP is thought to consist of at least two components, one with rapid onset and dependent largely on presynaptic changes which decay within the first hour and a considerably more prolonged postsynaptic component with a gradual onset. Memory processes have similarly been divided into acquisition and one or more consolidation phases. The precise temporal relations and mechanisms of these phases are a matter of debate. This study reports on interactions between LTP and a presumably presynaptically-mediated PPF (50 ms interpulse interval), estimated from population excitatory postsynaptic potentials evoked in CA1 stratum radiatum of rat hippocampal slices, in an attempt to resolve conflicts over the contribution of presynaptic mechanisms to the initial phase. Following induction of LTP with supramaximal stimulation, there was a transient decrease in PPF with recovery within 1 h. During the periods 15-20 min and 50 - 60 min after the tetanization (which correspond presumably to the earlier and the late phases of LTP) LTP magnitudes were 211 ± 24 % (mean ± s.e.m.) and 168 ± 16 % (n = 10). Post-tetanization PPF was significantly reduced at 15 - 20 min (85.5 ± 6 %, $P < 0.03$) but at 50-60 min PPF was not significantly different from pre-tetanic baseline values (92 ± 5 %). LTP magnitudes at 15 - 20 min were highly correlated ($r = -0.9$) with PPF changes at the same time-point across slices. The results suggest that PPF changes following maximal tetanization offers a physiological method of identifying different components of LTP which may also be applicable to studies in abnormal brains. (Supported by grant INTAS-93-732).

53.07 BICUCULINE / 2-HYDROXYSACLOFEN INDUCED THETA OSCILLATIONS IN THE HIPPOCAMPAL FORMATION SLICES.
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There has been a long lasting interest in the elaboration of mechanisms of neural synchrony and oscillations. The generation of EEG theta rhythm in the limbic cortex in vivo is a prime example of rhythmic activity involving central mechanism of oscillations and synchronization. Almost 10 years ago we discovered theta-like oscillations in the hippocampal formation slices perfused with cholinergic agonists. Since then the cholinergic mediation of the in vitro recorded theta rhythm has been well established. In the present study we emphasize the role of the hippocampal formation GABA-A and GABA-B receptors in elicitation of rhythmic slow waves. Specifically, we demonstrate that theta-like oscillations can be induced not only by direct cholinergic stimulation of the hippocampal neuronal network but also when both GABA-A and GABA-B receptors are simultaneously blocked by bicuculine and 2-hydroxysaclofen. This in vitro induced theta oscillations were antagonized by GABA-A agonist, muscimol and GABA-B agonist, baclofen.

53.08 ELECTROPHYSIOLOGICAL MAPPING OF THE STELLATE GANGLION SUBNUCLEI IN CATS AND RATS. K.Kukula*, P. Szulczyk, A. Urbanowicz Department of Physiology, I Faculty of Medicine, Warsaw 00-325, Poland

This study presents the localization of postganglionic sympathetic neurons with axons in different branches of the stellate ganglia in cats and rats. The ganglia, isolated from anesthesized animals, had their surrounding connective tissue removed in rats or were sliced - in case of cats, and placed in a recording chamber. Field potentials evoked by electrical stimulation of the stellate ganglion branches were then systematically recorded from different points on the tissue surface. It was established that a large area of the central upper half was occupied by the neuron bodies with axons in the vertebral nerve, while the central lower half by those with axons in cardiac nerves. The dorsal root gray rami neuron bodies were located in very narrow longitudinal strips at the medial border of the ganglia. The opposite, lateral narrow border of the ganglia contained neurons with axons in the upper and lower subclavian ansae. We conclude that postganglionic sympathetic neurons projecting to different stellate ganglion branches and thus, also functionally different, form distinct subnuclei within the ganglion. The location of these subnuclei was quite constant in different ganglia and varied not significantly in cats as compared to rats.
The work was supported by Komitet Badań Naukowych.

53.09 PROJECTIONS FROM THE PRIMARY TEMPORAL AREA TO THE ASSOCIATION CORTEX IN THE RAT.

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The rat temporal cortex displays projections to a series of areas that until now have been considered independent of the processing of auditory information. These association cortices, having multisensorial integration, comprise: A) the posterior parietal cortex (PPC), located very dorsally with respect to the primary temporal cortex (Te1); B) the perirhinal association cortices, which encompass part of the gustatory cortex (Gu) and of the agranular insular cortex (AIP), and C) the secondary visual cortex Oc2L, situated caudally to Te1 and rostrally to the primary visual area.

The existence of association cortices in the rat has recently been demonstrated in different anatomical and functional studies. The aim of the present work was to examine in depth the connections established by the primary temporal area Te1 with these association cortices. To do so, we performed injections in Te1 of two sensitive anterograde neuronal tracers: *Phaseolus vulgaris*-leucoagglutinin (PHA-L) and biotinylated dextran amine (BDA).

The results show that neurons located in Te1 have projections towards the association cortices, although such projections vary as a function of the location of the injections in different zones of Te1. Thus, injections performed in the ventral and rostral region of Te1 (Te1vr) project to PPC, Gu and AIP, mainly in a unidirectional fashion. Injections located in the ventral and caudal region of Te1 (Te1vc) project reciprocally to Oc2L, non-reciprocally to PPC and, to a lesser extent, to AIP. Finally, injections located in the dorsal-most zone of Te1 (Te1d) project reciprocally to PPC and non-reciprocally to AIP.

In sum, the results obtained here suggest the existence of at least three association areas, with poorly defined limits, in the rat cerebral cortex that participate in the processing of auditory information.

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53.10 THE CENTRAL AMYGDALOID NUCLEUS RECEIVES POWERFUL INPUTS OF VIP- AND CGRP-IMMUNOREACTIVE FIBERS IN MAN.

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Calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) are known to have profound centrally mediated cardiovascular effects. Previous immunohistochemical studies on mammals have demonstrated both neuropeptides to be present in high concentrations within axonal projections to the central amygdaloid nucleus (CE). Having widespread connections to different brain structures including neocortical areas, basal forebrain, diencephalon and brainstem autonomic nuclei, the CE occupies a strategic position in central neuronal circuits regulating behavioral and cardiovascular mechanisms. Thus, our intention was to provide a detailed description of the topographical distribution of CGRP- and VIP-immunoreactive (ir) neuronal elements in the subdivisions of the human CE.

Three autopsy brains (of 49, 56 and 74 year-old males) were fixed by perfusion 2 hours after death. Serial sections of the amygdaloid complex were immunostained with antisera against CGRP and VIP. Both neuropeptides were found in nerve fibers and terminals in the CE, but no perikarya were seen there. VIP-ir axons were clustered principally in the medial and the lateral subdivisions of the nucleus, where they form a high number of pericellular and peridendritic baskets surrounding unlabelled neurons. CGRP-ir fibers were concentrated in very dense plexuses within the dorsolateral and ventrolateral subdivisions of the CE. In the lateral subdivision they showed up in moderate density. Pericellular baskets of CGRP-ir axons were rarely seen.

The results revealed an extremely rich VIP- and CGRP-ir afferent fiber mass targeting distinct parts of the human CE. Consistently with reports on experimental animals, these fibers in the central amygdala might be involved in autonomic regulatory circuits.

53.11 AFFERENT CONNECTIONS OF THE NUCLEUS ACCUMBENS IN ANURAN AMPHIBIANS: ORGANIZATION OF DOPAMINERGIC PROJECTIONS.

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The nucleus accumbens (N.Ac.) in anurans consists of a group of closely-packed cells ventrally in the ventromedial wall of the rostral telencephalon. This area is characterized by a dense dopaminergic terminal field. By means of the retrograde tracers biotinylated or fluorescent dextran amines we have studied the source of afferent projections to the N.Ac. in *Rana perezi* and *Xenopus laevis*. Thus, labeled cells were observed rostrally in the olfactory bulb, medial pallium and the ventral aspect of the lateral pallium. Numerous cells were labeled among the fibers of the anterior commissure and, more ventrally, in the anterior preoptic area. Via the medial forebrain bundle, afferents to the N. Ac. arise in the anterior nucleus of the dorsal thalamus, the suprachiasmatic and ventral hypothalamic nuclei and the posterior tubercle. In addition, cells located medially in the rostral midbrain tegmentum and in several tegmental nuclei, more caudally, send projections to the N. Ac. Finally, labeled cells were also present in the rostral raphe nucleus and at istmic levels, medially and caudally to the isthmic nucleus.

The combination of tract-tracing with TH-immunohistochemistry revealed bilaterally double labeled cells in the dorsomedial part of the posterior tubercle and, in particular, in the rostral part of the midbrain tegmentum. This finding of a predominantly mesencephalic origin of a dopaminergic input to the N. Ac. clearly contrasts with our previous observation of a major dopaminergic input to the striatum of anurans originating in the dorsomedial portion of the posterior tubercle. Both data together suggest a rostrocaudal arrangement of the dopaminergic mesostriatal projections in anuran amphibians, while a medial-to-lateral organization is found in amniotes.

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53.12 SUBDIVISIONS OF THE TORAL MIDBRAIN COMPLEX IN THE CHICK (GALLUS GALLUS) AND IN THE GEKKOID (TARENTOLA MAURETANICA).

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In order to investigate the existence of a common pattern in the toral complex of sauropsids, we compared chemoarchitectural subdivisions in the chick with those in the gekkoid Tarentola mauretanica. The torus semicircularis was examined in sagittal, transverse and horizontal sectionns, prepared with Nissl staining, acetylcholinesterase histochemistry and inmunocytochemistry for L-EnK, ChAT, CaBP, CaR y NPY.

Three basic structural complexes of the torus can be distinguished in both species: the preisthmic superficial formation, the toral nucleus and the intercollicular area. In Tarentola, detailed subdivisions found in the chick are generally smaller in size, though some of them are less clearly delimited or could not be identified with this approach. The results nevertheless support a common structural schema which may apply to other sauropsids. DGICYT PB93-1137 mod. C.

53.13 CELL TYPES AND CIRCUITRY OF THE MORMYRID ELECTROSENSORY LATERAL LINE LOBE

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The mormyrid electrosensory lateral line lobe (ELL) is a laminated rhombencephalic brain center which receives topographically organized primary electrosensory input. In the process of forming central images of the environment, this sensory input is compared with corollary discharge feedback signals originating from the electromotor command nuclei. To investigate the synaptic basis of sensorimotor integrative mechanisms in this process, we analyzed the ELL neurons light and electron microscopically, using Golgi impregnations, neuroanatomical tracing and immunohistochemistry. The ELL contains at least 14 cell types, each with specific dendritic, somatic and axonal properties. Large ganglionic and fusiform neurons are glutamatergic and project to the midbrain torus semicircularis. Their somata are densely covered with GABAergic terminals which arise, in part, from medium-sized ganglionic interneurons. These three cell types all have spiny apical dendrites in the molecular layer of the ELL. The molecular layer also contains smooth dendrites from ganglionic cells with thick smooth dendrites, deep molecular layer cells and stellate cells. In the deeper intermediate layer, large multipolar GABAergic neurons occur. Interestingly, these have exclusively myelinated dendrites that form large presynaptic club endings contacting the ELL granule cells. The latter are the main recipients of primary electrosensory input (Bell et al, 1989, J. Comp. Neurol. *286:* 391-407). From the present data it is possible to construct a preliminary microcircuit diagram of the mormyrid ELL.

53.14 IMMUNOLOGICAL AND SURGICAL CASTRATIONS HAVE DIFFERENT EFFECTS ON HYPOTHALAMIC CATECHOLAMINERGIC AND ENKEPHALINERGIC STRUCTURES IN MALE PIG.

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In immunocastration, the hypothalamic hormone GnRH is neutralised by autoimmunity; consequently the pituitary and the gonads are deactivated; but after surgical castration hypothalamus and pituitary are activated. These differences in activation may be reflected in the immunocytochemical (ICC) expression of regulatory substances at the hypothalamic level. Therefore the ICC expression of catecholamines (CA) and enkephalins (Enk) in various hypothalamic structures was studied in intact, immunocastrated and castrated boars, 7 months old.

Immunocastration was accomplished by two vaccinations with GnRH in CFA (at 10 weeks of age) or IFA (at 18 weeks). Surgical castration was performed at 3 weeks of age. Sections of hypothalamus were stained by double immunofluorescent technique for TH, DBH, LEnk and MEnk. Results: Enk structures of preoptic (POA) and anterior hypothalamic (AHA) areas were decreased in immunised, but increased in castrated animals when compared to intact. In the median eminence (ME) localization had changed to the external lamina in castrated, but not in immunocastrated animals. In the arcuate nucleus, MEnk cell bodies appeared and became colocalised with TH in the immunised animals only, suggesting a change in chemical coding. CA cell bodies in POA were increased in both immunised and castrated animals. In the ME a decrease of CA terminals was present in both immunised and castrated, with a change in localisation to the external layer, in castrated animals only. In conclusion: the different effects of immuno- and surgical castrations suggest a direct role of the activated or deactivated pituitary on hypothalamic CA and Enk structures, involved in the regulation of GnRH secretion.

53.15 ELECTROPHYSIOLOGY OF THE HIPPOCAMPAL AND BASOLATERAL AMYGDALOID INPUTS TO THE NUCLEUS ACCUMBENS OF THE RAT: PATTERNS OF CONVERGENCE AND SEGRAGATION.

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The Hippocampus (HIP) and the basolateral amygdala (BLA), both part of the limbic system, project to the nucleus accumbens (Nacb) of the rat. The interaction between these two inputs in the Nacb is still unclear. Our study was conducted to determine how this interaction takes place. In male wistar rats (artificially ventilated, halothane anaesthetized), stimulation electrodes were stereotaxically placed in the Fornix/Fimbria fibers (Fo/Fi: the output fibers of the HIP) and the basolateral nucleus of the amygdala. Upon stimulation of these areas evoked field potentials (EFPs) as well as single unit activity were recorded in the Nacb. Characteristically Nacb EFPs upon Fo/Fi stimulation consisted of two positive synaptic components peaking at 10 and 25 ms, whereas the stimulation of the BLA resulted in negative synaptic fields peaking between 16 and 20 ms. Unit activity could be registered coïnciding with the peaks of the EFPs. In each rat systematically dorsal to ventral penetrations through the Nacb at various lateral coordinates, using glass micropipettes (5-20 MΩ), were performed. By now, in 6 rats, 49 and 28 cells were found that responded to stimulation of the Fo/Fi and BLA, respectively. Typically, convergence of inputs was found in the medial shell (mSH, n=9) but also in the medial core region (mC, n=4) of the Nacb. In the ventral core and the latero-ventral shell only BLA driven cells were found (n=13). On average, the spike latency in the medial BLA driven cell population is significantly shorter ($p<0.01$) than in the ventral population (mean ± sd: 16.5 ± 2.8 vs 19.8 ± 3.9, respectively). Cells responding only to Fo/Fi stimulation were found in the dorsal mSH and on the border of mSH and mC (n=36). No differences in spike latencies between these areas were seen (overall mean ± sd: 10.3 ±1.2). These results show that the medial shell and medial core regions are the primary areas of possible intra-accumbens interaction between HIP and BLA. The actual nature of these interactions have to be determined.

53.16 DIFFERENTIAL PROJECTION FROM THE BED NUCLEUS OF THE STRIA TERMINALIS TO THE HYPOTHALAMIC PARAVENTRICULAR NUCLEUS IN NORMAL AND ADRENALECTOMIZED RATS.

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The bed nucleus of the stria terminalis (BNST) plays a major role in the regulation of the stress response by funneling limbic information to the hypothalamic paraventricular nucleus (PVH). By means of anterograde tracing with biotinylated dextran we investigated the precise distribution of fibres originating from the medio-ventral BNST in the different subdivisions of the PVH. Particular attention was paid to the distribution of BNST fibres among the corticotropin-releasing hormone (CRH) neurons in the PVH, which were immunohistochemically visualized in adrenalectomized rats. In normal rats BNST fibres were more or less equally distributed among all subdivisions of the PVH. Remarkably, in adrenalectomized rats statistically significantly fewer BNST fibres were found in the PVH after similar tracer injections. Moreover, the percentage of fibers projecting to the CRH-rich part of the PVH was particularly lower in adrenalectomized rats, and EM analysis failed to show labelled synaptic contacts of BNST terminals with CRH neurons in such animals. These findings indicate an overall loss of input from the BNST to the PVH and a specific retraction of BNST terminals from CRH neurons in the PVH following adrenalectomy and suggest a large degree of stress-related synaptic plasticity in the PVH.

53.17 ASCENDING SPINAL PROJECTIONS IN THE DORSOLATERAL FUNICULUS OF ANURAN AMPHIBIANS. A. Muñoz*, M. Muñoz, A.González and H.J.ten Donkelaar., Dept. of Cell Biol., Fac. Biology, Univ. Complutense, Madrid, Spain and Dept. of Anat. and Embryol., Fac. of Medicine, Catholic Univ., Nijmegen, The Netherlands (H.J..t.D.).

The organization of ascending spinal projections through the dorsolateral funiculus (DLF), the cells of origin and its main targets were studied in the anurans *Rana perezi* and *Xenopus laevis* by means of *in vivo* and *in vitro* biotinylated dextran amine (BDA) tracing techniques. In addition to primary spinal afferents of Lissauer's tract, also non-primary spinal projections ascend from lumbar, thoracic and cervical levels in the DLF to reach spinal and supraspinal targets, mainly ipsilaterally. Lumbar fibers ascending in the DLF send off thin fibers to the dorsal, lateral and, less densely, to the ventral spinal fields, at thoracic segments. At upper cervical and obex levels many fibers turn dorsomedially and innervate a region considered as the possible equivalent of the lateral cervical nucleus (LCN) of amphibians. Through the medulla the fibers ascend ventrally to the descending trigeminal tract to terminate dispersely in the reticular formation, up to the level of the octaval nerve root. Thoracic fibers innervate the dorsal and lateral spinal fields at cervical levels. Both thoracic and cervical fibers innervate massively the area of the LCN. Some fibers reach the dorsal column and the solitary tract nuclei. More rostrally the fibers innervate the reticular formation, the trigeminal descending nucleus, and the medial aspect of the octaval ventral nucleus (VIIIv). The major projection, however, reaches the area between the facial motor nucleus and the VIIIv. More rostrally, a mediolateral band at subcerebellar regions, slighly extending into the cerebellum, and the caudal aspect of the posterodorsal mesencephalic tegmental nucleus are innervated. These projections arise in different shaped neurons located mainly at the ipsilateral deep dorsal and lateral fields of the spinal cord, although some ipsilateral neurons were present at the superficial dorsal and ventrolateral spinal fields and at the contralateral ventromedial field. The majority of the neurons were observed at cervical spinal levels although thoracic, lumbar and sacral spinal cells also send ascending fibers in the DLF.
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53.18 SELECTIVITY OF SUBICULAR PROJECTION NEURONS; A FLUORESCENT RETROGRADE LABELING STUDY IN THE RAT

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The subiculum constitutes the major output structure of the hippocampal formation, distributing projections to various cortical and subcortical regions. We have recently reported that specific populations of neurons that have different locations along the transverse or proximo-distal axis of the subiculum distribute their axons to a limited number of targets. Because of this organization, at least two populations of subicular neurons can be differentiated, one with a proximal and the other with a distal location. In this study we aimed to systematically analyze whether and to what extent projections that arise from either the proximal or the distal subiculum do so as collaterals. For this purpose, we used a fluorescent retrograde double labeling technique. In 30 animals injections of three different tracers were placed stereotaxically in either proximal or distal subicular target structures, which resulted in retrogradely labeled cells in only one of the two subicular parts. Neurons projecting to different targets were intermingled, but only a few double-labeled neurons were present. We conclude that subicular projections, originating from the proximal or distal subiculum, in most instances arise from specific neurons and that almost no collateralization to different targets is present. This implies that cells in the subiculum are specialized in terms of their efferent projections, such that two adjacent neurons influence different targets. Consequently, subicular neurons may have the ability to transfer any incoming information selectively to only one target structure.

53.19 THE DIENCEPHALIC LIMBIC SWITCH IN HOMO.

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In animal studies neurnal circuits mediating the coordination of endocrine, autonomic and behavioral responses was described in 1990 (1).
Case report: A 22 year old woman developed a severe anoxic injury after a 15 minutes cardiac arrest as part of a delivary complication. During the first five months she did not communicate and the cerebral activity was low as judged from EEG which showed a slow diffuse retarded activity. High serum cortisol and thyroxine concentrations were repeatedly found. The blood pressure was elevated and the baroreceptor reflex reacted paradoxically. Her goal directed motor behavior was impaired, as the ingestion behaviour.
Discusssion: This case shows that during low cerebral activity there is a high pituitary production of cortisol and thyroid hormons and an imparirement of the autonomic nervous system as well as the motor system. It is concluded that there excists in homo a network related to the median forebrain bundle that is controled by a diencephalic limbic swich which regulats the activities of the cerebral cortex, the pituitary gland and the autonomic and somatomotor systems as proposed from animal studies.
References:
1. Swanson L W. Eur J Neurosci. Supplement No 3 252 1990.

53.20 CHOLINERGIC m2 RECEPTOR-MEDIATED CONTROL OF HIPPOCAMPAL INHIBITION: THE STRUCTURAL BASIS OF A DUAL EFFECT

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Type 2 muscarinic receptor (m2) is expressed in non-pyramidal neurons of the hippocampus (Levey et al., J. Neurosci., 15:4077-4092, 1995). Cell bodies immunoreactive for m2 have horizontal dendrites, and are located at the stratum oriens/alveus border of the CA1 region, whereas in CA3 the positive cells are multipolar. Axon terminals positive for m2 are abundant in stratum pyramidale, they surround cell bodies of pyramidal cells in a basket like manner. Our aim was to identify the types - according to calcium binding protein and neuropeptide content - and GABA immunoreactivity of m2-positive neurons, and the source of m2-positive axon terminals. GABA was shown to be present in all m2-immunoreactive interneurons, but coexistence of m2 with calcium binding proteins (parvalbumin, calbindin D_{28K} and calretinin), VIP and somatostatin was rare throughout the hippocampal formation. Using retrograde HRP-transport some of the m2-positive horizontal cells were found to project to the medial septum. At the electron microscopic level the majority of m2-positive axon terminals were shown to be immunoreactive for GABA, and establish synaptic contacts with axon initial segments and somata of pyramidal cells. Since horizontal cells are unlikely to contact the perisomatic region of pyramidal cells, it appears that there is a differential axonal and soma-dendritic localization of m2 receptors on different interneuron types.

53.21 THE EFFECTS OF HIPPOCAMPAL LESIONS ON LEARNING AND MEMORY OF NONSPATIAL CONFIGURATIONS.
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In a series of experiments we have made an attempt to assess the contribution of the hippocampus to encode, store and retrieve nonspatial configurations. Hippocampus lesioned, sham-operated and unoperated rats were tested for the ability to perform two different tasks that require an animal to learn and remember the relationship among several stimuli. Subsequently, successively longer delays were imposed among the components of the information. The hippocampus lesioned rats appear to have used nonspatial cues to learn and recall associative information. The same damage impaired the performance on the task that imposed temporal intervals among the components of the configurations. It was concluded that the temporal demands included in the presentation of the information may define the hippocampal mnesic functions.

53.22 **LOCALIZATION OF NADPH-D AND NEURONAL NOS IN THE ISLANDS OF CALLEJA COMPLEX OF THE RAT BASAL FOREBRAIN**
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Nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) activity is implicated in enzyme mediated synthesis of nitric oxide (NO) for modulation of signal transmission and cerebral blood flow. Neuronal nitric oxide synthase (n-NOS) is the enzyme for NO biosynthesis in the brain. The highly vascularized islands of Calleja complex (ICC) are one of the brain areas with very high activity of NADPH-d, and strong n-NOS-like immunoreactivity. In previous studies the reaction product was very strong and a differentiation between the compartments of the ICC has not been demonstrated.. Therefore, the aim of the present study is to investigate whether NADPH-d activity and n-NOS-like immunoreactivity is differently expressed in the different compartments of the ICC.
Vibratome and cryotome sections of fixed adult Wistar rat brains were histochemically stained with NADPH-d and immunocytochemically for n-NOS, photographically documented, flat embedded in Araldite and prepared for semi- and ultrathin section series.
Three main ICC compartments can be distinguished in all sections stained for NADPH-d and n-NOS-like immunoreactivity. (1) The granule cell compartment exhibits strong reaction product in the neuropil between the negative granule cells. (2) The hilus area shows a moderate homogenously stained neuropil. (3) A marginal zone, a cell poor neuropil area along the rim of the granule cell compartment toward the adjoining areas, exhibits a very strong reaction product. Medium-sized neurons with NADPH-d activity and n-NOS-like immunoreactivity are located in all ICC compartments. Neighboured positive medium-sized neurons with deeply invaginated nuclei send their dendrites toward the ICC compartments.
The present results show that NADPH-d activity and n-NOS-like immunoreactivity are colocalized in the neuropil and in the neurons of the ICC. The reaction product is differently expressed in the ICC compartments. The associated positive medium-sized neurons are most likely neostriatal neurons.

53.23 SEGMENTAL MAP OF ACETILCHOLINESTERASE AND CALRETININ IN THE DIENCEPHALON OF THE FROG RANA PEREZI.
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Considering the renewed interest in segmental models of the central nervous system (Rubenstein and Puelles 1993), we have studied frog diencephalic neuronal populations and neuropils visible by AChE activity or CR immunoreactivity. In sagittal sections, as predicted by the model, there is a basal plate, with sparse neuronal populations and large numbers of longitudinal fibers, and an alar plate, with many neuronal groups and neuropils. Many neuronal groups are separated by limits perpendicular to the longitudinal axis. Some boundaries agree with the postulated interneuromeric limits. The CR immunostaining distinguishes the dorsal thalamic populations from adjacent regions. The synencephalic (P1), posterior parencephalic (P2) and anterior parencephalic (P3) alar plate regions correspond with the classical pretectum, dorsal thalamus and ventral thalamus subdivisions, respectively. The segmental viewpoint was of great help to distinguish new neuronal groups and serves as well to highlight a marked topological orthogonality of the prosencephalic tracts. DGICYT, PB93-1137.

53.24 SMI-32 IMMUNOCYTOCHEMISTRY OF THE HIPPOCAMPUS AND ENTORHINAL CORTEX IN SCHIZOPHRENIC PATIENTS
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There is a growing evidence of structural alterations of the hippocampus and entorhinal cortex (EC) in a significant number of schizophrenic patients. We tried to access possible structural changes of pyramidal neurons using a method for demonstration of SMI-32 immunoreactivity (SMI-32 is an antibody against nonphosphorylated neurofilaments). Adult postmortal brains of 2 schizophrenic patients and 3 normal controls were analyzed.

Compared to normal controls, the most prominent alterations in the brains of schizophrenic patients were found in CA1 field of hippocampus, particularly at the borders with presubiculum and CA2 field. In addition to the apparently reduced density of SMI-32-immunoreactive (ir) neurons, some other abnormal features were observed. The most prominent was the presence of parts of tortuous apical, as well as basal, dendrites of SMI-32-ir neurons. This alteration, similar to that found in fetal brains as a result of compression during development, was also found in CA2 field and occasionally in the deep layers of EC. Some neurons of CA1 field which showed such changes had "wind-blown" dendrite deflections without a predominant direction.

Our observations support the hypothesis of patchy neuronal disarray in the rostral part of the hippocampal pyramidal cell layer in the brain of schizophrenic patients. Moreover, a new, peculiar structural abnormality in a subpopulation of hippocampal projecting neurons, was found. This alteration, like neuronal disarray, could be a result of disordered embryogenesis. We concluded that further detailed quantitative analyses of the differences in the number, distribution and morphology of SMI-32-ir neurons should better define a profile of schizophrenic temporal lobe structures and give more specific insights into the cellular pathology of this disorder. *This work was supported by the Ministry of Science of the Republic of Croatia.*

53.25 EFFECTS OF ANTICIPATION OF VISCERAL PAIN ON THALAMIC ACTIVITY IN IRRITABLE BOWEL SYNDROME PATIENTS AND NORMAL SUBJECTS.
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Anticipatory anxiety is prominent in many patients with irritable bowel syndrome (IBS), as is lowered threshold to rectal pain. Anticipation of pain can modify its processing and ultimate perception. In the current study, the relationship between anticipation of rectal pain and regional cerebral blood flow was evaluated in IBS patients and normal subjects (NIs) using $H_2{}^{15}O$ positron emission tomography (PET). A rectal balloon catheter was placed in each subject 30 min prior to imaging sessions. Following IV administration of 1480 MBq $H_2{}^{15}O$, PET data were obtained in 5-sec frames, and summed for 75 sec proceeding entry of tracer into the brain. Eyes were closed during all scans. A baseline scan was first obtained with the balloon deflated. Then, pressure pulses of low (20 mm Hg) and moderate (45 mm Hg) intensity were delivered by a programmable pump for 45 sec each, with interim balloon deflation (20 min). A taped message subsequently announced the imminence of a very intense pressure pulse. Heart rate was recorded before and after this message. A scan was performed following the announcement, while the balloon actually remained deflated. Relative positron activity was measured in various brain regions normalized to the activity level in the superior occipital cortex, a quiescent area that was unaffected by this protocol or IBS status. During anticipation, NIs showed a significant reduction in thalamic activity compared with their baseline level ($p<0.05$); in contrast, thalamic activity in IBS patients failed to change significantly and was higher than in normals. Heart rate changes during anticipation were strongly positively correlated with thalamic activity in both groups ($r = 0.98$). No significant differences were detected in the activity of other brain regions, including the anterior cingulate cortex, left and right medial temporal lobes, left and right temporal poles, or cerebellum. As the thalamus is critically involved in facilitative and inhibitory pain neuropathways, its aberrant response in IBS patients may reflect dysregulation of central processing of visceral pain information.

53.26 DISTRIBUTION OF CALRETININ IMMUNOREACTIVE CELLS AND FIBERS IN THE HUMAN AMYGDALOID COMPLEX.
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Little is known about the organization of different GABAergic neuronal populations in the human amygdaloid complex. In this study, we analyzed the distribution of calretinin-immunoreactive (CR-ir) neurons and terminals in the amygdaloid complex of four human brains. Calretinin is a calcium binding protein that is known to colocalize with GABA in the cortex and hippocampus of rat and monkey. CR-ir neuronal population was composed of small neurons which had an appearance of aspiny or sparsely spiny local circuit neurons. Three morphological types of CR-ir neurons were characterized: small multipolar cells (Type 1), large multipolar cells (Type 2), and fusiform cells (Type 3). The highest densities of the neurons were observed in the lateral, accessory basal and anterior cortical nuclei, and in the nucleus of the lateral olfactory tract. The paralaminar, central and medial nuclei and the periamygdaloid cortex contained the lowest densities of CR-ir neurons. The cortical areas and the central nucleus were characterized by an intense neuropil labeling, while the deep nuclei contained a high density of CR-ir fibers and terminals. The calretinin immunoreactivity was also found in the stria terminalis and ventral amygdalofugal pathway. This suggest that calretinin immunoreactivity is also located in afferent or efferent projection neurons. This study provides baseline information about the organization of GABAergic inhibitory system in the human amygdaloid complex, which has significance in the understanding of the pathophysiology of some human diseases such as temporal lobe epilepsy.

53.27 SPONTANEOUS DISCHARGE CHARACTERISTICS OF NEURONS FROM THE MEDIAL PREOPTIC NUCLEUS IN RAT HYPOTHALAMIC SLICES.

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Neurons in the medial preoptic nucleus (MPN) of the rat hypothalamus were characterized electrophysiologically with whole-cell tight-seal recording techniques applied to a slice preparation, at 23°C. Spontaneous firing properties and passive membrane parameters were analysed.

Four different types of spontaneous impulse patterns were recorded. One group of cells (35%) displayed a burst-like firing pattern, 22% fired action potentials regularly, and 33% discharged in an irregular way. Ten per cent of the cells were silent. Current injection altered the firing patterns, as well as the firing frequencies of these cells.

The resting membrane parameters were similar in all the MPN neurons, irrespective of the type of spontaneous activity. They were on average: -44 mV (resting potential), 28 ms (membrane time constant), 1.6 GΩ (input resistance) and 18 pF (membrane capacitance).

53.28 PARVALBUMIN IMMUNOREACTIVE NEURONS IN THE MEDIAL SEPTUM AND BASAL FOREBRAIN ARE TARGETS OF NEURAL CONNECTIONS ORIGINATED IN THE MEDIAL SEPTAL AREA OF THE RAT.

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The present examinations were focused on the terminal field and target neurons of septal projections originated in the medial septal nucleus. PHAL anterograde tracing method was applied in combination with staining of the target cells by parvalbumin (PV)- and/or calbindin D28k (CaBP)- immunocytochemistry. On the other hand the septal connections of PV-ir neurons localized in the medial septum were investigated using PV- and CaBP double-label immunocytochemistry. The investigations revealed: 1.) PHAL-labeled axons from the medial septum terminate in the whole extent of the medial septal nucleus itself. Two distinct types of PHAL-labeled axons were seen in the terminal field areas. One of those was thicker, had large boutons and frequently formed contacts around cell bodies and proximal dendrites of PV-ir neurons localized in the MS and the ventral pallidum. 2.) The double-label experiment showed a dense PV-positive fibre network in the lateral area immediately close to the medial septal complex. The thick fibres having large boutons formed basket-like contacts around cell bodies and dendrites of CaBP-ir neurons. These findings taking together with previuos data suggest that medial septal PV-containing neurons that project predominantly to hippocampal targets also may contact PV-ir and CaBP-ir neurons in the medial area of the septum itself.

This work was supported by OTKA grant T6372.

53.29 PROJECTIONS FROM THE PARAVENTRICULAR NUCLEUS OF THE THALAMUS TO THE LIMBIC CORTEX.

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Previous studies indicate that the paraventricular (PV) nucleus of the thalamus projects primarily to the prelimbic cortex (area infraradiata; IRbα), and to the ventral striatum. However, our anterograde tracing studies suggest that many axons extend beyond these areas to synapse in more caudal limbic cortical areas. The present study used anterogradely and retrogradely transported tracers to characterize the projections of PV. Injections into PV label axons and terminals in the frontal polar, agranular insular, medial orbital and IRbα cortices, in the anterior olfactory nucleus and in the basolateral, central and lateral amygdaloid nuclei. In the caudal limbic cortex, labeled axons extend to the caudal piriform, and to perirhinal and entorhinal cortices, and the ventral subiculum. In addition to the cortical projections, PV projects to a number of subcortical areas; PV injections label a dense terminal field in the ventral striatum (nucleus accumbens) and a sparse terminal field in the olfactory tubercle and in the lateral part of the lateral septal nucleus. Further, labeled axons and terminals are in the rostroventral reticular nucleus of the thalamus and sparsely to the dorsal periaqueductal gray. Neurons in different parts of PV have distinct projections, e.g., only rostral parts of PV project to the subicular and entorhinal cortices. Axons of PV terminate primarily in layers I and V in most cortical areas, but the projections to the entorhinal and perirhinal cortices terminate in deep layers (i.e., layers V-VI). These results demonstrate that PV projects to functionally distinct limbic areas, e.g., regions implicated in learning and memory versus regions involved in cardiovascular regulation and control of emotions.

53.30 LIGHT- AND ELECTRON-MICROSCOPIC DEMONSTRATION OF A PRESUBICULAR GABAERGIC PROJECTION TO THE MEDIAL ENTORHINAL CORTEX OF THE RAT.

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Anatomical tracing studies have shown that the medial entorhinal cortex (MEA) receives a strong projection from the presubiculum. This projection distributes bilaterally, and selectively terminates in layer III of MEA. Interestingly, the presubiculum contains a rather high number of GABAergic neurons. The aim of the present study was to investigate whether these presubicular GABAergic neurons contribute to the projections to MEA.

Presubicular neurons projecting to MEA were identified by injecting small volumes of the retrograde tracer HRP in the superficial layers of dorsal MEA. HRP was visualized in frozen sections by a peroxidase reaction using DAB-nickel as a chromogen. Subsequently, sections were incubated with an antibody to GABA and stained with DAB. This procedure resulted in a black granular staining of projection neurons, whereas GABAergic neurons contained a brown precipitate. Many neurons in the dorsal presubiculum appeared to contain either HRP or GABA. However, a number of neurons were stained for both, indicating a GABAergic projection to the MEA. This finding was confirmed at the EM-level. Presubicular projections to MEA were labelled with the anterograde tracer biotinylated dextran amine (BDA). Subsequent EM-analysis revealed the presence of a number of BDA-positive symmetrical, i.e. presumably inhibitory, synapses next to many BDA-positive asymmetrical, i.e. excitatory, synapses in layer III of MEA. These results suggest that neurons in layer III of MEA receive an extrinsic inhibitory input through GABAergic presubicular projections.

53.31 THE FOREBRAIN OF THE AFRICAN MOLE RAT (CRYPTOMYS). AN ATLAS.

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The brains of eight adult specimens of the African mole rat (4m, 4f) were investigated by cryotomy and paraffine histology (cresyl violet stain).

In comparison with rat, the brain of *Cryptomys* is smaller, but more flattened and relatively broader. The commissural systems and the fornix are well developed; the same is true for the olfactory system. The visual system, in general, is much reduced (optic nerve and chiasm, lateral geniculate body, superior colliculus); however, the subgeniculate nucleus (Paxinos and Watson 1986) is distinct.- In the hypothalamus, the supraoptic nucleus is clearly larger while the paraventricular nucleus is distinctly smaller and contains less magnocellular neurons. The suprachiasmatic nucleus is moderately developed and does not show a clear borderline.- The limbic system comprises a somewhat broader septum and diagonal band. The hippocampus is relatively large and much rounded; its pyramidal layer is less marked than in rat. With the exception of the anteroventral thalamic nucleus, most nuclei are less distinct than in rat. In the habenula, the neurons stand in irregular clusters.- Within the extrapyramidal system, the globus pallidus seems to be somewhat larger and the zona incerta and nucleus ruber are more prominent, with the latter having a distinct magnocellular component. In contrast, the nucleus of Darkschewitsch is only small in the mole rat.

Some features of the mole rat brain are definitely correlated to its subterranean mode of life (visual system). Whether this is also true for the accentuated development of parts of the extrapyramidal system is still unclear. It remains open whether the remarkable size of the limbic system and parts of the hypothalamus (especially the supraoptic nucleus) might be connected with the phenomenon of eusociality (Burda 1995; Experientia, in press).

53.32 NON-'PLACE CELL' RESPONSES IN HIPPOCAMPAL CA1 COMPLEX SPIKE CELLS OF FREELY-MOVING RATS.

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In order to test for selective discharges related to arena rotations and to locomotion, twelve water-deprived Long-Evans rats were trained in a darkened square-walled open field. In the water search task, the rats repeatedly performed a series of identifiable behaviors in the same manner in each of four corners of the arena. At irregular intervals, the rat was rotated in total darkness.

Of 97 hippocampal CA1 complex spike cells, 21 'place' cells were found. In addition, each of 14 'task-event' cells discharged selectively as the rat performed one of the several task-related behaviors in most or all quadrants of the arena. Since the discharges were selective for approaches to the corners or to the center, these were not simply movement-related responses.

In addition, 11 'sensory-triggered' neurons fired after visual or rotational stimulus presentations, also irrespective of the position of the rat. Unlike classical sensory responses, the discharge onsets were up to several seconds after the trigger stimulus and the durations were up to 30-40 s; thus these discharges could serve as a memory trace.

These discharge correlates represent elements of the behavioral task as if it had been partitioned with respect to temporal sequence and cue qualities. Taken together they compose a comprehensive representation of the behavioral milieu. The role of the hippocampus in learning and memory would then be to facilitate associations between the diverse neocortical regions originating the synchronous excitation of its neurons. (Support:Human Frontiers,Cognisciences,CEE-ESPRIT)

53.33 DISTRIBUTION, MORPHOLOGY AND ULTRASTRUCTURE OF CALRETININ IMMUNOREACTIVE NEURONS IN THE ENTORHINAL CORTEX OF THE RAT.

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The entorhinal cortex of the rat contains a variety of interneurons of which a number are GABAergic. The latter neurons are of special interest since, although the entorhinal-hippocampal pathway is excitatory, inhibition appears to play a major role in the patterns of activity of principal entorhinal neurons.
In order to unveil the intrinsic neuronal wiring of the entorhinal cortex we analyzed the distribution, morphology, and ultrastructure of entorhinal neurons labeled immunocytochemically with an antibody against the calcium-binding protein, calretinin.
Calretinin-immunolabeled cells were seen in all subdivisions of the entorhinal cortex. They appeared in all cortical layers except layer II. The deep layers contained the highest concentrations of cell bodies. These cells had small somata and multipolar- and bipolar dendritic configurations, with smooth dendrites. The dendrites of bipolar neurons were radially oriented, and usually traversed several cortical layers. Immunopositive fibers were abundant in the deep cortical layers. In the electron microscope, immunoreaction product was observed in cell bodies, dendrites and in axodendritic and axospinous axon terminals. The immunopositive somata were small and inconspicuous. Immunopositive axon terminals were seen forming both symmetrical and asymmetrical synapses, mostly with unlabeled profiles. Thus, calretinin seems to be associated with a limited number of entorhinal interneurons.

53.34 POOR EEG ACTIVITY VS. HIGH SINGLE-UNIT ACTIVITY IN THE DEAFFERENTED PONS IN CATS.

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The pons was isolated by two brain stem transections, at the junction of medulla and pons and at the junction of pons and midbrain. In the deafferented pons the EEG activity was greatly depressed, whereas the spatial density of active units and the rate of their spontaneous spike activity remained at a quite high level. In control preparations, with brain stem transected only at the ponto-midbrain junction, the EEG activity was present, whereas the single-unit activity was such as in the isolated pons.

The electrical activity of the isolated pons was similar to that previously described in the isolated midbrain. The discrepancy between EEG and single-unit activity in the deafferented brain stem is presumably due to asynchronous autoactivity of many neurons. This assumption is consistent with anatomical data suggesting not numerous direct synaptic connections between reticular neurons.

53.35 DEVELOPMENT OF PARVALBUMIN IMMUNOREACTIVITY IN AUDITORY CORTEX FOLLOWS THE ONSET OF HEARING

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Recent studies, using 2DG autoradiography as metabolic marker, have shown that the auditory cortex of gerbils (Meriones unguiculatus) is acoustically activated at the end of the second postnatal week, i.e. 1-3 days after opening of the external ear channel (Stürmer et al., 1994). First appearance of acoustically induced 2DG uptake was observed in the anterior auditory field (AAF) at postnatal day 13 followed by the primary auditory field AI (DAB 15) while more sharply defined bands of 2DG uptake were found at postnatal days 19 and 27. To test whether the formation of clear 2DG patterns within these fields is correlated with maturation of inhibitory mechanisms we mapped the postnatal expression of the calcium binding protein parvalbumin (PV) within the auditory cortex from ear opening to adult (days after birth: 14, 21, 28, adult). Synthesis of parvalbumin, which in adult cerebral cortex is present in a subpopulation of GABAergic neurons, has been found to coincide with the arrival of excitatory synaptic input and the onset of spontaneous activity (Solbach and Celio, 1991).
Appearance of PV-immunoreactivity in the auditory cortex started with faintly stained individual PV-IR cell bodies in laminae IV-VI of AAF at DAB 14. At DAB 21 cortical fields AI and AAF displayed an increasing number of PV-IR somata in laminae III/IV and VI while neuropil staining remained rather undeveloped. At DAB 28 PV-IR cell bodies were spread through all cortical layers except layer I and dendritic fields as well as terminal-like structures of PV-IR neurons showed a prominent immunoreactivity. The data suggest that the expression of this calcium binding protein within GABAergic neurons may be relevant for the establishment of functional inhibitory properties within auditory cortex.
Supported by BMFT FKZ 07NBL06, TP4

53A. Poster Session: Computational approaches

53A.01 SINGLE NEURON CHAOS IS NATURAL.

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It will be argued that the human brain is very complex system built of subunits, neurons which possess potentially very complicated dynamics behaviour, too. A generalized McCullouch -Pitts neuron model with a time dependent thres hold will be studied in detail. It will be show n analytically that output dynamics of such more realistic neuron model, because of special properties of sigmoidal transfer function, can be chaotic. Then conditionsfor chaotic behavior of such single neuron will be explicitly determined. The message to experimentalists will be called to look for critical values of adequate parameters of biological neurons to behave chaotically.

The role of nonmonotonicity of transfer function as a consequence of gain dependence on a threshold of individual neurons upon the memory of single neurons as well as of neural networks of such neurons will be studied in the above mentioned context, too.

53A.02 COMPARATIVE MORPHOLOGICAL STUDIES OF SUPERFICIAL SUPERIOR COLLICULUS NEURONS IN RAT AND TUPAIA

H.Hilbig*, M.Merbach[1], U.Gärtner[1], U.Ohme[2] and A.Schierwagen[2]
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The aim of the study was to compare morphological characteristics of neurons in superficial superior colliculus in *Rattus norvegicus* and in *Tupaia glis*. The investigations included two types of neurons which have been divided on the basis of their dendritic architecture into two classes: narrow-field and wide-field neurons. Both types project to different targets and therefore seem to have distinct physiological functions. A detailed morphometrical analysis on dendritic dimensions (length, diameter, shaft area etc) and branching patterns of selected Golgi-impregnated neurons was undertaken by means of Kontron-Videoplan ® system. The morphological features of neurons can be splited up into metrical and topological ones. Specific correlations between various morphometric parameters (between dendritic shaft area and combined stem diameter, between number of dendritic tips and dendritic shaft area, between combined length and dendritic shaft area etc) are determed. Our intention was to examine the two collicular cell types. The topological structure of the neurons has been characterized by a measure called tree asymmetry, defined as the mean value of the asymmetry of its partitions. The tree asymmetry measure is sensitive for topological differences and independent of the size of the trees. These properties make the measure suitable for characterizing, comparing and interpreting sets of branching patterns. The available results suggest characteristic topological features as well as specific morphometric parameter correlations for the two cell types within and between the different species. There are'nt differences between the narrow-field but between the wide-field neurons: the smaller wide-field neurons of tupaia works faster than that of the rat.

53A.03 MATRIX REPRESENTATION OF DENDRITIC SIGNAL PARAMETERS
Michael Ohme and Andreas K. Schierwagen*
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Due to the fact that dendritic trees behave as delay lines, they play an important role in neuronal computing. The mathematical problems in describing dendritic delay in trees of arbitrary geometry, however, have rendered it difficult to obtain analytical solutions. Most attempts to study synaptic delay relied, therefore, on numerical computations.
One of the few theoretical approaches is due to Agmon-Snir. His method used the signal's 0th and 1st moments to characterize signal delay and velocity. As yet, moments of higher order than 1st have been not applied to explore analytically the behavior of the signal's width (defined by 0th, 1st and 2nd moments) and skewness (employing additionally the 3rd moment).
Combining van Pelt's matrix representation of the Laplace transformed cable equation with Agmon-Snir's method of moments we achieved a compact representation of moments of any order, in form of a matrix equation. The elements of the matrix are Taylor series expansions at the origin, up to the respective order of the signal's moments.
In this way, the behavior of the signal's width and skewness can now analytically be described. The knowledge of these signal parameters is of basic importance if the time window for synaptic integration is to be characterized.
[1] H. Agmon-Snir & I. Segev. Signal delay and input synchronization in passive dendritic structures. *J. Neurophysiol.*, 70: 2066-2085, 1993.
[2] J. van Pelt. A simpel vector implementation of the laplace-transformed cable equations in passive dendritic trees. *Biol. Cybern.*, 68:15-21, 1992.

53A.04 IMPACT OF TOPOLOGY ON DENDRITIC GEOMETRY AND ELECTROTONIC CHARACTERISTICS
Jaap van Pelt * and Andreas K. Schierwagen °
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The functional role of a neuron within a network is influenced by the geometry of its dendrites. In dendritic geometry, metrical and topological apects can be distinguished. We give a systematic account of the impact of topology on both metrical and functional properties by using a model for the outgrowth of topological trees in combination with a simple metrical parametrization.
We found that topological variation propagates into dendritic area and volume on the basis of intrinsic metrical constraints (branch power relation). The radial distribution of volume, surface area and length appears to be strongly influenced by topological variability in large dendrites (i.e. with many segments) but not in small ones, in agreement with the observation that large dendritic trees are not scaled-up versions of small ones.
Using three different estimators for electrotonic length, we found that (i) the electrotonic length of a dendrite depends on its topological structure and the branchpower, (ii) the three estimators give generally inconsistent outcomes, except for branch power $e = 1.5$ and symmetric trees, which is for larger trees a highly unrealistic assumption, and finally (iii) trees with realistic structures show transient responses different from those in symmetric trees. These qualitative outcomes are robust for different choices of the metrical and topological parameters. Result (ii) indicates that the electrotonic extent estimators are not exchangeable and should be used with great care.

53A.05 SELF-REPAIR IN NEURAL NETWORKS: A MODEL FOR RECOVERY FROM BRAIN DAMAGE.
J.M.J. Murre* and I.H. Robertson, Medical Research Council - Applied Psychology Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK.
We present a connectionist framework for modelling recovery from brain damage. The main focus of this research is how plasticity in the brain allow recovery from brain damage. This process is modelled by self-repair in neural networks. General and specific network models are studied in which modules and areas may inhibit each other. The logic of inhibition, stimulation, and the time-course of self-repair are compared with animal models, clinical cases, and general theories of the neuropsychology of rehabilitation. The neural network models are based on *(i)* sparse connectivity and modularity, *(ii)* sparse representations, within-module inhibition, *(iii)* Hebbian learning and unlearning, *(iv)* threshold control (i.e., of activation) and modulation of plasticity. The modules operate through k-winner-take-all competition. After lesioning, repair in the networks takes place, based on pattern completion followed by Hebbian learning. The following effects have been demonstrated: *(1)* Successful repair after moderate lesion. *(2)* No full completion without self-repair. *(3)* Faulty connections may develop during repair after severe lesion. *(4)* Effect of arousal: Better repair with high learning parameter. *(5)* Rehabilitation effect: Improvement may continue for a long time before faulty connections start to develop. *(6)* Serial-lesion effect: Two lesions show better repair than a single—equally severe—lesion. *(7)* Repair of representations with topological organizations. *(8)* Generalization of repair to items that were not used during re-training. *(9)* Sprague effect: Lesioning contra-lateral structure may disinhibit structure lesioned earlier, allowing self-repair. *(10)* Limb-activation effect: Stimulation of a lesioned structure may enable it overcome contra-lateral inhibition, causing improved self-repair. In addition, we have carried out analyses based on the theory of random graphs that allow prediction of the time-course of recovery and the expected life-time of a representation.

54.01 EMOTION AND THE LIMBIC SYSTEM CONCEPT

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The limbic system concept has dominated contemporary views of the emotional brain for many decades. While this concept has been extremely valuable in stimulating research into the brain mechanisms of emotion, it is now clear that the brain circuits underlying emotional functions are best identified empirically. With this in mind, a number of researchers have turned to studies of specific models of emotion rather than emotion in general. One of the most successful of these models has been classical fear conditioning. Studies of fear conditioning by several laboratories have contributed to a mapping of the basic neural circuits all the way from the sensory pathways processing the conditioned stimulus through the motor pathways controlling the conditioned responses. Some progress has also been made in clarifying the cellular mechanisms operative in these pathways that make the learning and remembering of conditioned fear possible. While some aspects of the limbic system have been implicated in fear conditioning, the empirical studies have identified contributions of limbic and non-limbic areas and have determined the role of the various areas in the information processing functions that underlie fear conditioning. Following the lessons learned from studies of fear conditioning, it may be possible to identify the brain systems that contribute to other emotions. Supported by USPHS Grants MH38774, MH46516, and MH00956.

55.01 CORPUS CALLOSUM AND INTERHEMISPHERIC INTEGRATION

G.Berlucchi, Dipartimento di Scienze Neurologiche e della Visione, University of Verona, Italy

The corpus callosum is necessary for several forms of hemispheric interaction and communication. The anatomical and physiological characteristics of the corpus callosum allow the interhemispheric transfer of different kinds of information at different speeds across the midline. The corpus callosum provides the anatomical and functional continuity between the sensory and motor half maps on the two sides by establishing discrete and selective connections between appropriate neurons of the two hemispheres. In addition, the callosal action on the bilateral synchronization of the bioelectric activities of neuronal populations on the two sides of the brain may be relevant for the unification of attention and perception across the midline. Recent studies of patients with congenital or acquired callosal defects have demonstrated specific deficits of interhemispheric communication. These deficits are particularly conspicuous in fast forms of interhemispheric communication required for integrating a sensory input channeled into one hemisphere and a motor response controlled by the other hemisphere. By relating these deficits to the location of the defects in the corpus callosum it may be possible to establish a functional callosal topography in man. Compensation of interhemispheric transfer deficits in callosal agenesis is usually good but incomplete; its mechanisms are largely unknown. Such compensation is best for abilities based on declarative knowledge, and worst for abilities which require the fast interehemispheric transmission of procedural knowledge. Paradoxically, compensation may be more efficient in partial than total callosal agenesis.

56.01 MOLECULAR ANALYSIS OF HINDBRAIN SEGMENTATION.

Patrick Charnay, INSERM U 368, Ecole Normale Supérieure, Paris, France

In the hindbrain region of the developing CNS, antero-posterior patterning involves a transient segmentation process which leads to the formation of morphological bulges called rhombomeres. The rhombomeres constitute cell lineage restriction units and participate in the establishment of a metameric pattern which is responsible for the segmental organisation of motor and reticular neurons. Like Drosophila compartments, rhombomeres also constitute domains of specific gene expression. Genes expressed in a rhombomere-specific manner so far identified encode various types of putative regulatory molecules, including transcription factors, like Hox proteins, the zinc finger protein Krox-20 and the basic domain leucine-zipper protein kreisler, and receptor type molecules, in particular several members of the EPH family of tyrosine kinase receptors. Such genes are thought to play a role either in the definition of segmental territories or in the specification of the identity of the rhombomeres. Initial analysis of the function of some of these genes, performed by gene inactivation in the mouse, have indeed supported this hypothesis. In addition, Krox-20 has been shown to be involved in the transcriptional activation of several other regulatory genes, providing a first glimpse at the organisation of the regulatory network governing hindbrain segmentation.

57. Symposium: the cerebral substrate of schizophrenia

57.01 SCHIZOPHRENIA AND CEREBRAL ASYMMETRY: AN EVOLUTIONARY THEORY. TJ Crow, University Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX

Two epidemiological findings constrain theories of aetiology:

i) Typical schizophrenic illnesses occur in all cultures probably at closely similar rates.

ii) Onsets occur throughout the reproductive period of life, and are associated (particularly in males) with a decrease in fertility. There must be an advantage to the relevant genes.

From studies of brain structure there is evidence of a loss of asymmetry - eg of the temporal horn, Sylvian fissure length and brain width. These anatomical changes are paralleled by evidence of diminished hemispheric specialisation. In the National Child Development Study hand skill assessed at the age of 11 was found to be a predictor of academic ability and behaviour. Pre-schizophrenics were found to be closer to the point of "hemispheric indecision" than the rest of the NCDS population.

Schizophrenia may be a consequence of the genetic variation generated and maintained by the evolution of the capacity for language and communication by a process of increasing hemispheric specialisation.

Reference: Crow TJ. Lancet 1993; 342: 594-598.

57.02 Abstract not received

57.03 PET STUDIES OF D1 DOPAMINE RECEPTORS IN SCHIZOPHRENIA

G Sedvall, P Karlsson, S Brené, L Farde, H Hall, Y Hurd, S Nyberg and S Pauli. Karolinska Institute, Department of Clinical Neuroscience, Psychiatry Section, Stockholm, Sweden

In the search for pathophysiological mechanisms in schizophrenia dopamine regulated transmission in the brain is still in focus. Dopamine signalling is mediated by five receptor subtypes each one having an unique distribution pattern to a variety of brain regions with separate functions. Questions related to laterality and regional specificity of alterations of dopamine signalling necessitate the simultaneous recording of dopamine regulated events in a vast number of brain regions. This can be achieved at low resolution (about 3 mm) using PET and SPECT methods with suitable radioligands binding to specific components of dopamine signalling pathways as neuroreceptors and transporters. Using the human post mortem brain and autoradiographic techniques a much higher resolution (about 20 μm) can be achieved in the visualization of radioligand binding sites and also for gene expression using in situ hybridization histochemistry. Besides dopamine D2, D3, D4 and recently D1 receptors have been suggested as components of pathophysiological alterations in schizophrenia. Using PET and the D1 receptor selective ligand [^{11}C]SCH 23390 we recently reported reduced D1 receptor binding in the basal ganglia of drug naive schizophrenic patients. Such an alteration has also previously been found in some but not all in vitro studies on post mortem brain tissue. These results may implicate that the ratio of D2 over D1 regulated dopamine signalling in the basal ganglia is increased in schizophrenia.

57.04 IN VIVO BRAIN IMAGING STUDIES ON SCHIZOPHRENIA

Vita A.
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Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) demonstrated the presence of several of neuromorphological abnormalities in schizophrenia in particular lateral ventricular enlargement and a mild degree of cortical atrophy. Functional studies performed with Single Photon Emission Computed Thomography (SPECT) and Positron Emission Thomography (PET) pointed out metabolic abnormalities in different cerebral areas (frontal, temporal, basal ganglia hypometabolism) and, even if with some contradictory evidences, alterations of receptor densities.

Neuromorphological abnormalities have been correlated with symptomatological patterns and clinical evolution of schizophrenia. We demonstrated an high specificity of ventricular enlargement and a significant prognostic value of cortical atrophy evaluated with CT in predicting respectively progression of schizophreniform disorder in schizophrenia after 5 years (Vita et al 1991a) and poor outcome in social and clinical areas for chronic schizophrenia, after 2 years (Vita et al. 1991b). We are presently performing a study addressed at re-evaluating prognostic value of neuromorphological variables; the study has been completed till now for 15 schizophrenic subjects. We have evaluated with MRI the volumes of prefrontal, temporal lobe and lateral ventricles. In a multivariate model where volume measurements were considered as dependent variables, good and poor outcome evaluated by means of Strauss Carpenter Scale (SCS) independent variable and baseline evaluation of SCS as covariate, emerged a significant reduction of frontal ($F=5.2$; d.f.=1,12; $p=.04$) but not temporal or ventricular volumes in patients with poor vs good outcome.

References

Vita et al. Lancet ii, 338: 1458, 1991a.
Vita et al. Am. J. Psychiatry,148: 1577-1579, 1991b.

58.01 CONSTRUCTION OF THE ODOUR WORLD DURING EARLY DEVELOPMENT

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Like the immune system, the olfactory system is confronted by an almost infinite variety of chemical substances, few of which are predictable in their occurrence or composition. This explains why an understanding of olfactory learning is critical for understanding odour perception.

The role of experience is particularly evident during early life when the olfactory system is still undergoing rapid development. In the rabbit, for example, there is a 5-fold increase in the number of receptor cells and a 3-fold increase in the area of the olfactory epithelium from birth to weaning. During the perinatal period, rabbits acquire olfactory information under at least three distinct conditions:

(1) Intra-uterine environment. This is clear from the preference shown by pups in later life for the odours of foods eaten by their mother during pregnancy. This early experience also has an odour-specific effect on the development of olfactory sensory cells, enhancing their sensitivity.

(2) The nest. Following birth, the ambient odours of the nest environment are learned incidentally by exposure, and even after one day of experience, result in a preference.

(3) During suckling. Pups acquire context-specific responses by associative learning during just one suckling episode. This rapid odour learning is characterised by two features, a consolidation period of 12-16 h before the full response is expressed, and a sensitive period to Day 4.

Evidence suggests that at puberty the postnatal odour world is redefined so that similar but somewhat unfamiliar odours are now preferred, presumably promoting dispersal and incest avoidance.

58.02 SYNAPTIC PLASTICITY IN THE ACCESSORY OLFACTORY BULB DURING OLFACTORY LEARNING IN MICE

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Female mice form an olfactory memory to the pheromones of the mating male, during a critical period after mating. Previous experiments have shown that the neural changes underlying this memory are located in the accessory olfactory bulb, are dependent on noradrenergic neurotransmission, and most likely involve changes at mitral/granule cell reciprocal synapses. Using the technique of in vivo microdialysis we have followed changes in a range of neurotransmitters before, during and after memory formation. The increase in GABA levels in response to a glutamate challenge was found to be greater after memory formation. The ratios of glutamate/GABA and aspartate/GABA were decreased following memory formation, during exposure to the pheromones of the mating male. These findings are consistent with our hypothesis that memory formation involves a long-lasting increase in the inhibition of the subset of mitral cells that respond to the mating male's pheromones. Unexpectedly, there were increases of the excitatory transmitters glutamate and aspartate in non mating females, immediately following male exposure, and 2 days later in response to re-exposure to the same male pheromones. These results suggest that exposure to male pheromones alone, without the association of mating, causes a long-lasting decrease in the inhibition of the subset of mitral cells responding to these pheromones. Despite their different anatomical projections and biological consequences, there appear to be many similarities between the neural mechanisms of learning in the accessory olfactory bulb and the main olfactory bulb.

58.03 MATERNAL BEHAVIOR IN SHEEP: A MODEL OF LEARNING IN THE MAIN OLFACTORY BULB.

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An appealing characteristic of maternal behavior in sheep is the primary importance of olfactory cues provided by the newborn that permit the formation of an exclusive bond. The interest of the mother in these sensory cues is triggered by the process of parturition which results in changes in the olfactory sensory processing system and in particular in the main olfactory bulb (OB), the first relay of olfactory information. Lamb odors have little effect on either neurotransmitter release or electrical activity of neurons in the OB before parturition. However, after birth there is an increase in the number of mitral cells, the principal cells of the OB, that respond to lamb odors, which is associated with increased glutamate and GABA release from the dendrodendritic synapses between the mitral and granule cells. The odor of the familiar lamb, but not the odor of the alien one, increases both the electrical and neurochemical activity of a subset of mitral cells. Furthermore, after birth, lamb odors stimulate transmitter release from noradrenergic and cholinergic inputs which are essential for olfactory learning of the ewe's own lamb. Maternal experience also influences OB neurotransmitter release. In ewes without previous maternal experience, parturition does not induce the normal pattern of transmitter release from both intrinsic and centrifugal pathways observed in the OB of maternally experienced ewes. However, vaginocervical stimulation, which mimics parturition, conducted 6 h after birth reveals no differences between both groups suggesting that birth would induce a neural maturation within this period. These changes within the OB which result from the first maternal experience and last for life could be related to the disturbances in selective bonding observed in inexperienced ewes.

58.04 NEURAL CONSTRAINTS OF ODOUR CODING AND REPRESENTATION

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The field of olfactory neurobiology is rapidly developing. Several new ways have been opened in recent years : A large gene superfamily coding for olfactory receptors has been identified in a number of species; several transduction pathways have been discovered; classical approaches to the topographic organization of sensory projections to the olfactory bulb are being renewed by a powerful method of "molecular dissection"; many findings illustrate the plasticity of the olfactory bulb; finally, the olfactory system attracts modellers of neuron network dynamics.

New findings uncovered in these fields justify some updating of our views on neural coding and representation of odour attributes. It is also possible to go a step beyond pure neurobiology and examine how characteristic features of olfactory perception and memory emerge from - and are constrained by - spatial and temporal parameters of neural activity.

62.01 THE NEURAL BASIS OF RECOVERY FROM APHASIA AND SPATIAL HEMINEGLECT. PET STUDIES IN BRAIN DAMAGED PATIENTS

S.F. Cappa*, D. Perani, F. Fazio. University of Brescia, INB-ITBA CNR, University of Milano, Italy

There are two basic approaches to the study of recovery form neuropsychological disorders, such as aphasia and unilateral neglect, in stroke patients using positron emission tomography: 1) measurements of regional cerebral metabolism or perfusion in patients before and after recovery in a resting condition 2) measurement of the regional cerebral perfusion associated with cognitive activation in recovered patients. The first approach has been applied by our group to the study of recovery from unilateral neglect and aphasia: the main finding is that clinical recovery parallels the return towards normal values of metabolism in structurally undamaged areas, in the same as well as in the contralesional hemisphere. These results suggest that the overall impairment observed in the acute stage reflects the additional effects of the lesion plus remote functional depression (diaschisis) in structurally undamaged brain areas, and that the rapid recovery which is frequently observed during the first months after stroke may be related to the regression of distance effects. The second approach has became feasible only in recent years, due to the developments in PET technology and in methods of data analysis. An European research program has been established to study recovery from aphasia with activation methods: the first results, from the Essen and the London groups, have shown an extensive reorganisation of the cerebral networks activated by language tasks in recovered aphasic patients. A predominantly ipsilateral reorganisation has been found in patients with unilateral neglect studied during an exploratory task in Milano.

PET appears to be a promising tool to investigate the crucial issues of cerebral plasticity and reorganisation of function. The interaction of drugs or rehabilitation with spontaneous recovery remain to be explored.

62.02 REHABILITATION OF SPATIAL HEMINEGLECT

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A set of procedures has been developed in order to improve the visual scanning of patients with hemineglect.

These techniques showed to be effective in improving the patient's ability to explore the space: the changes generalized to every-day activities and remained stabel in follow-up tests. New experimental stimulations, such as vestibular, optokinetic, vibratory and elctrical-transcutaneous, will be discussed as possible condidates for reducing the attentional bias toward the ipsilesional side.

The integration of traditional and experimental techniques can produce in a future a substantial improvement in the rehabilitation of hemineglect.

62.03 SENSORY MOTOR ACTIVATION AND CUEING: IMPROVEMENT OF SPATIAL HEMINEGLECT

Ian H Robertson
Medical Research Council Applied Psychology Unit, Cambridge, UK

Unilateral spatial neglect is in part due to competitive inhibition of lesion circuits in the damaged hemisphere by partner circuits in the undamaged hemisphere. This competitive imbalance can be reduced in a number of ways, resulting in both short-term and long-term improvements in spatial neglect. A number of examples of such short-term manipulations are given, including eye-patching and dynamic stimulation. Detailed consideration is then given to limb activation methods whereby perceptual motor circuits implicated in neglect are activated by a contralesional limb activation. Secondly, the behavioural manipulation of arousal levels is shown to significantly reduce neglect, possibly via a right-hemisphere dominant noradrenergic activation, particularly influencing inferior parietal lobe functioning. The clinical and behavioural effects of these manipulations are described, and the theoretical underpinnings of this approach to rehabilitation discussed.

62.04 Treatment of Executive Dysfunction in Brain-Damaged Patients - What can we learn from single-case studies ?

D.Y. von Cramon & G. Matthes-von Cramon
MPI of Cognitive Neuroscience, Leipzig, Germany

Executive dysfunction after acquired brain damage causes devastating effects in almost every domain of human life. In most cases executive dysfunction, including thought disorder and behavioral alterations, is accompanied with deficits of attention and memory. Pragmatic treatment approaches have been developed to help patients cope with their handicap. Five single-case studies of patients with frontal lobe damage are presented. Although heterogeneous with respect to their performance profiles, they all had no insight into the consequences of their cognitive deficits and in particular showed marked impairment of planning and problem-solving in everyday situations.

They were treated in their natural environment, the main therapeutic principle being a domain-specific adaptation of self-instructions in order to support action control and monitoring. Our findings stress the point that self-instruction as an internal strategy can be efficient even in severe executive dysfunction, provided that memory power is mainly intact. Given severe mnestic deficits, therapy may profit from conditioning procedures.

63. Symposium: Functions of the amygdala

63.01 THE AMYGDALA COMPLEX: MULTIPLE ROLES IN ASSOCIATIVE LEARNING AND ATTENTION.

M. Gallagher University of North Carolina, Chapel Hill, NC 27599 USA.

Kluver and Bucy observed that monkeys became remarkably tame after surgical removal of the temporal lobes, a phenomenon noted as early as 1888 by Brown and Schaefer. Subsequent research extended these observations to indicate that the amygdala complex plays an important role in the expression of emotional behavior, and in the association of cues with biologically significant events. Although this neuropsychology of the amygdala seems well-established, the purpose of this presentation will propose that an additional conceptualization of amygdala function is now needed. The research provides evidence that a subsystem within the amygdala provides a coordinated regulation of attentional processes. An important aspect of this new neuropsychology of the amygdala is that it may aid in understanding the importance of connections between the amygdala and other neural systems in information processing.

63.02 THE AMYGDALA COMPLEX AND CONDITIONED REINFORCEMENT: INTERACTIONS WITH THE VENTRAL STRIATUM AND IMPLICATIONS FOR ADDICTION.

Barry J. Everitt. Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, England.

The basal and lateral parts of the amygdaloid nuclear complex project substantially to the ventral striatum, including both the core and shell regions of the nucleus accumbens. Interactions between the amygdala and ventral striatum and their modulation by dopamine appear critically to underlie appetitive behaviour under the control of conditioned reinforcers.

Excitotoxic, axon-sparing lesions of the basolateral amygdala profoundly disrupt the processes by which environmental stimuli gain incentive properties and thereby control over behaviour as conditioned reinforcers. This in turn depends critically on serial interactions between the basolateral amygdala and the ventral striatum as, for example, a disconnection lesion between the amygdala and nucleus accumbens disrupts a conditioned place preference as effectively as bilateral lesions of either structure alone. Infusing D-amphetamine into the nucleus accumbens increases greatly the control over appetitive behaviour by conditioned reinforcers, an effect of psychomotor stimulant drugs that is a major determinant of their abuse potential. Indeed, lesions of the basolateral amygdala impair the acquisition of cocaine self-administration under a second-order schedule of reinforcement, i.e. acquisition in circumstances where cues associated with the effects of cocaine are of major importance. Similar lesions also disrupt conditioned opiate withdrawal in morphine-dependent rats. Thus, the amygdala is involved in the formation of associations between previously neutral stimuli and both positive and negative reinforcers, while interactions with the ventral striatum appear to underlie instrumental response output.

63.03 THE MONKEY AMYGDALA: CURRENT HYPOTHESES OF FUNCTION. D. Gaffan. Exp Psychology, Oxford University, Oxford OX1 3UD, U.K.

The two major hypotheses of amygdala function which have been put forward in the last 10 years are (1) the cross-modal association hypothesis and (2) the primary-reward association hypothesis. Recent results favour the second of these against the first, that is, they argue against a specific role for the amygdala in cross-modal learning, and instead support the idea that the amygdala is specifically involved in associating discrete external stimuli with primary reward. One important aspect of this function is in maintaining the effectiveness of secondary reinforcers, which are themselves associated with primary reward. In visual learning for an auditory secondary reinforcer, the auditory modality but not the visual modality needs to interact with the amygdala. Therefore, the question arises, by what pathways do the visual stimuli and the secondary reinforcer interact in visual learning for an auditory secondary reinforcer? Recent results suggest strongly, though indirectly, that this interaction takes place in the corpus striatum. Other possibilities have been excluded by negative results from section of other possible output pathways from visual association cortex, for example the projection to the prefrontal cortex via the uncinate fascicle. These findings therefore suggest that in visual reward-association learning a three-way interaction takes place between cortex, amygdala and corpus striatum.

63.04 WHAT HAS AMYGDALA PATHOLOGY TOLD US ABOUT AMYGDALA FUNCTION? J.P. Aggleton School of Psychology, University of Wales College of Cardiff, Cardiff, UK

Studies of amygdala damage in nonhuman primates have long suggested that the structure is vital for normal social interactions. Recent convergent findings from single case studies of people with bilateral amygdala damage are now beginning to reveal the subtle ways in which this same structure influences social signalling. Studies on the patient DR, who received a partial bilateral amygdalotomy for the treatment of epilepsy have revealed a number of deficits in the perception of affective expressions. Although DR is able to perceive the distinctive features of unfamiliar faces she is impaired in both the matching and recognition of facial expressions. These impairments are found for moving as well as static faces. DR is also impaired when requested to describe facial expressions of emotion, but she can answer questions about the facial appearance of famous people. The selective deficits help to explain how amygdala damage often impairs facial recognition, and also highlight its particular contribution to affective signalling and perception. Consistent with what is known about the anatomy of the amygdala, other studies of DR indicate that these affective deficits extent to information from other sensory modalities e.g. auditory information (prosody). Deficits concerning the recognition of facial expressions have recently been observed in other cases with bilateral amygdala damage.

64. Oral Session: Synaptic plasticity

64.01 BIDIRECTIONAL REGULATION OF PROTEIN KINASE Mζ IN THE MAINTENANCE OF HIPPOCAMPAL LONG-TERM POTENTIATION AND LONG-TERM DEPRESSION. S. Hrabetova*, T. C. Sacktor. Departments of Pharmacology and Neurology, State University of New York at Brooklyn, 450 Clarkson Ave., Brooklyn, NY 11203, USA.

Long-term potentiation (LTP) and long-term depression (LTD) are bidirectional activity-dependent modifications of synaptic efficacy. Differential states of phosphorylation have been implicated in the maintenance of these opposing forms of synaptic plasticity. Recently, protein kinase Mζ (PKMζ), the constitutively active catalytic fragment of protein kinase Cζ (PKCζ) was shown to be up-regulated in the maintenance of LTP in hippocampal CA1 region (Sacktor *et al* PNAS 90: 8342, 1993). We now report the down-regulation of PKMζ in the maintenance of homosynaptic long-term depression.

Hippocampal slices were prepared from 16-21 days old Sprague-Dawley rats. Field EPSPs were recorded from stratum radiatum using standard extracellular technique. LTD was induced by 3Hz stimulation of Schaffer collaterals for 5 min. Biochemical assay of PKC isozymes in LTD vs control slices revealed down-regulation of PKMζ in LTD maintenance. The loss of PKMζ was not observed when LTD was either prevented by an NMDA-receptor antagonist or reversed by high-frequency stimulation. Bath application of chelerythrine, a specific inhibitor of PKC's catalytic domain mimicked and occluded LTD. Conversely, saturated LTD occluded the effect of the PKC inhibitor.

We conclude that 1) down-regulation of PKMζ is important in the maintenance of LTD and may contribute to persistent decrease of phosphorylation and 2) the regulation of PKMζ is a unifying molecular mechanism for bidirectional synaptic plasticity.

64.02 LOSS OF DENDRITIC "SPINE COLLARS" IN DENTATE GYRUS FOLLOWING LTP IN THE AWAKE RAT. D.A.Rusakov*, M.G.Stewart, G.Richer-Levin, M.Sojka, H.A.Davies, T.V.P.Bliss. The Open University, Milton Keynes MK7 6AA; National Institute for Medical Research, Mill Hill, London NW7 1AA; U.K.

Relatively homogeneous groups of dendritic spines from granule cells of hippocampal dentate gyrus (middle segments of the perforant path) were studied 24 hours after LTP was induced unilaterally in seven awake rats. Golgi stained preparations from both hemispheres were analysed using computerised microscopy. Arrangement and lengths of spines were estimated using an image recognition routine and the line skeleton transformation[1]. Statistical hypotheses were tested using hierarchical *ANOVA* (Randomised Blocks) with the potentiated, and non-potentiated hemispheres matched. 3D (true) spine density was estimated using an unbiased tilting disector routine[1].

Our data have shown: (i) the statistically significant presence of the clusters of spines ("spine collars") along dendrites in most experimental samples; (ii) a decrease in the occurrence of "spine collars" after LTP (iii) a decrease in the mean visible spine length, and a decrease in the true spine density along dendrites in the potentiated, versus non-potentiated hemisphere.

The data obtained are suggestive of synaptic re-arrangements which contribute to the increased synaptic efficacy during LTP.

[1]Rusakov DA, Stewart MG (1995) *J. Neurosci Methods* (in press)

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64.03 CYCLIC AMP-DEPENDENT INDUCTION OF LONG-TERM POTENTIATION AND DEPRESSION IN THE NEOCORTEX. N. Kato[1,2] * and H. Yoshimura[2] Research Development Corporation of Japan[1], and Department of Integrative Brain Science, Kyoto University Faculty of Medicine, 606 Kyoto, Japan[2]

cAMP-dependent phosphorylation has been reported to be necessary for a late phase of long-term potentiation (LTP) but not for the early period within 1 hour after finishing the induction protocol. Requirement of cAMP at such a late phase has led to the hypothesis that cAMP-dependent gene expression may be involved. On the other hand, cAMP-dependent phosphorylation has been known also to modulate non-NMDA-type glutamate receptors rather acutely, raising the possibility that cAMP may exert its influence at the early phase of LTP induction as well. To study the acute effects of postsynaptic cAMP on synaptic efficiency in visual cortex slices, we increased intracellular cAMP concentrations by using photolysis of caged cAMP, which had been injected into the cell through the recording electrode. In half the recorded cells, the amplitude of excitatory postsynaptic potentials were enlarged within a few minutes after the photolysis and lasted up to the end of the 30-min recording session. In complementary experiments, relation of cAMP and long-term depression (LTD) was studied by intracellular recordings from visual cortex slices. Trans-1-aminocyclopentane-1,3-dicarboxylic acid (tACPD) at the concentration of 10μM is known to activate cAMP-linked subtypes of metabotropic glutamate receptors, but not to stimulate inositol-coupled subtypes very much. Tetanic stimulation in the presence of tACPD and d-(-)-2-amino-5-phosphono-pentanoate (APV), but not tACPD alone, was effective in eliciting LTD, which lasted for at least 30 min. These findings implicate roles of cAMP at early phases of induction of synaptic plasticity, during which time a direct involvement of cAMP-dependent gene expression appears to be less likely than during the late phases.

64.04 LONG-TERM DEPRESSION CHANGES EPSP RECOVERY FROM SHORT-TERM DEPRESSION IN NEURONS OF *HELIX POMATIA*. T.S.S. Schilhab and G.R.J. Christoffersen*
Neuroscience Unit for Cognition and Memory, August Krogh Instituttet, University of Copenhagen, Denmark.

After a single EPSP has been elicited in neuron RPa3 in *Helix pomatia* a subsequent EPSP displays short-term depression. The level of depression depends on the delay between the initial EPSP and the second EPSP, but also upon the time interval spacing the pairs of stimuli. This effect can be expressed in recovery curves, showing the ratio A2(t)/A1 as a function of the delay (t, sec.). A1 and A2 are measures of the amplitudes of the first and second EPSP in a pair.

When using at least 6 minutes between the pairs of EPSP's, it was found that the initial part of the recovery curve was dominated by a period of "inverse recovery", rendering for instance A2(3)/A1 larger than A2(45)/A1. It was further found, that this characteristic feature was only exhibited, if the recovery curve was based on results obtained early in the experiment. In contrast to this, if the recovery curve was obtained later in the experiment, after the induction of long-term depression (LTD), then the period of inverse recovery was abolished. LTD was induced by four series of 30 EPSP's (at 1/10Hz); the series were spaced by 10 minutes.

Since A2(t)/A1 was larger for t = 3 sec. than for t = 45 sec., it follows that EPSP series of 1/3 Hz should depress less than EPSP series of 1/45 Hz. This was found to be the case. After LTD, A2(t)/A1 was less for t = 3 sec. than for t = 45 sec. Consequently series of EPSP's depressed more at 1/3 Hz than at 1/45 Hz.

It can be concluded, that the formation of LTD abolished the period of "inverse recovery" and thereby reversed the frequency dependency of short-term depression.

64.05 ROLE OF PHOSPHORYLATION PROCESSES IN SYNAPTIC PLASTICITY: AN IN VIVO TESTABLE MODEL. Di Luca M. Institute of Pharmacological Sciences, University of Milano, Milano, Italy.

An animal model characterized by cellular ablation occurring within cortex and hippocampus has been obtained by exposing rats "in utero" to a potent antiproliferative agent: Methylazoxymethanol (MAM). This compound shows a peculiar selectivity of action for actively dividing neuroepithelial cells and when administered at gestational day 15 is able to produce a hypoplasia of cortex and CA areas of hippocampus so that in adulthood the treated animals show alterations of cognitive processes, as evidenced in several tests for learning and memory. Moreover in hippocampal slices obtained from MAM-treated animals both LTP and LTD cannot be induced in CA1 region. Furthermore the pretreatment with D-serine, an agonist at the glycine site of the NMDA receptor complex, was able to restore LTP in CA1 field. Molecular studies in the hippocampus of MAM-treated rats have shown that: a) basal phosphorylation of B-50/GAP-43, a specific presynaptic substrate for PKC, studied by means of quantitative immunoprecipitation is increased by 51.4±7% if compared to control animals; these results have been confirmed by measuring directly the in vivo phosphorylation state of PKC substrates, such as B-50 and neurogranin, in acidic extracts of specific brain areas with electrospray mass spectrometry, a technique allowing for the determination of molecular masses of dephospho- and phospho-forms of B-50 and neurogranin simultaneously in single rat brain areas; b) the proportion of PKC isozymes present at presynaptic level is increased in the membrane compartment c) basal and potassium evoked release of glutamate is increased. On the contrary at postsynaptic level, the translocation of PKC γ, is markedly reduced in hippocampus of these animals. These data further confirm the role of PKC in mechanisms underlying long term changes in synaptic efficacy ,suggest that different subspecies may play a differential role.and that this animal model is of particular interest in studying the in vivo the role of phosphorylation processes in synaptic plasticity.

64.06 PTU TREATMENT REDUCES LTP IN AREA CA1 OF NEONATAL RATS W.D. Niemi[1,2*], K. Slivinski[1] and D.O. Carpenter[2] Dept. of Biology, Russell Sage College[1], Troy, NY 12180, and Wadsworth Center[2], N.Y.S. Dept of of Health, Albany, NY 12201, USA

Unweaned neonatal Wistar rats were subjected to 1g/L propylthiouracil (PTU) in their drinking water and via nursing. The mothers were not subjected to PTU during pregnancy nor the first wk postpartum. The pups were not weaned in this study. Four pups were sampled at 1 wk intervals and transverse hippocampal slices (450um) were made on a vibrating slicer and allowed to recover for 90 min in 34 °C oxygenated Krebs after which time they were mounted in the recording chamber. Paired-pulse facilitation (PPF), post-tetanic potentiation (PTP), and long-term potentiation (LTP) were assessed. Neonates from PTU-treated mothers showed significant decreases in PPF ($p<.05$) and PTP ($p<.05$), with the greatest decrease occurring in LTP (1 hr) ($p<0.01$) when compared with age-matched controls.

64.07 CA^{2+} SIGNALS ASSOCIATED WITH THE INDUCTION OF LONG-TERM POTENTIATION AND LONG-TERM DEPRESSION IN PYRAMIDAL CELLS OF THE RAT VISUAL CORTEX. C.Hansel*, A.Artola[1] and W.Singer. Max-Planck-Inst. for Brain Research, Deutschordenstr.46, 60496 Frankfurt,FRG. [1]Present address: Dept. of Neurobiology, ETH-Hoenggerberg, CH-8093 Zürich.

We characterized Ca^{2+} signals evoked by tetanization patterns suitable for the induction of LTP and LTD in layer II/III pyramidal cells of rat visual cortex slices, using the fluorescent Ca^{2+} indicator fura-2. Slices (200-250μm) were obtained from 5-7 week-old rats. Sharp microelectrode recordings were used to measure responses to stimulation in either layer IV (conditioning pathway) or lateral layer II (control pathway). Three different plasticity patterns were established in cells not filled with the indicator dye. LTD was reliably induced by 5x repeated 50Hz stimulation (8/9 cells). Application of only one 50Hz burst reduced the success rate in LTD induction to 50% (3/6 cells). Pairing of the repetitive 50Hz stimulation with a postsynaptic 20mV-depolarization and lowering of $[Mg^{2+}]_o$ led to reliable induction of LTP (6/7 cells). These tetanization patterns were applied to cells filled with fura-2 and changes of dendritic $[Ca^{2+}]_i$ were assessed using an intensified CCD camera. Repetition of 50Hz bursts (LTD pattern) increased burst-induced Ca^{2+} elevations, although Ca^{2+} levels nearly completely recovered to baseline during the 10s long interburst-intervals (1x50Hz burst: n=12; 5x: n=7). In contrast,Ca^{2+} levels accumulated during application of the LTP inducing tetanization pattern (n=5) to levels higher than those measured during LTD induction. In summary, Ca^{2+} signals measured during induction of LTD and LTP differed in terms of both amplitude and duration, thus supporting the assumption of different Ca^{2+} dependent thresholds for the induction of LTD and LTP.

64.08 LONG-TERM POTENTIATION IS NOT IMPAIRED IN THE DENTATE GYRUS OF *mdx* MICE IN VIVO A.K. Sesay*, M.L. Errington, K. Voss, F.A. Lai and T.V.P. Bliss. Division of Neurophysiology, MRC National Institute of Medical Research, Mill Hill, London NW7 1AA

Moderate non-progressive cognitive impairment is a consistent feature of Duchenne muscular dystrophy (DMD) although no CNS abnormality has yet been identified. Marked alterations in calcium channel physiology and elevated intracellular calcium concentrations have been demonstrated in DMD myocytes, and in the *mdx* mouse strain, a dystrophin-deficient mouse model. The increased susceptibility of the hippocampal CA1 pyramidal neurones from *mdx* mice to hypoxia-induced loss of synaptic transmission suggests that loss of brain dystrophin correlates with impaired cognitive function (1).

We have previously identified a distinct dystrophin transcript in the brain post-synaptic density which is phosphorylated in a calcium and calmodulin (Ca^{2+}-CaM) dependent manner (2). In this study we have compared long-term potentiation (LTP) in vivo in dentate gyrus in *mdx* mice and in age-matched normal mice. There was no significant difference in the LTP produced in the two groups (26.5 ± 5.4% *mdx*, 26.7 ± 3.8% control, 55 mins after potentiation; mean±SEM, n=8). No obvious changes were observed in the endogenous Ca^{2+}-CaM dependent protein kinase activity in tissue homogenates prepared from the dentate gyrus 55 minutes following LTP induction in the two groups. These experiments suggest that the genetic deficiency of murine dystrophin in the brain does not impair this type of synaptic plasticity in the dentate gyrus of *mdx* mice.

1.Mehler et al (1992), PNAS 89, 2461-2465
2.Sesay et al (1995), 12th Brain Research Association Abstracts, 30.7

65. Oral Session: Cognition

65.01 MODULATOR ROLES PREDICTED BY COGNITIVE MODELS. A. de Callataÿ, PhD, XL Knowledge Lab, av. Général de Gaulle, 49/11, Ixelles, Brussels, B-1050, Belgium.

The presentation shows how recent biological findings have made more plausible a mapping of cognitive models for some brain functions. Rule-based models predict rhythms synchronized (by thalamus), winner-takes-all symbol choice (by chandelier cells), synaptic all-or-none learning (by altering the *self-maintained homeostasis* restoring the dendritic spine shape), and time-changing sequential control of *processing modes* (by modulators directed to interconnected groups of cortical neural networks).

Invariant temporal rules associate the symbols of position and speed at decision and result time. Rules cannot be memorized before the result. Thus, when the recognizing *passive mode* of a network group is changed in a synchronized *active mode* for all-or-none decisions (perception, planning, command or memorization), the active symbols must be kept. Ach bursts hold the On/Off cell states and cancel inputs. Channel responses are changed by second messengers triggered *by fast up-and-down variations of modulators* produced by bursts (or fast firings) of midbrain radial cells and *not by the measured average concentrations*. The sparse logical impulses required by AI models are here only the Ca-dependent cell bursts.

For delays between decision and result, Ach neurons are here kept active by dopamine. In basal ganglia, a striatum motivation neuron held active by Ach starts learning when dopamine is suddenly reduced. This reward induces proteins reinforcing the circuits of the recently active loop commanded by bursting dopamine evaluation cells. For sparsity, serotonin bursts *enable* decisions only in few brain areas. NE bursts *keep active* few interesting representations. Decisions produce *rhythmic sleep-like activity,* but only in few regions selected. Memorization produces *epileptic-like activity,* but in very few neurons. Besides explaining many human behaviors, models computing in steps explain some aspects of brain diseases (developed in *Natural and Artificial Intelligence,* Elsevier, 1992).

65.02 A PET study of Visual Imagery in memory retrieval P.C. Fletcher, C.D. Frith, T. Shallice, R.S.J. Frackowiak and R.J. Dolan
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Activation of a medial parietal area, the Precuneus, has been demonstrated in previous functional imaging studies of memory[1] and it has been suggested that this activation may reflect the use of a visual imagery as a mnemonic strategy. We tested this hypothesis by measuring regional cerebral blood flow (rCBF) in healthy volunteers engaged in cued paired associate retrieval. During 6 measurements the associates were strongly visually imageable (e.g. River...Stream); during the other 6 measurements, the associates were only weakly imageable (e.g. Justice...Law). The degree of imagery used was measured using subjective rating scales and differed significantly across the conditions.

Recall of strongly imageable paired associates was associated with significant activation of the Precuneus, confirming our prediction of its involvement in visual imagery. Recall of weakly imageable paired associates was associated with a left prefrontal activation, possibly indicating the tendency towards phonological/semantic strategies when visual imagery was less possible.

[1]Shallice, T. et al *Nature*. 368. 633-635 (1994).

65.03 THE INFLUENCE OF SPATIAL PERCEPTUAL BIAS ON THE MOTOR RESPONSES IN NEGLECT PATIENTS.

E. Làdavas*, R. Rubini, A. Farnè Department of Psychology, Univ. of Bologna and Hospital "I Fraticini" INRCA, Firenze.

The aim of the present study was to verify the ability of neglect patients with right hemisphere lesion to localize stimuli presented in the left (LVF) and right (RVF) visual fields. A central fixation stimulus (FS) and three stimuli (LEDs) were presented to the left (LVF) and to the right (RVF) of the FS. Three different conditions were run. In the first condition (Detection task), the patients were instructed to release the response button when a stimulus appeared in one of the six positions. In the second condition (Detection and Manual Localization task), the patients had to release the response button and to point at the location where the stimulus had been presented. In the last condition (Verbal Localization task), the patients had to localize the position of stimuli by naming the number written above each stimulus position. The results show that the accuracy of the responses in the detection and localization tasks differed significantly in the two visual fields: the patients were impaired only when the tasks required responses to the LVF stimuli. Moreover, the deficit was more pronounced in the localization than in the detection task, without significant differencies between verbal and manual localization responses. This type of error showed a systematic dislocation towards the side of the lesion. In conclusion, the results seem to show that one specific aspect of neglect is a deficit in localizing visual stimuli and that many observed abnormalities in motor performance may have resulted from a spatial perceptual bias in sensory coding.

65.04 SYNTACTIC CONSTRAINT IN AUDITORY WORD RECOGNITION. AN EVENT-RELATED-POTENTIALS STUDY.

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Psycho linguistic studies demonstrated that syntactic information given by the article facilitates auditory word recognition processing in language with grammatical gender marking. In order to precise the electrophysiological correlates of this gender effect on auditory lexical access for nouns, two experiments using ERPs were conducted.

In the first one, subjects were presented with three syllable noun phrases in which the singular definite article was either compatible or incompatible with the gender of the related noun. The plural article served as a neutral context. ERPs were recorded while the subjects were passively listening to the noun phrases. Contrary to behavioural data, the ERPs did not show any effect of the degree of gender marking on lexical processing, particularly no effect of gender incompatibility on N400 component. But a significant effect of electrode sites was observed between 300 and 600 ms with larger responses on midline, and 900-1400 ms with larger responses over the left temporal area. In the second experiment, ERPs were recorded during a lexical decision task performed on real noun phrases presented at random within a list of pseudo-noun phrases consisting of a non word preceded by one of the French definite article. The ERPs did not show any effect of gender marking on lexical decision considered to be related to word recognition processing.

The results are discussed within the theoretical framework of the Cohort based model of auditory word recognition.

65.05 AUDITORY P300 AND NEUROPSYCHOLOGICAL TEST PERFORMANCE IN SCHIZOPHRENIA.

A. Heidrich* and W.K. Strik. Department of Psychiatry, University Hospital, Fuechsleinstr. 15, 97080 Wuerzburg, Germany.

Introduction: Previous work on auditory P300 topography in schizophrenia reported on right-sided lateralization of P300 peaks, which has been considered as evidence of left hemispheric dysfunction (1). However, inverse solutions may be possible. We investigated the hypothesis that P300 lateralization correlates with results on regional-specific neuropsychological tests that have been shown to be sensitive to lateralized dysfunction in neurologic patients. Method: The patient sample comprised 13 stabilized DSM-III-R schizophrenic subjects. Auditory P300 topographical analysis was based on a reference-independent approach; neuropsychology involved tests sensitive to lateralized temporal-lobe dysfunction, i.e. the paired associates test (2) and the nonspatial conditional associative learning test (NCAL-test, 3). Results: A significant inverse correlation was found between right-sided lateralization of the P300-maxima and the number of correctly remembered verbal paired associates ($r = -0.81$; $p < 0.001$). Moreover, there was a significant association between right-sided lateralization of the P300-maxima and the degree of impairment in the NCAL-test ($r = 0.65$; $p < 0.04$). Conclusion: The study further supports the evidence that hemispheric P300 asymmetries result from dysfunction of left hemispheric neuronal generators. Patients with impaired performance on tests sensitive to left temporal function had right-sided lateralization of the P300 peak.

Literature: (1) McCarley, R.W. et al. (1993): Arch. Gen. Psychiatry 50:190. (2) Goldstein, L.H. et al. (1988): Cortex 24:41. (3) Petrides, M. (1985): Neuropsychologia 23:601.

65.06 TEMPORAL CONSTRAINTS OF COGNITION: TEMPORAL INFORMATION PROCESSING IN DIFFERENT PATIENT GROUPS WITH ACQUIRED BRAIN LESIONS AND IN HEALTHY CONTROLS.

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Neuropsychological and psychophysical findings suggest that sensory information is processed in a discrete fashion. Here we report experimental evidence on temporal constraints of information processing in brain-injured patients with pre- or postcentral, left- or right hemispheric aquired brain lesions and healthy controls for three different temporal ranges. On a high-frequency level system states with a duration of approx. 30 ms are suggested to provide a logistical basis for elementary event identification. In this temporal range assessed by order threshold measurements patients with aphasia show selective impairments (prolongations of the order thresholds up to 200 ms). On a low frequency level elementary events are automatically linked together. This temporal integration appears to be limited to intervals up to approx. 3 seconds. Experimental evidence for this kind of pre-semantic integration comes from a number of different paradigms: in sensorimotor synchronisation subjects can anticipate stimulus occurrence up to approx. 3 seconds, but not beyond. This temporal range can be assessed with different paradigms like temporal reproduction of optic and acoustic stimuli and spontaneous alteration rates of visual and auditory ambiguous figures. Here only patients with left or right frontal lobe lesions show altered temporal behaviour. In a personal tempo tapping test assessing a temporal range which lies between the two levels mentioned above again only patients with aphasia show selective alterations in central timing.

65.07 COGNITIVE UNCONSCIOUS AND CEREBRAL LATERALITY.

E. Szelag*[(1)], K. Łazowska[(1)], E. Pöppel[(2)]. [(1)]Department of Neurophysiology, Nencki Institute of Experimental Biology, 02-093 Warsaw, POLAND, [(2)]Forschungszentrum Jülich GmbH, D-52425 Jülich, GERMANY.

The present study was designed to investigate hemispheric differences in the consciousness control. Fourteen right-handed students were presented with a computer generated pure tone. The task was to react as fast as possible or with a specific time delay to the tone-switch off by pressing a button with the index finger. The requested delays varied in their duration and the target reaction time which the subject should follow was from 200 ms to 750 ms, in steps of 50 ms. The responses were given with the left hand (addressing the right hemisphere) and with the right one (addressing the left hemisphere). There were analyzed the transformed standard deviation of the mean reaction time used to measuring response precision in 13 tasks (one with the fastest reaction and the remaining 12 with mentioned various delays). More performance variability was found rather for the short delays (target up to 350 ms) than for the long ones (target above 350 ms), especially, for the right hand responses. These results allow the conclusion that brief phases of information processing tend to less precise performance whereas those substantially longer ones elicit improved performance. This relation was considerably more distinct for the left hemisphere. To conclude, the left hemisphere specialization for speech, in particular sequential mode of information processing would then require an integration period over which new inputs can add information to a perceived stimulus event. Accordingly, it seems probable that a detection of individual phoneme could represent an unconscious mental process, whereas an increasing duration may be related to identification of particular temporal order. Unconscious left-hemisphere mental processes observed in our study may be crucial, as it seems, for speech perception.

66.01 **DISTURBANCES OF THE SPATIOTEMPORAL COORDINATION OF REACHING FOR GRASPING MOVEMENTS IN PATIENTS WITH PARIETAL LESIONS WITH AND WITHOUT APRAXIA.** F. Binkofski*, Ch. Dohle, H. Hefter, M. Schnitt+, T. Kuhlen+, H.-J. Freund. Dep. of Neurology, University Düsseldorf, +Dep. of Technical Informatics Aachen Technical University, FRG.

Reaching for grasping movements were analyzed in 5 patients with lesions of the left parietal cortex (3 with clinical signs of ideomotor apraxia [Florida Apraxia Screening Test] and 2 without apraxia) and in 3 patients with lesions of the right parietal cortex. Arm, hand and finger positions were recorded using a Selspot II optoelectronic movement recording system.

In comparison to the non apraxic patients all 4 patients with apraxia showed significantly prolonged deceleration time of the transport component. This finding was more pronounced on the side contralateral to the lesion. The evaluation of the inverse kinematics of the elbow- and shoulder joint movements (1) revealed the lack of invariant synergies of the joint velocities in the apraxic patients resulting from an initial overshoot in vertical direction of hand trajectory. This finding was less pronounced in patients with right sided parietal lesions and left sided parietal lesions without apraxia. Inverse dynamic equations (1) were used to estimate the torques (inertial, centripetal and Coriolis) at the elbow and shoulder joints. Preliminary data show that apractic patients produced abnormal torque profiles responsible for the initial overshoot and the prolonged deceleration phase.

As compared to normals and non-apraxic patients. all apraxic patients showed almost no early aperture formation (preshaping) and a marked delay in the time of maximal hand aperture which was exaggerated and performed significantly later in the deceleration phase of the reaching movement and in the close vicinity of the object.

The impairment of preshaping and the delayed and oversized maximal finger aperture in apraxic patients indicate that in apraxia the pragmatic representation of the grasped object might be disturbed. Furthermore, the impaired coordination of the proximal joint synergies and the disturbed transport component indicate that patients with left parietal lesions might problems with the transformation of extrinsic into intrinsic coordinates. The results stress the role of the left parietal cortex for visuomotor coordination during goal directed movements.

(1) Soechting, J.F and Laquaniti, F, J. Neurosci, 1981, 1, 7, 710-720.

66.02 **JOINT ROTATIONS IN SHOULDER AND ELBOW DURING POINTING AND GRASPING.**

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Although the shoulder joint has three degrees of freedom, only 2 degrees of freedom are used in pointing tasks with the extended arm (see Hore et al., J. Neurophysiol. 1992; Miller et al., Exp. Brain Res. 1992). As a consequence of this reduction of degrees of freedom, the orientation of the arm is uniquely determined for each pointing direction.

We have studied pointing movements to distant targets and to targets nearby, which requires flexion/extension movements in the elbow in addition to shoulder rotations. During these movements, the rotation vectors describing the position of the proximal arm segment lie in a 2-dimensional surface, indicating a reduction of degrees of freedom. This surface is the same as that for pointing with the extended arm. When the subjects are instructed to grasp a ball at various directions and distances from the subject, the position and orientation of the upper arm is again described by the same surface of rotation vectors. When subjects are instructed to reach and grasp for a cylinder, which requires a specific orientation of the hand, the rotation vectors for the shoulder are in the same 2-D surface as before and the final orientation of the hand is adjusted by supination/pronation of the forearm.

These results generalize previous findings on the reduction of degrees of freedom for shoulder rotations to pointing and grasping of objects at various locations relative to the shoulder. Moreover, they are compatible with previous suggestions that the transport phase (corresponding to shoulder movements) is independent of the grasping phase, which requires supination/pronation of the hand.

This study was supported by the EEC ESPRIT project MUCOM (Nr. 6615)

66.03 HIPPOCAMPAL THETA RHYTHM MODULATION DURING PASSIVE ROTATIONS AND TRANSLATIONS OF RESTRAINED RATS TRANSPORTED ON A ROBOT.

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To study the contributions of self-movement and especially vestibular information on spatial processing in the hippocampus, slow wave activity was measured in water-deprived rats restrained in a hammock with the head fixed in a stereotaxis-like holder mounted on a mobile robot (Robosoft, France). The rats were trained to receive a drop of water only in one corner of a square arena. The recordings were made from high-impedance glass micropipettes with a screw in the frontal cranial bone or an electrode in adjacent hippocampus as reference; filter settings were 0.1-100 Hz.

In experiments in light and in darkness the rats were passively translated or rotated in different directions at various speeds (50-600 cm/sec (linear); 50-300 deg/sec (rotations)). Each experimental session lasted about 30 minutes and included about 100 movements. For rotations and for translations, power spectrum analysis of 2 sec intervals were made and the amplitudes were compared by paired t-tests. In 15 sessions in 5 rats the amplitude of the theta-frequency band (7-10 Hz) was significantly greater ($p<.05$) during rotations as compared with translations. This effect was maintained in light as well as in darkness indicating a role for vestibular inputs. Support: Human Frontiers Program, ESPRIT/MUCOM 6615 & Cognisciences CNRS.

66.04 VERTICAL DISCONJUGATE PLASTICITY: EFFECT OF VIEWING DISTANCE. Z. Kapoula*, T. Eggert and M.P. Bucci, LPPA, CNRS-Collège de France, Paris, France

We tested the effect of viewing distance on disconjugate plasticity of vertical post-saccadic eye drift. Identical patterns consisting of a circle with a fixation point and 53 randomly segmented lines were presented one to each eye (dichoptic viewing). At first the patterns were superimposed; subj perceived a fused pattern. At the end of each vertical saccade along the midline (typically 8°, recorded by an IR device), one pattern drifted up the other down. Subj were trained for 3 hrs. Four experiments were done. *1) Far viewing*: four subj seated at 1 m from the screen; the horizontal vergence angle was 3.4°. *2) Natural close viewing*: five subj seated at 0.57 m from the screen; the vergence angle was 6°. *3) Partial simulation of close viewing*: three subj seated at 1 m from the screen but a crossed offset of 6° was applied to the patterns so that vergence was 6°. *4) Quasi-complete simulation of close viewing*: Three subj seated at 1 m; the patterns were offset by 6° and accommodation was adjusted by the use of spherical lenses (-0.75 diopters). The size of the patterns was always 35°. The drift of the patterns was always exponential with its amplitude 5% of the antecedent vertical saccade, producing a vertical disparity of 10%. Pre- and post-training binocular recordings were made with search coils. Adaptation was assessed from saccades in an open-loop condition.

Training at far viewing induced a small disconjugate change in vertical post-saccadic drift that did not persist in the open loop condition (group mean 0.07°, range: -0.36 to 0.33°). By contrast, natural close viewing induced a larger change that persisted in the open loop condition (mean 0.30°, range: 0 to 0.71). Partial simulation of close viewing produced a smaller change (0.16°, range: -0.15 to 0.57). Quasi-complete simulation produced a stronger, less variable change (0.22°, range: 0.04 to 0.39), but still smaller than that obtained in natural close viewing.

We conclude that vertical disconjugate plasticity increases with proximity. It seems to be modulated by a central mechanism based on both the horizontal vergence angle and accommodation; this mechanism is also sensitive to the subjects'awareness of proximity using other high level cues.

66.05 EYE CONJUGATION DURING BUILD-UP OF OPTOKINETIC NYSTAGMUS IN THE PIGMENTED RAT.

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We studied the binocular responses to both binocular and monocular constant velocity (5-80°/s) and sinusoidal (0.05-2 Hz, peak velocity 15°/s) optokinetic hoizontal stimulation in intact pigmented rats and in rats that had recieved bilateral lesions to the visual cortex at least one month in advance. Binocular eye movements were recorded by means of a phase detection coil system with the head restrained. The velocities of both eyes were measured 0.5 and 1.0 s after the onset of optokinetic stimulation anbd after the response had reached a steady state. After 0.5s of binocular stimulation, the velocity of the temporonasally stimulated eye was about 5% higher than that of the nasotemporally stimulated eye for all stimulus velocities and for both directions of stimulation. The difference of velocities between the two eyes was smaller 1 s after stimulus onset, and negligible in the steady state. This indicated an improvement in conjugation during the build-up of the velocity of the optokinetic response. This conclusion was supported by the better conjugation observed with sinusoidal stimulation at lower frequencies of oscillation, when the contribution of velocity storage is predominant, compared to stimulation at higher frequencies. Lesions of the visual cortex did not affect velocity differences bewteen the two eyes. Our data indicate therefore, that, in the rat, subcortical structurew mediate the coordination between the two eyes during optokinetic nystagmus and suggest that, for good conjugation, the velocity storage mechanisms must be charged.

66.06 VESTIBULAR AND OPTOKINETIC EFFECTS ON EYE PURSUIT IN MACAQUE MONKEYS. G. Schweigart*[1], Th. Mergner[2]. [1]Dept. of Neurophysiology, Ruhr-University MA4, 44780 Bochum, Germany; [2]Neurocenter, 79106 Freiburg, Germany

Interaction of smooth eye pursuit with the vestibulo-ocular (VOR) and the optokinetic reflex (OKR) was studied in two macaque monkeys. Stimuli consisted of horizontal sinusoidal oscillations (usually, +/-8°) of a visual target (light spot, 0.5°; eye pursuit), a rotation chair (vestibular stimulation, VEST) and a projected patch pattern (optokinetic stimulation, OKS), as well as of various combinations thereof.

The eyes tended to remain near the target, independently of the pursuit-VEST-OKS combinations used. However, there were clear effects on pursuit gain. OKS had some effect at stimulus frequencies below 0.1 Hz; depending on whether OKS was counter-phase or inphase with respect to the pursuit stimulus, pursuit gain varied between 0.7 and 1.3 (at 0.025 Hz). VEST effected pursuit gain at frequencies above 0.2 Hz; at 0.8 Hz, gain varied between 0.5 and unity. Since both, VEST and OKS seem to effect pursuit in a graded way, the effects can be described in terms of linear interactions.

The VOR 'helps' eye pursuit only if the head-in-space rapidly moves opposite to the target-vs-head motion. In contrast, OKS 'helps' pursuit only if it slowly moves in the same direction with the target.

66.07 DEVELOPMENT OF POSTURAL ADJUSTMENTS IN SITTING INFANTS - EFFECT OF MATURATION AND TRAINING.

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Postural responses during sitting on a moveable platform were studied longitudinally in 20 healthy infants at 5-6, 7-8 and 9-10 months of age. Testing consisted of sitting on a moveable platform, which produced sudden forward (FW) and backward (BW) translations. Meanwhile surface EMGs of neck-, trunk- and legmuscles and kinematic data were recorded. The parents of nine children trained their child's balance daily (3x5 min.) during the whole study period.

At the youngest testing age, when none of the infants could sit independently, highly variable but direction-specific muscle activation patterns were present. FW translations resulted predominantly in an activation of 'ventral' muscles while 'dorsal' muscles were inhibited. During BW translations 'dorsal' muscles were preferably activated. This suggests that postural adjustments develop via an innate repertoire of primary direction-specific response patterns. With increasing age the variation in muscle activation patterns decreased, resulting in selection of the most complete patterns of synergist activation. Next, the ability developed to modulate the amplitude of the selected responses. Training facilitated response selection and accelerated the development of response modulation.

66.08 A QUANTITATIVE STUDY OF SACCADES AND SLOW DRIFTS PRODUCED IN RESPONSE TO THE ELECTRICAL STIMULATION OF THE SUPERIOR COLLICULUS IN THE CAT.

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A quantitative study of rapid eye movements produced in response to the electrical stimulation of the superior colliculus (SC) in alert, behaving, head-fixed cats demonstrated that their amplitude and direction is influenced by the intensity of stimulation, the electrode location and the initial position of the eyes, while their duration also depended on the intensity of stimulation. Besides saccades, electrical stimulation of the feline SC gave rise to slow drifts. A quantitative study of slow drifts demonstrated that they can be as sensitive to the initial position of the eyes as saccades. The time course of slow drifts was such that they could be due to a projection of the SC onto extraocular motoneurons either directly (infrequent) or via the neural integrator (frequent). A model that includes such a variety of connections between the SC and extraocular motoneurons can produce realistic combinations of fast and slow eye movements when its input is a step function of time (supported by HCM Grant #ERBCHRXCT-940559).

67. Poster Session: Cell biology II

67.01 KINETICS AND SODIUM INDEPENDENCE OF ^{3}H TIAZOFURIN TRANSPORT FROM BLOOD INTO THE GUINEA PIG BRAIN.

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Tiazofurin, a nucleoside analogue, is a selective inhibitor of the inosine monophosphate dehydrogenase (IMPDH) activity. Transport of tiazofurin from blood into the brain was investigated using brain vascular perfusion technique in guinea pig. The obtained results showed that transport of ^{3}H tiazofurin from blood into the brain could be inhibited in the presence of increasing concentrations of unlabelled tiazofurin. Therefore, that process seems to be carrier mediated. Kinetics parameters of transport were determined for three examined regions (hippocampus, nucleus caudate and cortex). Values of Michaelis-Menten constants (K_m) were from 279.34 ± 60 to 370.81 ± 104.94 µmol/l and suggested low affinity of tiazofurin to carriers at the luminal side of the blood brain barrier (BBB). Maximal capacity of transport ranged from 652.89 ± 108.67 to 743.72 ± 180.70 pmol/min/g. Those values are in the same range as the values for capacity of transport of endogenous nucleosides *via* adenosine transport system. Perfusion with sodium free perfusing medium did not cause significant change in ^{3}H tiazofurin blood-to-brain transport. Therefore, it can be concluded that sodium dependent cotransport is not involved in ^{3}H tiazofurin transport through the BBB.

67.02 A DOUBLE LABELING IMMUNOHISTOCHEMISTRY AND IMMUNOGOLD STUDY OF THE RADIAL GLIA AND ASTROCYTES IN THE MESENCEPHALON OF *Gallotia galloti*.

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In the postnatal and adult mesencephalon of the lizard Gallotia galloti Astrocytes and Radial Glia coexist. More glial cell types can be distinguished by using specific antibodies directed against Glutamine Synthetase and GFAP. Optical (immunofluorescence) and electron (immunogold) microscopy show GFAP$^+$ (strong label) and GS$^+$ (weak label) perikarya located in the walls of the mesencephalic ventricule and of Silvius aqueduct. Strongly GFAP immunopositive but weakly GS$^+$ radial fibers ending with subpial and feet originate from these cells. In addition to GFAP$^+$/GS$^+$ radial fibers, GS$^+$ ovoidal cells (either isolated or aligned or assembled in small clusters) and strongly GFAP$^+$ star-shaped cells with multiple processes were observed in the central layers of the optic tectum and in the nuclei in the tegmentum.

At the EM level, the immunogold technique shows that neurons always are GFAP$^-$/GS$^-$, whyle some cells in the ventricular wall are GFAP$^+$/GS$^+$ and GFAP$^-$/GS$^+$, mature astrocytes are GFAP$^+$/GS$^+$. Many GFAP$^-$/GS$^+$ ovoidal cell are oligodendrocytes but other have the caracteristics of astroblast. End feet on blood vessels, whether originating from star-shaped perikarya or from perikarya located in the ventricular wall were strongly GFAP$^+$ and GS$^+$ in immunofluorescense but weakly immunopositive in immunogold. It would appear that vascular end feet even when originating from GFAP$^+$/GS$^+$ cells contain only very low amounts of GS. In conclusion, detectable amounts of GS appears to be present in some astrocytes and in radial glia. The enzyme appears to be segregated within the cell: i,e. more abundant in the cell body, absent or very scarce in the end feet. The GFAP$^+$/GS$^+$ astroblasts might be quiescent glial cell precursors, activated in case of CNS lesion. Differently from what decribed in mammals, GS is present also in oligodendrocytes but never in neurons.

67.03 ASTROCYTES EXPRESS REGIONAL HETEROGENEITY AFTER γ-IFN INDUCTION OF THE IMMUNO-REACTIVE PHENOTYPE

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γ-interferon (γ-IFN) induces the astrocytes to adopt a reactive phenotype. There are a few major points that characterise this reactive state: cell proliferation, *in vivo and in vitro* expression of MHC I and II, expression of several adhesion molecules, an increased production of interleukin (IL)-1 and IL-3 and as recently shown the synthesis of an inducible nitric oxide (NO)-synthase. γ-IFN also primes astroglial cells to release IL-6 and TNF-α.

Quite a number of works document that cerebral astrocytes do not constitute a homogeneous population inside the brain (for review see Wilkin et al.,1990). In this *in vitro* study, we analysed the regional heterogeneity of this population after induction of the immuno-reactive phenotype. We studied the astrocyte heterogeneity by investigating the ability of γ-IFN to induce the expression of Ia molecules on cultured astrocytes, as well as the production of NO radicals and the synthesis of IL-6. These studies were performed on five different brain regions: cortex, brain stem, hippocampus, striatum and septum. The hippocampus expresses the highest levels of Ia molecules and the striatum and the septum the lowest, cortex and brain stem MHC class II showing intermediate levels. The production of NO radicals follows the same scheme as the MHC class II expression, in fact the hippocampus shows the highest levels. The basal IL-6 production also varies between brain regions. γ-IFN incubation does not affect this differences. We conclude that immunological activation reveals regional differences in the cerebral astroglial population.

67.04 CD9 IS INVOLVED IN NEURONAL CELL ADHESION AND HAS A SIGNALING PATHWAY INDEPENDENT FROM INTEGRINS

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CD9, originally discovered on hematopoietic cells, is also expressed on the cell surface of neurons and glia. The interaction of CD9 with a yet unknown ligand partially mediates cell adhesion. The intracellular signaling cascade triggered through CD9 is independent of the integrin signaling. We are using the rat pheochromocytoma cell line -PC12- to investigate the role of CD9 in adhesion and neurite outgrowth. The results will be presented.

67.05 REGULATION OF NERVE GROWTH FACTOR- GENE EXPRESSION IN VIVO IN MICE. K.Müllhofer*, K.Dethleffsen, M.Meyer, E.Wolff §, G.Brehm § and H.Thoenen. Max-Planck-Institut für Psychiatrie, 82152 Martinsried, FRG; § LMU, 81375 München, FRG

Nerve growth factor (NGF) is essential for the development of the peripheral nervous system. Temporal and spatial expression patterns as well as strength of expression are precisely controlled. However little is known about mechanisms regulating NGF expression in developmental context. To approach this question, we fused 5kb and 2kb NGF-promoterfragments including the first exon and a part of the first intron of the NGF-gene to a lacZ-reporter gene. These constructs were used to generate transgenic mice by pronucleus injection. LacZ-expression was examined by histochemical staining of tissue sections in four transgenic mouse-lines with the 2kb and two with the 5kb promoterfragment: The lacZ-expression in the submandibular gland of adult mice paralleled that of the endogenous NGF-gene in all six lines. Although in other tissues the pattern of lacZ expression differed between the lines, characteristic features appeared repeatedly and paralleled the expression of the endogenous NGF-gene. No lacZ-expression could however be observed after lesion of the sciatic nerve, in iris-cultures and in cultured kidney-fibroblasts.

In conclusion the 2kb-NGF-promoterfragment appears to contain several elements needed for correct temporal and spatial expression of the NGF-gene during development. However, the precise pattern of lacZ-expression was highly influenced by the site of its integration in the mouse genome. Furthermore, additional regulatory elements seem to be necessary for expression of the NGF-gene in cultured fibroblasts, iris-culture and after lesion of the sciatic nerve.

67.06 ESTABLISHMENT OF ENTERIC GLIAL CELL CULTURES FROM ADULT HUMAN GUT M. Manghetti, M.G. Mumolo*, P. Bongioanni[2], M. Castagna[1], M. Morisi[1], F. Costa, M. Bellini, S. Marchi, G. Maltinti, *U.O. Gastroenterologia (I Clinica Medica), [1]Istituto di Anatomia Patologica - University of Pisa; [2]Scuola Superiore di Studi Universitari e di Perfezionamento Sant'Anna - Pisa (ITALY).*

The enteric nervous system is diffusely located throughout the intestinal wall; it consists of nervous plexuses and ganglia, comprising neurons and gliocytes. Enteric glial cells differ from peripheral nervous system gliocytes and share some histological and functional features with central nervous system astrocytes. To our knowledge, enteric glial cultures have been established only from some animal species.

The aim of the present study was to establish enteroglial cell cultures from the adult human gut. Surgical specimens were washed in balanced salt solution with antibiotics and antimicotics, and dissected to get muscle layer (containing myenteric plexus). Some fragments were incubated in collagenase, others in collagenase, and then in trypsin. Cell suspensions were incubated in culture chambers poly-l-lysine-coated with DMEM/F12 supplemented with fetal calf serum, antibiotics and cytosine arabinoside. Cultures underwent cytolysis in the presence of complement and specific antibodies (Ab,) against neurons and fibroblasts. Culture medium was renewed twice a week, and cells cultured for 4 weeks. Cell types were identified with immunocytochemistry using anti-S100, anti-glial fibrillary acidic protein (GFAP), anti-neurofilaments (NF), anti-actin and anti-vimentin Ab,. After 4 weeks, we observed GFAP$^+$, S-100$^+$, rare NF$^+$ cells and few, if any, actin$^+$ and vimentin$^+$ cells. Combined collagenase and trypsin treatment allowed us a better cell dissociation than the only collagenase treatment. Ab-dependent complement cytolysis allowed us to get highly purified enteroglial cultures. Our study provides a method for the establishment of purified enteroglial cell cultures, an useful "in vitro" model for investigating the role of human enteric glia in certain physiological and pathological conditions.

67.07 EFFECTS OF DETERGENTS ON RAT BRAIN DIPEPTIDYL AMINOPEPTIDASE ACTIVITIES. MC. Muñoz*, C. Arenas, M. Ramírez, C. Aguirre and F. Alba. Department of Biochemistry. University of Granada. Spain.

Dipeptidyl aminopeptidases (DAPs; EC 3.4.14.-) are a group of enzymes that catalyze the sequential release of dipeptides from the N-terminal end of many bioactive peptides. The DAP enzymes have strict substrate requirements, and are only able to split dipeptide residues from peptides and proteins with an unprotected NH_2-terminus. At least four distinct enzymes with DAP activity have been purified and identified from brain. DAP I to IV were assayed, using the corresponding ß-naphthylamide derivatives of glycyl-L-arginine-, L-lysyl-L-alanine-, L-arginyl-L-arginine- and glycyl-L-proline, in the soluble and membrane-bound fractions of rat brain, and the effects of the detergents Triton X-100 and sodium deoxycholate on their activities were studied. Dipeptidyl aminopeptidases I and II were significantly inhibited in the presence of sodium deoxycholate, but were not affected by Triton X-100. However, dipeptidyl aminopeptidase III was not influenced by either detergent, whereas the activity of dipeptidyl aminopeptidase IV was stimulated in the presence of Triton X-100, but remained unaffected by deoxycholate. These effects were partially or totally reversed after detergents were removed from the medium with adsorbent polymeric beads (Biobeads SM2). Although detergents may have different effects on each DAP activity, the behavior of each enzyme activity in the presence of these substances was similar regardless of their subcellular location. These findings suggest that, as with other aminopeptidases, each of these proteins corresponds to the same molecular species in two different cell compartments. In addition, our results indicate that DAPs are not integral membrane proteins, because the detergents can be removed by Biobeads without loss of activity. An integral membrane enzyme would normally be expected to aggregate in the absence of detergent, and to lose at least part of its catalytic activity.

67.08 CHANGES IN THE CONTENT AND COMPOSITION OF RAT BRAIN GANGLIOSIDES UNDER HYPOXIC CONDITIONS N.Nalivaeva*, I.Vassiljeva, V.Bayev. Institute of Evolutionary Physiol. Biochem., RAS, M. Thorez av.44, St.Petersburg, 194223, Russia

Hypoxia as a factor accompanying various diseases induces severe brain disorders. As we have shown previously i.p. ganglioside (G) injections resulted in a retardation of the development of main neurological syndromes under severe hypoxia. Moreover, i.p. administrations of total bovine brain gangliosides (30 mg/kg, daily for 4 days) to rats led to an increase in an average time of animal survival under hemic hypoxia induced by injections of lethal doses of sodium nitrite. Analyzing G content and composition in the brain of rats subjected to hypoxic conditions (pO2 8%) we have found an increase in G content 15 min after the beginning of exposition to hypoxia. The pattern of brain G and the composition of their fatty acids under these conditions were also significantly changed. The increased G content was observed in the brain of rats during 2 hours of the influence. Similar dynamics of the changes in G content and composition was revealed when animals were subjected to repeated exposition of hypoxia. The accumulation of G in the brain and mainly in the membranes of nervous endings under hypoxia seems to be an adoptive reaction of the organism to studied pathological factor.

67.09 MONOAMINE CONTENTS AND IMMUNE REACTIONS IN RIGHT-BIASED RATS AFTER IPSILATERAL REGIONAL ABLATIONS Anica Nikolić*, Anuška Andelković, Katarina Hladni, Vera Cvijanović and Dejan Mićić•

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This study deals with effects of regional right neocortical ablations on humoral and cell-mediated immune responses and monoamine content in the brain and lymphoid tissues. Male Wistar rats (250-300 g) were tested for amphetamine-induced rotational behaviour. Right-rotators, performing 15 or more net turns/hour in dominant direction, were subjected to the regional ablation of ipsilateral frontal (FC), parietal (PC) and occipital (OC) neocortex. After recovery, rats were immunized with bovine serum albumin (BSA) in complete Freund's adjuvant (CFA). Hypersensitivity skin reactions and antibody production to BSA were determined 14 and 21 days after the immunization. On day 22 after the immunization monoamines were quantified in different brain areas and lymphoid tissues by high-performance liquid chromatography (HPLC) with electrochemical detection. Arthus reaction to BSA was increased only in FC-lesioned animals on day 14. Delayed hypersensitivity skin reactions were similar in all groups on day 14 and 21 after the immunization. ELISA-levels of anti-BSA antibodies increased in FC- and PC-lesioned rats both on day 14 and 21 in comparison with other groups. Norepinephrine, dopamine and serotonin levels in cerebral cortex, hippocampus, hypothalamus and lymphoid tissues (thymus and spleen) in FC-, PC- and OC-lesioned animals displayed marked changes. Therefore, right frontal and parietal cortex exerte immunomodulatory influence on humoral response in right-biased rats and this effect is accompanied by significant changes in monoamine levels in different brain areas. (Supported by Ministry of Sciences and Technology of Serbia.)

67.10 COMPLEMENT 5A (C5a) ENHANCES THE MOTILITY OF MURINE MICROGLIAL CELLS IN VITRO VIA AN INHIBITORY G-PROTEIN AND THE REARRANGEMENT OF THE ACTIN-CYTOSKELETON Christiane Nolte*, Tilmann Walter and Helmut Kettenmann. Cellular Neurosciences, Max-Delbrück-Center for Molecular Medicine, Robert-Rössle-Str.10, D-13125 Berlin, FRG

Microglial cells are resident, immunocompetent cells within the CNS. Under pathological conditions including inflammation they rapidly respond by transition from a quiescent to an activated phenotype. The latter is characterized by increased cytotoxicity and motility. To investigate the regulation of microglial motility by inflammatory mediators we studied cultured microglia from mouse cortex using time lapse videomicroscopy and a computer-based motility assay.

Microglial cells exhibit a high basic motility characterized by the retraction and protrusion of cellular processes. The acute application of complement 5a (C5a), but not of TNFα, fMLP or bacterial endotoxin (LPS), immediately induced intense ruffling of microglial membranes followed by the formation of velum-like protrusions and spreading on the substrate. This process was accompanied by rapid rearrangements of the actin cytoskeleton as demonstrated by labeling with FITC-phalloidin. Inhibition of the actin-turnover by Cytochalasin B reversibly blocked the C5a-induced motility. Preincubation with pertussis toxin also blocked the reaction, suggesting that intracellular signalling after C5a-receptor activation is mediated via an inhibitory G-protein. C5a-induced motility was not impaired by removal of Ca^{2+} from the extracellular medium; however, motile activity was restricted to a defined concentration range of intracellular Ca^{2+} level ($[Ca^{2+}]_i$). Both lowering (by BAPTA-AM) or increase of $[Ca^{2+}]_i$ (by A23187) blocked the cellular motility response to C5a stimulation. Since complement factors are released at pathologic sites, this signal cascade could serve to direct microglial cells to the lesioned or damaged area by means of a clasical G-protein dependent pathway and via the rearrangement of the actin-cytoskeleton.

67.11 USE OF PROPIDIUM IODIDE TO DETECT NEURONAL DEATH IN ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES.

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Organotypic slice cultures of hippocampal tissue are with increasing interest being used as a model system in studies of various kinds of neuronal death, including hypoxia, hypoglycaemia, excitotoxicity and organic solvent toxicity. The aim of this study was to determine whether cellular uptake of the fluorescent dye propidium iodide could be used as a reliable and quantifiable marker for neuronal cell degeneration in organotypic hippocampal slice cultures. For this purpose we attempted to quantify the "spontaneous" neuronal death occurring in the cultures in relation to media changes and investigate whether this might involve glutamate receptor activation.

Slices of hippocampal cultures (350 μm) from 5 day old rats were grown on glass cover slips in tubes rotated in a rollerdrum. After 4-5 weeks a drop of 1 mM propidium iodide (PI) was added to the culture medium to achieve a final concentration of 2 μM PI. After 24 hours the cultures were examined and photographed using an inverted fluorescent microscope with rhodamine filter. After medium change and another 24 hours in the fresh media also containing 2 μM PI, new pictures were taken. All neurons were then killed by exposure to excess glutamate (50 mM) for one hour and a final set of pictures taken 24 hours later. All pictures were digitized and analyzed densitometrically using NIH Image software. The intensity from different regions of hippocampus was used to express the degree of neuronal death induced by media change and appeared in the following order: FD > CA1 > CA3. The observed cell death increased by increasing the concentration, of glutamine (which can be converted to glutamate) in the medium from 1 to 4 mM, and was reduced by addition of Mg^{2+} (10,5 mM) which blocks synaptic transmission. Addition of the non-competitive NMDA-antagonist MK-801 (30 μM) had a minor effect.

In conclusion, we found that propidium iodide fluorescence with some caution and under standardized conditions can be used quantitatively as a marker for neuronal cell death in organotypic hippocampal slice cultures.

67.12 DISTRIBUTION OF C-FOS-LIKE IMMUNOREACTIVITY IN THE DIENCEPHALON OF NON-STIMULATED RATS

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The expression of immediate-early genes has been used as a marker of neuronal activity related with different stimuli, such as pain, electric stimulation, light... However, c-fos expreses in different brain nuclei under standard conditions of rats' mantainment. The aim of this work is to determine the distribution pattern of c-fos activity in the diencephaloo of rats.
Rats were anesthetized with ketamine and transcardially perfused with saline and fixative. The brains and spinal cord were removed and were immersed in the same fixative. After sucrose cryoprotection, 40 µm coronal criostate sections were obtained and free floating proceed for ABC immunocytochemistry. Antisera anti pan-c-fos product from sheep (C.R.B.) was used as a primary anibody.
Fos-like immunoreactivity (FLI) was present in neuronal nucleus and fibers. Nuclear labeling was present at the thalamic and hypothalamic levels. In the hypothalamus FLI appeared in the medial preoptic area, lateral area, dorsal hypothalamic area, posterior hypothalamic area, zona incerta, and in the lateroanterior, dorsomedial, entopeduncular and supramammilar nuclei. In the last one the reactivity was more evident. The subthalamic, premammilary dorsal and ventral nuclei also showed neuronal labeling. At the thalamic level FLI was present in the paraventricular, centralmedial, anteriordorsal and anteroventralventrolateral thalamic nuclei.
Labeled fibers and terminals were prominent in all areas in which nuclear labeling was present. That labeling was also present in several areas with no nuclear labeling, i.e. nucleus rhomboid and reuniens nuclei in the thalamus and supraoptic nucleus in the hypothalamus.
We noticed the absence of nuclear and fiber labeling in thalamic areas, that receives direct sensory afferences such as geniculate complex and ventrolateral, ventromedial and reticular nuclei.

67.13 PHOSPHO- AND DEPHOSPHO- B-50 AND NEUROGRANIN CAN BE SIMULTANEOUSLY MEASURED IN RAT BRAIN EXTRACTS BY ELECTRO-SPRAY MASS SPECTROMETRY

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The evaluation of the phosphorylation state of nervous tissue specific proteins is important for determining their functional role under physiological and pathological conditions. Electrospray mass spectrometry coupled to liquid chromatography has been utilized to measure two specific PKC substrates, B-50/GAP-43 and neurogranin in single rat brain extracts of cortex and hippocampus. Proteins present in the crude perchloric acid extracts are directly injected into LC-ES/MS and mass spectra recorded throughout the elution. In the same extract at least 9 proteins can be observed. Among them B-50/GAP-43 and neurogranin can be identified on the basis of their molecular mass (23602.64: B-50; 7450: neurogranin). Moreover the presence of these PKC substrates in the extracts was unequivocably confirmed by western blot analysis. Molecular mass of dephospho- and phospho-forms of B-50/GAP-43 and neurogranin can thus be accurately determined. The values obtained for the dephospho-forms are in excellent agreement with the values deducted from cDNA. Moreover, the presence of molecular species shifted by 80 Da for both B-50 and neurogranin indicate that a substantial amount of these proteins are present as phospho-forms in these brain extracts. Beeing the overall sensitivity of the method in the order of few nanograms per protein in the same extract, the method is applicable to determine the phosphorylation state of B-50 and neurogranin in single rat brain areas with a high degree of accuracy.

67.14 ASTROCYTES PROMOTE SYNAPSE FORMATION BETWEEN RETINAL GANGLION CELLS IN *VITRO*.

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In the vertebrate central nervous system most synapses are ensheathed by astrocytic processes suggesting that neuroglia may play a role in synapse formation and function. To test this hypothesis we are studying synaptic transmission between purified retinal ganglion cells from eight day old rats that are cultured in the absence or presence of tectal astrocytes. After five days *in vitro* retinal ganglion cells form excitatory synaptic contacts as indicated by whole-cell recordings of spontaneous postsynaptic currents. Their somata are evenly distributed throughout the culture dish and their neurites spread irregularly. In the presence of astrocytes, however, retinal ganglion cells sit on top of glial islands, their axons are strongly fasciculated, and dendritic areas are covered by astrocytic processes. In cocultures the frequency of spontaneous postsynaptic currents is significantly increased and large (>100 pA) postsynaptic currents occur that are not observed in astrocyte-free cultures. These findings suggest that astrocytes promote the formation or function of synapses either by increasing the number of presynaptic terminals per neuron or by enhancing the efficacy of individual synaptic contacts.

67.15 MICROGLIA IN THE DEVELOPING LIZARD MIDBRAIN. NDPase-ULTRASTRUCTURAL STUDY.

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It is well known that in the lizard brain neurogenesis and gliogenesis are a normal process extending along the posnatal life (1,2). Moreover, neurogenesis and gliogenesis may be induced after experimental injury during the adult life, microglial cells play an active role in these processes. In the present study we describe the ultrastructural morphological features of the microglial cells populating the mesencephalon of postnatal lizards by using the nucleoside diphosphatase (NDPase) method as specific marker. The histochemical reaction was carry out according to (3) and subsequently several sellected sections were processed for E.M.. Our observations showed that in tegmentum ramified microglia displayed an irregular dark nucleus, a scanty cytoplasm with ribosomes and some dense bodies and the NDPase activity was located in the outer surface of the plasma membrane of the microglial cells and in relation to blood vessels.

The present report shows the normal location and ultrastructural features of microglia in the lizard midbrain. Futher studies using experimental lesions will show the involvement of this cell type in SNC regeneration events.

(1)Monzón-Mayor, M. et al. 1990. Glia 3:81-97.
(2)López-García, C. et al., 1994. Glia 12:52-61.
(3)Castellano, B. et al., 1991. J. Comp. Neurol. 15:434-44.

67.16 HEAT-SHOCK TREATMENT MODIFIES GENE EXPRESSION FOLLOWING BRAIN INJURY.

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Focal cortical lesions induce the expression of immediate early genes (IEGs) throughout the ipsilateral hemisphere and the inducible 70-kDa heat shock protein (HSP71) around the injury site. We used this model to determine whether a hyperthermic treatment before brain injury could alter the stress response *in vivo*.

Male Sprague-Dawley rats (250-300 g), 24 hours after a 15-min hyperthermic treatment (42°C) and control rats were subjected to unilateral cortical wounding. At 1 and 3 hours after surgery, brains were removed and frozen for analysis by Northern blotting using specific oligonucleotide probes for IEG (*c-fos*, *c-jun*, *ngfi-a* and *ngfi-b*) mRNA and *hsp71* mRNA. Northern analysis revealed that *ngfi-b* and *hsp71* transcripts accumulate at higher levels in the lesioned side of 24 hr post-heat shocked animals compared to controls. *In situ* hybridization was performed to detect differences in mRNA distribution in the brain of heat shocked and control animals.

This demonstrates that hyperthermic treatment before cortical wounding can alter the expected expression of stress-induced genes.

67.18 STRUCTURE OF THE GEPHYRIN GENE, ISOLATION OF A NEW cDNA AND ITS DISTRIBUTION IN THE BRAIN

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Gephyrin, a polypeptide which is essential for the formation of glycinergic synapses in spinal neurons, binds with high affinity to tubulin and was recently shown to interact with the ß subunit of the glycine receptor (GlyR). Therefore, gephyrin is thought to link the GlyR to the subsynaptic cytoskeleton. cDNA sequencing revealed, that gephyrin occurs in several splice variants which are expressed in most synaptic regions of the rat brain. In addition, Northern blot analysis indicates the existence of additional isoforms in liver, heart, and kidney.

We isolated an additional splice variant of gephyrin from a mouse cDNA library and demonstrate its distribution by *in situ* hybridisation and immunocytochemistry.

The structure of the mouse gephyrin gene was deduced from both, lambda and P1 clones. Subcloning and sequencing of the coding regions and intron/exon boundaries led to the identification of 26 exons, which represent at least 240 kb of genomic DNA. 5 of these exons encode alternativ sequences of the different gephyrin variants, corroborating that all the variants isolated so far, were transcribed from the same gene.

67.19 MECHANISM OF TRANSPORT OF ^{3}H L-ALANINE THROUGH THE GUINEA PIG BLOOD-BRAIN BARRIER.

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Transport of ^{3}H l-alanine through the guinea pig blood-brain barrier (BBB) was studied using the in situ brain vascular perfusion method. Obtained results showed that l-alanine transport through the BBB is mostly mediated by a saturable mechanism, but another, nonsaturable component is also involved in its transport (about 30% of total transport). Presence of unlabelled l-serine caused significant inhibition of ^{3}H l-alanine transport through the BBB in all studied regions (hippocampus, nucleus caudate and cortex). Therefore, it could be concluded that small neutral amino acids share same transport system(s) at the luminal side of the BBB. Addition of unlabelled BCH (synthetic analog of large neutral amino-acids) did not cause significant decrease of ^{3}H l-alanine blood to brain transport, which implicates that L-transport system plays minor role in brain uptake of small neutral amino-acids. Presence of l-lysine in perfusing medium caused increased in ^{3}H l-alanine brain uptake. This effect could be a caused by intracellular accumulation of l-lysine and, consequently, stimulation of the exchange of amino acids across the endothelial cells' luminal membrane.

These results suggest that saturable transport of small neutral amino acids is mediated by at least two different mechanisms, and that a kind of free diffusion cannot be disregarded when discussing this problem.

67.20 **HETEROGENEITY OF MICROTUBULE-ASSOCIATED PROTEIN 1A IN THE BARREL CORTEX OF THE ADULT MOUSE**

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MAP1a is one of the high molecular weight microtubule proteins and involved in the late neuronal maturation. Its immunohistochemical distribution was studied in the somatosensory cortex of the mouse with two monoclonal antibodies, monoclones A and BW6. The distribution in the area of mystacial vibrissae revealed differences in that monoclone A stained pyramidal cells and their dendrites. Many apical dendrites were clustered between the barrels. Whereas monoclone BW6 recognized finer dendritic processes, mainly localized in the hollow of the barrels. On the ground of these immunohistochemical differences we suggest that MAP1a is present at least as two isoforms, and may be subject of differential posttranslational modifications within neuronal elements of the mouse barrel cortex. Such spatial differences may be due to differences in the cortical processing of somatosensory inputs. Supported by Swiss NSF grants 31-33447.92 and 31-39184.93.

67.21 IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL STUDY OF THE S100 PROTEIN IN THE MESENCEPHALON OF A LIZARD.

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We have studied the localization of the S100 protein in the adult *Gallotia galloti*, a lizard indigenous of Canary Islands, by optic and electron microscopy using a policlonal rabbit antibody against cow S100 protein (both A and B). We have observed oligodendrocytes intensely S100 positive in most of the mesencephalic tracts. At this respect, cells S100 positive that resemble type 4 oligodendrocytes were observed in the optic nerve of Goldfish[1] and oligodendrocytes were S100B positive in postnatal cat visual cortex[2]. Radial glia processes were highly stained too in this lizard, mainly in the tectum. Radial glia were also S100 immunoreactive in the hippocampal fimbria of human foetuses[3]. Recent studies indicate that S100 protein might be implicated in the proliferation and differentiation of cultured glial cells[4] and in regenerative and remyelination processes in the teleost *Tinca tinca*[5]. These data are interesting for the studies about regeneration of the adult lizard brain in which we are involved at present.

[1]Nona et al., J. Neurocytol. 21:391 (1992); [2]Dyck et al., Dev. Brain Res. 72:181 (1993); [3]Stagaard-Janas et al., Anat. Embryol. 184:549 (1991); [4]Selinfreund et al., Proc. Natl. Acad. Sci. USA 88:3554 (1991); [5]Vecino et al, Abstract ARBO 1203:74 (1994).

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67.22 Abstract withdrawn

67.23 CYCLIC AMP REGULATES B-50/GAP-43 GENE EXPRESSION IN PRIMARY SCHWANN CELLS.

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Following peripheral nerve crush or transection, the B-50 mRNA expression increases dramatically in the distal nerve stump as studied by Northern blotting and in situ hybridization (Plantinga et al., Brain Res. 602, 69-76, 1993). This increase has been fully attributed to an up-regulation of B-50 synthesis in reactive Schwann cells.

In primary Schwann cell cultures the B-50 mRNA expression is strongly down-regulated in 24 h by concentrations of forskolin as low as 200 nM. Six hours after addition of forskolin, the B-50 mRNA was almost completely degraded, indicating a half-life of less than 5h (Plantinga et al., Neuroreport 5, 2465-2468, 1994). The distribution of B-50 after treatment with forskolin was studied by immunocyto-chemistry. In cells treated with forskolin for 2 days, B-50 immunoreactivity (BIR), studied by confocal scanning laser microscopy (CSLM), was found in tubular structures surrounding the nucleus, possibly multivesicular bodies. In Schwann cells cultured without forskolin increasing amounts of extensions were formed in time bearing BIR varicosities in the extensions.

The rat B-50 promoters P1 and P2 were tested by transient transfection with and without forskolin. Promoter P2, but not P1, is active in Schwann cells and the activity of P2 is inhibited 2.5 fold by forskolin. P2 does not contain a consensus sequence of a known cyclic AMP responsive element suggesting that the effect of forskolin is indirect. At present we are co-transfecting CREB, SCIP and other POU domain binding proteins to investigate whether any of these transcription factors can mimic the effect of cyclic AMP on the expression of B-50 promoter constructs. Moreover we are preparing nuclear extracts from Schwann cells treated with forskolin to perform EMSAs with P2 promoter fragments.

67.24 **TRANSFORMING GROWTH FACTOR (TGF)-β1: LOCAL EXPRESSION IN INFLAMED RAT SPINAL CORD DURING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS.** T. Schweitzer*, R. Kiefer, S. Jung, K.V. Toyka and H.-P. Hartung, Department of Neurology, Univ. of Würzburg, Würzburg, Germany

Experimental autoimmune encephalomyelitis (EAE) of the Lewis rat is an acute inflammatory disorder of the spinal cord and brain which is self-limited by mechanisms yet unknown. We have investigated the expression of mRNA encoding the immunosuppressive cytokine TGF-β1 in rat spinal cord during EAE which was induced by adoptive transfer (AT) of P2-specific autoreactive T-cells or by active immunization with myelin basic protein. In AT-EAE, quantitative Northern blot analysis revealed a rise in TGF-β1 mRNA as early as 3 days after transfer of autoreactive T-cells. Peak levels were reached by day 5, just prior to the first signs of clinical recovery, and thereafter declined. In situ hybridization localized TGF-β1 mRNA to mononuclear cell infiltrates frequently in a perivascular position. In addition, isolated parenchymal mononuclear cells as well as cells with small heterochromatic nuclei possibly representing microglial cells expressed TGF-β1 mRNA. Combining in situ hybridization with immunohistochemistry for T-cell and macrophage cellular markers on one section revealed hybridization signal to be associated with both T-cells and macrophages. In actively induced EAE, similar results were obtained. However, elevated levels of TGF-β1 mRNA were observed earlier in the disease and persisted for a longer time. Our data suggest that immunosuppressive TGF-β1 locally expressed in the inflamed spinal cord might be one factor involved in recovery from EAE.

67.25 **IMMUNHISTOCHEMICAL DETECTION OF FUCOSYLGLYCOPROTEINS IN RAT BRAIN**

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Fucosylated glycoproteins are important constituents of cell membranes and are known to be involved in processes of cell differentiation, cell recognition and cell-substrate interactions. The functional significance of glycoprotein fucosylation for mechanisms underlying long-lasting changes in synaptic connectivity, i.e. hippocampal long-term potentiation (LTP), long-term memory formation has been demonstrated earlier.
Recently, it was shown that specific inhibition of fucosylation supresses the maintenance of LTP while intrahippocampal injections of fucosyl saccharides lead to a long lasting prolongation of LTP. To monitor the cellular distribution of corresponding fucosylglycoconjugates we raised polyclonal antisera against neoglycoproteins containing Fucα(1-2)Gal epitopes. Immunhistochemical studies revealed strong immunreactivity at membranes of distinct neuronal populations in many parts of the brain. Most pronounced staining occured in brain regions particularly relevant for learning and long-term memory formation, i.e. in the hippocampal pyramidal cell layer, certain cortical neurons and cerebellar Purkinje cells. Westernblot analysis revealed five major immunreactive proteins which have to be characterized in further investigations.

67.26 EXPERIMENTAL STUDIES ON MECHANISMS OF TELLURIUM ENCEPHALONEUROPATHY.

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Previous experimental studies on the intoxication with tellurium demonstrated a transient paralysis of hind legs and segmental peripheral demyelination only in the weanling rat.It has been postulated that the tellurium neuropathy is connected with a block of squalene epoxydase activity in the pathway of cholesterol synthesis. Our ultrastructural studies showed that tellurium produced neuropathological changes both in the PNS and in the CNS in the adult rat too.Dynamics of the electron microscopic changes suggested primarily a degeneration of myelin sheath and myelin forming glia with secondary damage in axons of the cerebral white matter structures. The mechanism of the peripheral tellurium neuropathy was characterized by a direct injury of Schwann cells with secondary myeloclasis.Squalene administration confirmed the hypothesis that increased level of this compound may be taken as a factor in the tellurium neurotoxic process in the rat.

67.27 BLOOD BRAIN BARRIER BREAKDOWN IN CHRONIC LEAD TOXICITY.

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Cerebrall microvessels, beside astrocytes and neurons are an important target of lead toxicity, respecting their restrictic role in relation to the blood-borne substances.In young organisms immature blood-brain barrier is not a sufficient protection against developing of lead encephalopathy. It is thought that together with maturation process of BBB the brain resistance to lead toxic effects increase. The study was performed to determine whether prolonged exposure to low lead levels in drinking water affects brain microvasculature in adult rats.3-week-old Wistar rats received 200mg/L lead acetate in drinking water for 3 months. After that time the functional state of BBB was estimated using horseradish peroxidase as the tracer of vascular permeability.Light- and electron microscopic studies revealed extravasation of the tracer, especially in sections from hippocampus and cerebrallcortex from temporal lobe area.Enhanced pinocytotic process as well as opening of endothelial tight junctions were observed as evidences of increased microvessels permeability. We noted numerous phagocytizing cells of pericytes origin with numerous phagolysosomes filled in with the HRP-reaction product - the "scavenger cells" mobilized in the CNS in the intoxicative processes.Estimation of lead level revealed its signifficant accumulation in capillaries and synaptosomal fractions. Biochemical examinations of capillaries have shown increased phosphatidylserine plus phosphatidylinositol level.It has to be remarked that lead enters the brain of not only young but also adult rats, causing disturbances in vascular permeability. It seems that mentioned abnormalities may arrise from altered lipid composition of membranes and in turn from altered membrane structure and function.

67.28 MUTATION IN PLP GENE INFLUENCES OLIGODENDROCYTES MATURATION IN HYPOMYELINATED PT MUTANT. Joanna Sypecka* and Krystyna Domańska-Janik, Medical Research Centre, Polish Academy of Sciences, 3 Dworkowa Str., 00-784 Warsaw, Poland

Paralytic tremor (*pt*), a hereditary neurological disorder of rabbits is a recessive, X-linked point mutation in exon 2 of Plp gene. The mutation results in substitution of histidine^{36} by glutamine in PLP molecule (Tosic et al 1994) what leads to severe hypomyelination of CNS. Affected animals, although strictly controlled for their *pt* trait, differ significantly in their phenotype. An onset of neurological disorders takes place usually at 10th postnatal day. Typical first symptoms include: a tremor, an exaggeration of tendon reflexes and a weakness of limbs. Mutants are smaller and lighter than age-matched controls. As they age, the intensity of enumerated neurological symptoms increases especially in the mild or severe courses of the disease. In most severe cases a spastic paresis of the hindlimbs may develop, followed occasionally by paresis of forelimbs; a lifespan of so strongly affected animals is reduced to a few months. Morphological studies showed that in spite of observed severe hypomyelination, the glia cell number is not reduced in *pt* rabbits which is in contrast to other X-linked mutants. In present study we have investigated developmental expression of the glycolipid (01; R-mAb; 04) and protein (CNP, MBP, PLP) markers of oligodendrocyte (OL) maturation. It was shown that from initially equal number of progenitors bearing proligodendroblast (POA) antigen in pt brain only a minute fraction of these cells could pass the more advanced maturation stages to the phenotypes expressing 04 and 01 antigens. Studies of gen expression for typical OL protein markers evaluated on transcriptional as well as translational level confirmed that process of OL maturation is significantly retarded in *pt* mutant rabbit. Severity of the observed neurological symptoms depends on amounts of myelin produced by a small fraction of differentiated OL.

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67.29 **Targeted disruption of the *Bcl-2* locus by replacement with the *LacZ* gene**

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Programmed cell death (PCD) is a widespread phenomenon which plays a fundamental role in development and homeostasis. One of the best studied genes associated with PCD, is the protooncogene *bcl-2*. This gene encodes a membrane-associated protein which interferes with apoptotic cell death in different experimental models. Bcl-2 protects cultured neurons from degeneration induced by the withdrawal of neurotrophic factors. Although it is widely expressed in both the central and peripheral nervous systems, the role of *bcl-2* under physiological or pathological conditions remains unclear.

In order to evaluate the function of *bcl-2* for the neuronal cell survival and differentiation as well as its involvement in neurodegenerative conditions, we have created transgenic mice carrying a null mutation of the *bcl-2* gene by homologous recombination. The second exon of *bcl-2* which encodes most of the Bcl-2 protein was replaced by the E. coli. *lacZ* gene. In this way, the *lacZ* was placed under the transcriptional regulatory seqences of the *bcl-2* gene (including its 5' untranslated sequence, which might also have a regulatory role in its expression), providing a genetic marker of the mutation which allows us to monitor the developmental time course and the sites of *bcl-2* expression. Three out of 47 G418 resistant ES clones were found to carry the desired allele. Heterozygous offspring of the chimeras showed a normal phenotype. The basic phenotype of the *bcl-2-/-* mice was similar to that described earlier by two other groups. In our analysis we have focused on the effects of the absence of the *bcl-2* gene in both the central and peripheral nervous systems, at different developmental stages under physiological and experimental pathophysiological conditions. The results of this analysis will be presented.

67.30 APOPTOSIS IS ASSOCIATED WITH SPECIFIC STAGES OF CELL CYCLE IN THE SUBVENTRICULAR ZONE OF NEWBORN RATS.

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There is now increasing evidence that mitosis and apoptosis, two of the most basic processes during development, are closely related.Using terminal deoxynucleotidyl transferase mediated biotin-dUTP nick end labelling (TUNEL), a method that labels fragmented DNA occurring during apoptosis *in situ*, we found that approximately 10% of the cells in the subventricular zone (SVZ) of newborn rats are undergoing apoptosis, a percentage that is much higher than in all other areas of the developing cortex. This was confirmed with DNA analysis of SVZ cells in an agarose gel where we observed the DNA fragmentation pattern which is a characteristic feature of apoptotic cells. In order to correlate apoptosis with specific stages of the cell cycle, we carried out TUNEL *in situ* end labelling on SVZ cells at different times after ^{3}H-thymidine injection that corresponded to S (2 hrs), G2/M (6 hrs) or G1 (8-10 hrs) phases of the mitotic cycle. We found that TUNEL positive SVZ cells were never labelled by ^{3}H-thymidine incorporation two hrs after the injection, suggesting that cells do not undergo apoptosis in S phase. However, 8 hrs post-injection, when the majority of the ^{3}H-thymidine labelled cells are in G1 phase, 25% of apoptotic cells were also labelled with ^{3}H-thymidine.These results confirm that G1 phase is most likely the time in the cell cycle when most of the proteins that act as regulators of cell death, including Rb, cyclin D1, c-fos, c-jun and c-myc, are active.

67.31 EFFECT OF TNFα ON THE PROLIFERATION AND THE MORPHOLOGY OF A MEDULLOBLASTOMA CELL LINE

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Tumor necrosis factor alpha (TNFα) was first described on 1975 for its cytotoxic effect on tumor cell lines in vitro. This effect is variable in different cell line depending on the type of original tumor. In particular, TNFα is mitogen for the majority of tumor cell lines derived from nervous system neoplasms (neuroblastomas or gliomas).

Medulloblastoma is a highly malignant primitive neoplasm that occurs most often in children. This tumor could be derived from cerebelar undifferentiated neuroectodermal cells. We studied the effect of TNFα on a medulloblastoma cell line (Dev). We first showed using flow cytometry that 10 % of cells express p60 TNF receptor and that the p80 subtype was not detected. TNFα (0,1 ng/ml) induced the death of 10 % of the cells and surviving cells were less proliferative since 12 h treatment. The potential doubling time increased from 40 to 100 hours and the study of the cell cycle showed a decrease of the percent of cells in S phase. This occured in a dose dependant manner and could be related to reorganization of the cytoskeleton as suggested by the increase of vimentin expression observed after TNFα treatment. Furthermore, major histocompatibility complex class I molecules expression was up-regulated on all cells. Class II molecules were not detectable. So, THFα not only reduced cell proliferation but may increase the capacity of cells to present tumoral antigen to the immmune sytem and thus facilitate an anti-tumoral response.

TNFα is used as anti tumoral agent in other pathologies and could be interesting in the treatment of medulloblastoma.

67.32 REGULATION OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) BY BASIC FIBROBLAST GROWTH FACTOR (bFGF) AND TRANSFORMING GROWTH FACTOR-ß1 (TGF-ß1) IN CULTURED RAT ASTROCYTES

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There is growing evidence that the plasminogen activator system plays a role during tissue remodelling after injury of the brain. Axotomy of the rat facial nerve after 3 days leads to an increase of PAI-1 synthesis in perineuronal astrocytes in the facial nucleus. We have used an in vitro approach to investigate the signalling mechanisms regulating PAI-1 expression in astrocytes. Astrocyte-enriched cultures of neonatal rat cortex were treated with bFGF or TGF-ß1, both of which have been proposed as signal molecules in the events following axotomy. PAI-1 mRNA expression was analyzed by northern blotting. Both factors stimulate PAI-1 mRNA synthesis with the maximum at 4 h decreasing to basal values within 32 h. bFGF (5-fold increase) had a much weaker effect compared to TGF-ß1 (30-fold increase). Secretion of the mature protein measured by [^{35}S] methionine incorporation was associated with transcriptional activation starting 4 to 8 h after application of factor. Regulation of PAI-1 mRNA expression at 4 h occured in a dose-dependent manner with an ED_{50} of 1-2 nM bFGF and 6-7 pM TGF-ß1. Inhibition of transcription by actinomycin D completely abolished the effects of bFGF and TGF-ß1; both factors stabilize the PAI-1 message as shown by preincubation with factor before adding actinomycin D. Transcriptional regulation of PAI-1 depends on protein synthesis: application of the protein synthesis inhibitor cycloheximide suppresses stimulation by TGF-ß1, but enhances the effect of bFGF. TGF-ß1 thus requires de novo synthesis of transcription factors to mediate its effect while stimulation by bFGF is possibly reduced by a repressor protein, inhibition of which results in full transcriptional activity. In addition, bFGF transiently increases nuclear transcription of the PAI-1 gene over a 4 h time course, but no induction could be observed during this period with TGF-ß1. These results suggest that bFGF and TGF-ß1 exert their same stimulatory effects on PAI-1 mRNA expression via different intracellular mechanisms.

67.33 BRAIN ENDOTHELIAL CELLS AS SIGNAL TRANSDUCERS FOR ENDOTOXIN-INDUCED NON-SPECIFIC SYMPTOMS OF SICKNESS IN RATS

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An inflammatory response includes physiological changes such as fever, neuroendocrine changes, behavioural modifications, increased sleepiness, depression, anorexia and are called non-specific sickness symptoms. Interleukin-1 appears to play a pivotal role in the orchestration of sickness symptoms. We have shown the appearance of immunoreactive IL-1ß in the rat brain after peripheral administration of endotoxin. So far, receptors for IL-1 in rat brain parenchyma are difficult to detect using both species heterologous or homologous ligands in IL-1 receptor binding studies. However, in mouse and rat brain, mRNA for IL-1 receptor type I has been demonstrated in brain endothelial cells. This celltype may be important in the communication between the periphery and the brain during inflammatory processes as it can be reached from both sides. An IL-1 receptor type I can be detected on rat brain endothelial cells in vitro by IL-1 competition studies and polymerase chain reaction experiments. Furthermore, IL-1 induces the production of other pro-inflammatory factors: interleukin-6 (IL-6) and prostaglandins (PG) by these brain endothelial cells. In addition, we have observed immunoreactive PGE2 in rat brain endothelium after peripheral administration of endotoxin or IL-1. Receptors for IL-6 and PGE2 have been demonstrated in the rat central nervous system and IL-6 as well as PG can induce non-specific symptoms of sickness. Therefore, these results have led to the hypothesis that after injection of endotoxin, IL-1 produced in the brain and periphery can act on its brain endothelial receptor to induce the production of IL-6 and PGE2 which by themselves can induce non-specific symptoms of sickness.

67.34 CHARACTERIZATION AND EXPRESSION OF THE RAT TR4 ORPHAN RECEPTOR IN THE BRAIN

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To identify new transcription factors involved in the regulation of the oxytocin (OT) gene in the hypothalamo-neurohypophyseal system (HNS) a PCR cloning strategy was used, based on homologies within the DNA binding domain of AGGTCA binding factors. This resulted in identification of 9 members of the steroid hormone superfamily, one of which was a novel orphan receptor (PNAS 91:6040 (1994)). This factor, called TR4 orphan receptor, is closely related to the orphan receptor TR2. The high homology between TR2 and TR4 suggests that these two orphan receptors constitute a unique subfamily within the steroid receptor superfamily. In situ hybridisation experiments have shown that TR4 is expressed in the hypothalamus at low levels and at high levels in pyramidal and granule cells of the hippocampus and the cerebellum of adult rats. At stages E14 and E19 of the development of the rat, low expression of TR4 is found throughout the embryo and high expression in the central nervous system (CNS). At stage E19 high expression of TR4 is also found in the thymus, suggesting a function of TR4 in both the nervous and immune system. In post-natal rats (P0) TR4 is mainly expressed in the hippocampus and cerebellum. The level of expression in different organs and parts of the brain of embryonic and post-natal rats during development will be determined by Northern blot analysis and RNase protection assays. Further studies aim to determine the DNA binding and transactivating properties of this factor and its role in the regulation of neuronal genes.

67.35 GUILLAIN BARRÉ SYNDROME PATIENTS PRODUCE AUTOANTIBODIES AGAINST ASTROCYTES

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A potential role for autoimmune mechanisms has been repeatedly implicated in the pathogenesis of a large variety of neurological and psychiatric disorders. To further investigate possible autoimmune processes in neurological diseases, about 200 samples of sera or cerebrospinal fluids, patients and controls, were tested for the presence of autoantibodies against brain proteins on Western blots and mildly fixed tissue sections from rat, porcine and human brains.

Samples from patients often displayed immunoreactivity. Some individual samples stained all neurons. Others were specific for certain structures such as cerebellar Purkinje or Golgi cells, cell groups in the ventral horn of the spinal cord, or for basket cell axons. No correlation between these types of staining and neurological disorders was apparent.

Several samples, however, showed immunoreactivity for astrocytes, alone or together with neuronal staining. Most of these belonged to patients suffering from GBS. Anti-astrocyte reactivity was detected in about 60% of the GBS-patients. The question, whether these autoantibodies are involved in the pathomechanism or whether they just represent an epiphenomenon of the desease, requires further investigation.

67.36 DIFFERENT TYPES OF VESICLES TRANSPORT B-50/GAP-43, IN THE REGENERATING RAT SCIATIC NERVE, TO THE GROWTH CONE AND TO THE AXOLEMMA.

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During regeneration of neurons of the peripheral nervous system, the synthesis of the growth-associated phosphoprotein B-50/GAP-43 is upregulated. B-50 is transported to the growth cone with the fast component of anterograde axonal transport. Previously, we have shown that during sciatic nerve regeneration B-50 immunolabeling is increased, not only in sprouts distally, but also, in the region proximal to the injury, at the plasma membrane of unmyelinated axons. Subsequently, we have used the crushed regenerating rat sciatic nerve as a model to study the anterograde transport of B-50 at the ultrastructural level.

Proximal to a ligature placed on a regenerating rat sciatic nerve, there was an accumulation of anterogradely transported organelles and vesicles. We show that the B-50 immunolabel was also increased just proximal to the ligature as compared to a region closer to the cell body. This immunolabeling was associated with small 50 nm vesicles, present in both unmyelinated and myelinated axons. The B-50 immunostained vesicles were partly double immunolabeled for synaptophysin, a protein marker for vesicles trafficking to the growth cone.

Our results suggest that B-50 is transported by anterograde axonal transport in two types of vesicles; one type is targeted to the growth cone, and the other is destined to the axolemma. The proposed local axolemma incorporation of vesicular carried material would be in line with our previous findings of increased B-50 axolemma association. Targeted transport of B-50, not only to the growth cone, but also to the axolemma, could indicate a function in plasma membrane dynamics.

67.37 LOCALIZATION OF STEROID INDUCED ANNEXIN-1 mRNA IN RAT BRAIN

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The anti-inflammatory effects of glucocorticosteroids may be mediated by the Annexins (Anx); a protein superfamily. Anx inhibit the formation of eicosanoids from arachidonic acid by Phospholipase A_2. With immunohistochemical studies the occurence of Anx has been shown in meningeal and endothelial cells, ependyma, choroid plexus and oligodendroglia in the rat brain after induction with a steroid. These observations however do not exclude penetration of Anx from peripheral sources. *In situ* hybridization (ISH) may show which cells express *Anx* mRNA.

With a Polymerase Chain Reaction a nonradioactive probe was made and used for ISH on brains from rats treated with methylprednisolone (2 mg/kg) or the 21-amino-steroid U74389F (10 mg/kg) and a control group.

Anx-1 mRNA was found in the hippocampus (CA1, 2 and 3 area), the granular layer of the dentate gyrus and scattered cells in the cortex. Contrary to the immunohistochemical studies no signal for *Anx-1* was found in the choroid plexus, meningeal and endothelial cells.

Anx-1 is known to be produced in several other organs where it can be excreted, so it is possible that the protein is transported to the brain where it can enter into structures which lack a blood-brain barrier. The areas in which *Anx-1* mRNA has been observed all express glucocorticosteroid receptors. In the control group an *Anx-1* mRNA signal is present in the same areas as in the treated animals, but it was less intense and fewer cells were labeled. Stress from vehicle injections may have caused a rise in plasma corticosteron levels in the control animals, which subsequently initialises the transcription of *Anx-1* mRNA.

These results show that the tested steroids and probably also stress induce the expression of Anx-1 in various cells in the rat brain.

67.38 BEHAVIORAL AND IMMUNOLOGICAL EFFECTS OF PERIPHERALLY ADMINISTERED METHIONINE-ENKEPHALIN: MODULATION OF PAIN PERCEPTION, OPEN FIELD ACTIVITY AND NONSPECIFIC IMMUNITY

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The aim of the present study was to investigate behavioral and immunological effects produced by single intraperitoneal (i.p.) administration of methionine-enkephalin (Met-Enk). For this purpose, 8-week-old male Wistar rats (n=10-15 per group) were i.p. injected with 0.2 mg/kg of Met-Enk or saline 5 minutes prior to their exposure in open field. Rats were observed for horizontal locomotor activity, rearing, grooming and defecation for 3 minutes. Immediately afterwards, each rat was i.p. injected with 0.6% acetic acid and their algesic response determined by the writhing assay for 40 minutes. After 24 hours peritoneal macrophages were drawn from the same animals and tested for hydrogen peroxide (H_2O_2) production. Met-Enk produced the following effects: a. significantly increased horizontal and vertical open field activity without affecting grooming and defecation; b. significantly reduced number of writhes; c. significantly increased H_2O_2 production by peritoneal macrophages. Additional experiments revealed that all effects of exogenous Met-Enk were completely blocked by pretreatment with specific anti-Met-Enk antibodies (5 mg/0.5 ml/rat) and quaternary naltrexone (5 mg/kg). Injections of anti-Met-Enk antibodies and quaternary naltrexone alone produced opposite effects from Met-Enk in the analgesic and macrophage assays (i.e., hyperalgesia and suppressed H_2O_2 production), but did not affect open field behavior. These data suggested that peripheral opioid peptides tonically regulate nonspecific immune responses and pain perception, but not open field behavior. (This work was supported by the Ministry of Science and Technology of the Republic of Serbia.).

67.39 COUNTING *IN SITU* HYBRIDIZED NEURONS WITH OPTICAL DISECTORS

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Neuron number is a parameter of fundamental importance when evaluating the functional consequences of structural changes related to development, aging, pathology, toxic substances, injury, and plastic responses to injury. The advent of methods for selectively labeling neurons of specific phenotypes provides an opportunity to refine the quantitative characterization of neuron loss related to these phenomena. Among the new methods are *in situ* hybridization techniques for labeling neurons expressing RNA messages for specific proteins and thereby subpopulations of neurons with specific functional characteristics and roles. While recently developed stereological techniques for counting neurons and other cells potentially provide a means for obtaining data about neuron number in classically stained histological material, there are a number of practical problems that have precluded the application of these techniques to *in situ* hybridized preparations. In this presentation we discuss these problems, describe how they can be overcome by tailoring the preparation of the tissue so that it meets the requirements for the application of one of the most powerful and versatile of the new stereological counting methods, the optical fractionator, and provide an example of how this approach can be used to estimate the total number of neurons expressing the message for somatostatin in the striatum of laboratory rats.

67.40 **RAPID PURIFICATION OF GLIAL CELLS USING IMMUNOMAGNETIC SEPARATION**

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The purification of glial cells from brain tissue containing a heterogeneous cell population provides a means to examine the cell interactions that define cell types within the central nervous system. By culturing purified glial cell types separately or in combination with other enriched glial cells it has been found that growth factors control glial cell diversification (see rev. Dubois-Dalcq *et al.*, 1990). The current methods used for purifying glial cells, however, are both time consuming and costly.

In this study we have adapted the technique of immunomagnetic separation to separately enrich, O-2A progenitor cells, astrocytes, and oligodendrocytes from the rat optic nerve. Firstly, postnatal day (P)4 rat optic nerves were enzymatically dissociated and incubated in primary antibody specific to a surface antigen on the target cell type (e.g. A2B5, RAN-2, or GalC). The dissociated cells were washed and incubated in media to which was added iron-containing polystyrene beads (Dynabeads™) that had been precoated with a secondary antibody specific to the primary. Bead-bound cells were then drawn out of suspension using a strong magnet, plated onto silane-coated coverslips and placed in a CO_2 incubator overnight.

We found that, prior to separation, P4 rat optic nerves contain approximately 30,000 cells, 25% of which are O-2A progenitor cells. The immunomagnetic separation procedure, which was completed within 2 hours, produced an almost completely pure population of these cells (>99%). This was confirmed by the absence of unbound cells in the bead-bound fraction . The viability of bead-bound cells was evident by the prescence of processes as shown by both immunohistochemistry and scanning electron microscopy. Similarly, purified populations of astrocytes and oligodendrocytes were obtained using this method.

This study shows that glial cell types can be separated out of brain tissue to near purity using immunomagnetic separation. The speed and low costs of this procedure make it a viable alternative to immunopanning and fluorescence activated cell sorting (FACS) techniques.

67.41 EFFECT OF LATERAL HYPOTHALAMIC (LH) LESIONS ON THE NUMBER OF LARGE GRANULAR LYMPHOCYTES (LGL) AND THEIR NATURAL KILLER CYTOTOXICITY FUNCTION.

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Numerous studies have shown that ablation of specific areas in the brain is associated with dramatic alterations in immune functions. However, the relationship between changes in immune functioning and changes in distribution of immune cells is not well established. In the present study we have investigated effects of bilateral electrolytic destructions of lateral hypothalamus (LH) on both peripheral natural killer cytotoxicity (NKC) and number of large granular lymphocytes (LGL) in rats. Percent of NKC was measured against two different target cells YAC-1 and K-562 in a standard 4 h ^{51}Cr-release assay and number of LGL was determined with a standard hematological technique. In LH-lesioned rats highly significant positive correlations during the whole experiment (from prelesion baseline, through the 2nd, 5th up to 21st day after lesioning) between LGL number and NK cytotoxicity changes against both target cells ($r = 0.89$, $df = 46$, $P < .00000$ and $r = 0.93$, $df = 46$, $P < .00000$, for YAC-1 and K-562 cells, respectively) were found. No correlation between these parameters was shown in both control groups: LH-sham animals ($r = 0.26$, $df = 30$, $P > .15422$ and $r = 0.06$, $df = 30$, $P > .72654$ for YAC-1 and K-562, respectively and in rats with food and water deprivation (FWD) group which served as a control for possible metabolic changes evoked by LH lesion-induced aphagia and adipsia ($r = 0.19$, $df = 28$, $P > .30095$ for YAC-1 and $r = 0.20$, $df = 28$, $P > .29294$ for K-562 cells). It can be concluded that damage to LH which is a dynamogenic and stressogenic brain area, induce large and long-lasting changes in LGL distribution which are reflected by changes in blood NK cell activity. It indicates the significant role of lateral hypothalamus in mechanisms responsible for the functioning and effectiveness of an immune response.

67.42 OLIGODENDROCYTE ULTRASTRUCTURE, GLUTAMINE SYNTHETASE AND BASIC MYELIN PROTEIN DISTRIBUTION, IN AN ADULT LIZARD FOREBRAIN.

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In mammalian CNS, Glutamine synthetase (GS) is essentially an astrocytic enzime, while in adult lizard is also present in cells not containing the astrocytic marker GFAP. These cells could be atypical astrocytes or oligodendrocytes (O).

In the adult lizard, three type of oligodendrocytes (O) can be distinguieshed in electron microscopy (EM): the most common are the "dark O.", with myelin processes ensheathing thick axons while the "light O. processes ensheath thin axons, " medium O." suply myelin to thin and thick axons. The three O. types are intermegled within myelinated tracts. Myelinated tracts and myelin distribution were studied by immunohistochemistry with immunesera recognizing myelin basic protein (MBP). Some tracts are intensely immunolabeled (i.e. mfb, lfb, tolf, tsh, tpoc, the forebrain bundle, the alveus); in the commissura anterior only few fibers were immunopositive.

The distribution of the GS positive cells does not correspond to that of the O.and of myelinated tracts, hence these cells do not correspond to the whole O. population but possibly to a special subclass of either O. or astrocytes. Double labelling experiments are in progress to verify this point.

67.43 GANGLIOSIDE GM1 POTENTIATES THE EFFECTS OF CHOLINERGIC AGONIST CARBAMYLCHOLINE (CARBACHOL) CHLORIDE

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Injections of an agonist of the cholinergic system carbachol (0.03-3 mkg) into the cortex and the striatum of rats induce significant changes in animal motor behavior. The administration of more than 10 mkg of carbachol results in the development of tremor and seizures. This effect of carbachol was more pronounced when ganglioside GM1 (1.6 ng) was injected into these brain structures during 3 days before the agonist administration. In this case lower concentrations of the agonist (3 mkg) had the convulsive effect at 9-11 days after GM1 injections. In the same experiments on rats treated with total bovine brain gangliosides (6 days, i.p., 30 mg/kg of body weight, 4 months before the experiments) the convulsive effect of carbachol (3 mkg) was observed on the first day after GM1 injections. Moreover *in vitro* experiments we have found that preincubation of synaptosomal membranes with 10^{-6}–10^{-9} M GM1 results in an increase in the activity of AChE. Thus, gangliosides can modify the activity of cholinergic system of the brain and potentiate the effects of its agonists. These data should be taken into account for searching a strategy for therapy of brain disorders both with gangliosides and cholinomimetics.

67.44 ANTISENSE OLIGODEOXYNUCLEOTIDES TO *BAX* mRNA INCREASE SURVIVAL OF SYMPATHETIC NEURONS *IN VITRO*.

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Previous *in vitro* studies have shown that the ratio of *bcl-2*, which promotes cell survival, to *bax*, which facilitates cell death, determines the susceptibility to apoptosis following growth factor deprivation. Expression of *bcl-2* and *bax* has been detected in sympathetic neurons *in vivo*, and overexpression of *bcl-2* in cultured sympathetic neurons prevented apoptosis after deprivation of nerve growth factor (NGF). Here we describe the effects of a 20-mer 3',5'-terminal phosphorothioated *bax* antisense oligodeoxynucleotide (ASO) on the survival of rat superior cervical ganglion neurons in cultures supplied with suboptimal concentrations of NGF.

Half of the cell number was maintained in cultures grown in 0.5 ng/ml of NGF for 2 days as revealed by tyrosine hydroxylase (TH) immunolabeling. Addition of a random sequence control oligodeoxynucleotide having the same base composition (1 µM) had no effect on cell survival when compared with vehicle-treated controls. By contrast, the number of TH positive neurons was significantly ($p<0.001$) increased and lactate dehydrogenase release into the medium was reduced in cultures treated with *bax* ASO (1µM). Furthermore, administration of *bax* ASO retarded neurite fragmentation. Levels of *bax* mRNA remained unchanged in antisense-treated cultures speaking against a RNase H mediated degradation of *bax* transripts. Since Bax antibodies were not available, we could not investigate a reduction in protein levels due to a translational block. However, ASO complementary to rat *bax* mRNA did not prevent apoptosis of chicken ciliary ganglion neurons indicating a sequence-specific mechanism of action. Administration of fluorescein-labeled oligodeoxynucleotides demonstrated intracellular uptake into cultured neurons. Thus, our data suggest that administration of *bax* ASO and a subsequent decrease in the ratio of pro-apoptotic *bax* to anti-apoptotic *bcl-2* may increase neuronal resistance to programmed cell death.

68. Poster Session: Disorders of the nervous system III

68.01 **APOLIPOPROTEINS E AND J IN RAT ISCHEMIC BRAIN: COLOCALIZATION WITH AMYLOID PROTEIN PRECURSOR.**

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Apolipoproteins were recently found to be bound to ß-amyloid peptide in brain and cerebro-spinal fluid and proposed to be a chaperone for ß-amyloid peptide. Since the aggregation/ conformation state of ß-amyloid peptide is important for its neurotoxicity, interactions with apolipoproteins may affect ß-amyloid peptide neurotoxicity. To test the hypothesis that apolipoproteins may modulate ß-amyloid peptide neurotoxicity we investigated it in ischemic brain. For the first time, evidence is provided that transient global cerebral ischemia lead to colocalization of apolipoproteins E, J and A-1 with amyloid protein precursor in brain. The close association between apolipoproteins and amyloid deposits suggests that apolipoproteins may play a crucial role in the conversion of ß-amyloid peptide to its ß-pleated form.

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68.02 **THE QUINOLINIC-ACID MODEL OF HUNTINGTON' S DISEASE IN RATS: BEHAVIOURAL AND "IN VIVO" AND "IN VITRO" ELECTROPHYSIOLOGICAL STUDIES**

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The influence of bilateral intrastriatal injections of quinolinic acid (QA, 300 nmol) was studied in male Wistar rats. Behaviourally, QA-lesioned rats showed motor hyperresponsiveness to d-amphetamine and place learning deficits in the Morris water maze (a test of spatial learning). Computerized EEG studies showed, in QA-lesioned animals, a significant reduction in voltage amplitude and EEG power at the level of frontal cortex. "In vitro" electrophysiological experiments on hippocampal slices revealed a significant reduction of post-tetanic potentiation (PTP) induction in the dentate area, while no differences between lesioned and sham-operated rats were observed in the induction of both long-term potentiation (LTP) and PTP in CA1 area. Finally, a significant loss in body weight and a marked striatal gliosis (GFAP staining) were observed in lesioned rats. The present data confirm the suitability of QA lesions of rat striatum as a model of HD Moreover, since QA is an NMDA receptor agonist, they support the excitotoxic hypothesis of HD. Animal care and use followed the directves of the Council of the European Communities.

68.03 EFFECT OF VERAPAMIL ON SPONTANEOUS MOTOR ACTIVITY AND TWO-WAY AVOIDANCE LEARNING IN NUCLEUS BASALIS-LESIONED RATS.

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It has been established that altered calcium homeostasis plays key role in neuron death, causing decline in motor and cognitive behaviors in patients with Alzheimer disease (AD). Therefore the present study was done to investigate the effect of Ca-antagonist, verapamil (1.0, 2.5, 5.0 and 10.0 mg/kg s.c., 30 min before the tests), on spontaneous motor activity (SMA) and two-way avoidance (TWA) learning (acquisition and performance) in adult male Wistar rats, 10 days after electrolytic lesions of nucleus basalis magnocellularis (NBM) - an animal model of AD. Significant decrease of both types of TWA learning with no changes in SMA was noticed in NBM lesioned rats, compared to intact and sham controls. Verapamil in dose of 2.5 and 5.0 mg/kg significantly improved TWA learning in NBM lesioned rats, not changing their SMA. This implies the therapeutic potential of Ca-antagonists in the treatment of AD.

68.04 MOVEMENT PREPARATION IN PARKINSON'S DISEASE INDEXED BY LATERALIZED MOVEMENT-RELATED CEREBRAL ACTIVITY

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Akinesia and bradykinesia in Parkinson's disease (PD) have been attributed to an impairment of movement planning, mainly on the basis of reaction time (RT) studies. We combined measurements of RT with recordings of movement-related cerebral potentials using a movement precuiing technique. Movement-related potentials were derived from the scalp-recorded EEG (26 ch). Central preparatory activity prior to movement was indexed by the Lateralized Readiness Potential (LRP), which represents isolated lateralized activity preceding uni-manual hand movements. Ten patients with moderately severe PD and an equal number of age matched control subjects were examined. There was a significant RT advantage for cued compared to uncued movements. RT was significantly slower in PD with cued as well as noncued movements. For both groups the LRP had an earlier onset when movements were cued than when they were uncued. The LRP in PD showed no delay and had the same topography as in normal subjects.

The RT results confirm earlier studies suggesting that PD patients, although generally slower, are able to use advance information for the planning of movement. The electrophysiological findings indicate a normal pattern of cortical activation preceding movement, which suggests that (at least until an intermediate stage of disease) PD patients do not invoke compensatory strategies in the preparation for movement.

68.05 BEHAVIORAL, NEUROCHEMICAL AND MORPHOLOGICAL OBSERVATIONS IN I.C.V. STREPTOZOTOCIN-TREATED RATS.

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In earlier studies we found that rats treated with an i.c.v. injection of streptozotocin (STREP) showed a cognitive impairment which was related to hippocampal choline acetyltransferase activity (Brain Res. 674, 142, 1995). Morphological studies showed that STREP causes neurodegeneration although the precise mechanism of action of STREP is not fully understood. Several explanations can be offered to explain the effects of STREP. STREP could decrease the central metabolism of glucose or STREP could induce oxidative stress, either directly or by formation of nitric oxide. Therefore, we performed a series of experiments to correlate the effect of STREP on behavior with neurochemical and neuroanatomical parameters. Preliminary results indicate that the effect of STREP on cognitive performance is related to the strain and age of the rats, and the type of behavioral test used. Further, it was found that STREP caused septal degeneration and thus disrupted the cholinergic input to the hippocampus. In addition, it was observed that STREP increased cyclic guanosine monophosphate levels in the brain, which suggests that nitric oxide may be involved in STREP-induced neurodegeneration.

68.06 PENICILLIN STIMULATES ACUTE POSTTRAUMATIC EPILEPTOGENESIS

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Time course of the lowering of convulsive threshold that follows brain lesions is an important variable that does not seem to have caught much experimental attention.The present study was aimed at determing the altered brain sensitivity to penicillin after acute cortical injury in the rats using EEG criteria. For this purpose 25 Wistar male rats (320-400gr) were bilaterally implanted with cortical electrodes over the sensorimotor cortex and with plastic guide cannula (1.5 x 7mm) rested on dura near the left recording electrode. The rats were brought into the experiment after 4 postoperative days. During the recording of EEG activity the mechanical brain injury was performed with stainless steel stylus (1mm wide) which was lowered in guide cannula 2.0 mm under thex dura.Crystalline penicillin (1.500.000 IU/kg) was injected 15 min after cortical lesion. EEG was monitored continuously during next 5 hours. In all rats the initial EEG changes in the injured cortical area were a low-voltage desynhronization (3-4 min) and an appearance of high-voltage monophasic negative spike with frequency of 0.5-1 Hz and amplitude of 100-350 uV.Monophasic negative spikes with the same frequency but larger amplitude were recorded in the contralateral homologous area. This posttraumatic irritative EEG activity lasted 15-35 sec. Spontaneous posttraumatic bilateral spikes were recorded sporadicly. No behavioral laterality was ever observed. The injection of penicillin following the cortical injury produced an increase of amplitude of single posttraumatic spike 5-6 times at the injured side and 2-3 times at contralateral side in all rats. Mild mioclonic jerks of head and forelimb coincided with generalized discharges in EEG. The increased frequency of bilateral discharges resulted in the development of GRAND MAL seizure activity. In the next 3-5 h paroxysms tended to disapear. These results indicate that the i.p.injection of penicillin after the acute brain injury increases neuronal excitability and enables ictal activity.

68.07 LOCAL ADMINISTRATION OF ß-AMYLOID (ß25-35) PEPTIDE IN THE NUCLEUS BASALIS OF MEYNERT AFFECTS CHOLINERGIC NEURONS.

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Alzheimer's Disease (AD) is accompanied by changes in neuronal morphology and by cell loss. A profound decline in the number of nerve cells occurs in the nucleus basalis of Meynert (NBM), which accounts for the severe cholinergic deficiency in the cortex of Alzheimer patients. The cognitive decline during this disease may, for a large part, be attributed to such a cholinergic defect. Other characteristic features of AD are senile plaques, of which the primary constituents are aggregated and deposited ß-amyloid fibrils. *In vitro* studies showed that large quantities of ß-amyloid peptide hampers neuronal function and may eventually lead to neuronal death. This way ß-amyloid peptide could play an important pathogenic role in AD.

The aim of the present study was to investigate whether *in vivo* local administration of ß-amyloid damages cholinergic neurons in the NBM. Therefore, the NBM of male Wistar rats (± 300 gr) were unilaterally injected with 1 µl synthetic ß-amyloid peptide (Bachem, USA; 5 nmol dissolved in double-distilled water). Animals were sacrificed 3, 14 and 21 days after injection with the ß-amyloid peptide, by means of transcardial perfusion. Brain sections were histochemically stained for acetylcholinesterase (AChE). Subsequently, the degree of cholinergic innervation of layer 5 of the parietal cortex was determined by counting the number of AChE positive fibers.

The density of cholinergic terminals in the ipsilateral parietal cortex 3 days after injection was significantly decreased with 21% ± 4.7. Longer survival periods (2 and 3 weeks) yielded a similar loss of AChE positive fibers (16% ± 2.9 and 15% ± 1.9, resp.).

The present data indicate that the ß-amyloid peptide affects cholinergic neurons in the NBM in such a way that the cholinergic innervation of the parietal cortex was reduced. Taken together, *in vivo* administration of ß-amyloid can mimic the cholinergic deficiency observed in the human AD brain.

68.08 KINETIC PATTERNS OF THE GERBIL BRAIN Na,K-ATPase IN THE PRESENCE OF VARYING CONCENTRATIONS OF ATP IN EXPERIMENTAL HEPATIC ENCEPHALOPATHY

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Na,K-ATPase, the enzymatic basis in the active transport of Na^+ and K^+ ions across the plasma membrane, plays an essential role in brain functions. It was suggested that under neuropathological conditions including hepatic encephalopathy (HE) it is more reasonable to study the brain Na,K-ATPase activity in the presence of varying instead of constant ATP concentrations. Therefore, our study was designed to determine kinetic patterns of hippocampal (Hippo), caudate nucleus (NCd), cortical (Cx) and hypothalamus (Hyth) Na,K-ATPase in the presence of varying concentrations of ATP in controls and gerbils with galactosamine-induced HE. In experimental animals Na,K-ATPase activity was determined 24, 48, 72 and 96 hours after galactosamine application. The kinetic pattern of Na,K-ATPase activity in controls in all examined brain regions is the same. Namely, the increase in ATP concentration produces the increase in the enzyme activity. After galactosamine injection the enzyme activity is inhibited in all regions up to four days. In Hyth ATPase kinetic pattern resembles that of controls, whereas the pattern of Hippo, NCd and Cx Na,K-ATPase activity differs from controls - the increase in ATP concentration produces the decrease in the enzyme activity. Hyth which has the highest control Na,K-ATPase activity among investigated brain regions, looses almost half of the activity after galactosamine administration, but without significant time-course variability observed in other brain regions. This difference in the behavior of Hyth enzyme during HE is not surprising because of it's complex homeostatic neuroendocrine role.

68.09 IMAGING OF LOCAL CEREBRAL BLOOD FLOW USING HIGH RESOLUTION THERMOGRAPHY. *Rausch M, Eysel UT. Ruhr-Universität Bochum, Inst.Physiol., 44780 Bochum, Germany

Blood flow varies due to activation of nerve cells and in response to a variaty of pathological states of the brain. Cerebral blood flow is accompanied by emission of thermal energy into cortical tissue. Accordingly, measurement of cortical temperature fields allows to access temporal and spatial changes in local cerebral blood flow (lCBF). To measure the two dimensional temperature fields we used a thermocamera (AGEMA, Sweden) with a resolution of 0.1°K. The theoretical spatial resolution is only limited by the attached optical system (in our case 70µm per pixel). The camera measures IR-radiation (2-4µm) originating from the upper 100µm of the cortical surface. Experiments were performed on adult wistar rats (350-450g) initially anaesthetised with pentobarbital (30mg/kg), and maintained under constant anaesthesia by continuous infusion of ketamine hydrochloride (3.6 mg/kg h). We measured temperature fields before and after induction of focal cortical lesions (photochemically induced thrombosis ond heat lesions). The lesioned area differed from the surrounding tissue by 0.2°K or less. To estimate the accuracy of this method we compared the results obtained by thermoimaging with histological controls and found a very close correlation for position and diameter of the lesion. We used theoretical modelling to assess the influence of heat conduction within the tissue. Interestingly, the results suggest that heat conduction only insignificantly lowers the spatial resolution of the method. Physiological changes in metabolism as well do not significantly affect the temperature distribution on the cortical surface. Consequently blood perfusion is the only relevant source of changes in cortical temperature.

From experiments and theoretical modelling we conclude, that thermography can be successfully used for high resolution imaging of cortical temperature distributions, and hence of cortical blood flow. The results are well reproducible and the technical expenditure is less than in most comparable methods.

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68.10 **ANTIRETROVIRAL THERAPY WITH 2'.3'.-DIDESOXYCYTIDINE (ddC) PROMOTES HIV-1-ASSOCIATED NEUROPATHY.**

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Infections with the neurotropic Human Immunodeficiency Virus Type 1 (**HIV-1**) are associated with peripheral nerve damage (HIV-1-associated polyneuropathy (**PNP**)). The rate of electrophysiologically detectable prevalence and clinical incidence of HIV-1-associated PNP parallels the increasing survival time of HIV-1-infected individuals.

Some antiretroviral drugs, e. g. 2'.3'.-dideoxycytidine (**ddC**), are known to cause PNP as a side effect. It is unknown, whether this is caused by a "neurotoxic" effect of the drug alone or whether it is due to a synergy with existent nerve damage, e. g. HIV-1-associated PNP.

Therefore we performed a clinical and electroneurographic follow-up of 101 HIV-1-infected individuals (20 CDC II, 19 CDC III, 62 AIDS) with different antiretroviral treatment (41 without treatment, 43 treated with Azidothymidin (**AZT**) and 27 treated with ddC). Electroneurographic tests were performed from the peroneal, the sural and the sensory and motor ulnar nerve.

HIV-1-associated PNP clinically presents as distal, symmetrical sensory type. Electroneurographically it is most often a demyelinating PNP. Electrophysiological signs of PNP could be detected in 37% of the AIDS-patients without clinical symptoms. Patients treated with ddC showed a higher rate of HIV-1-associated PNP than patients treated with AZT or without antiretroviral treatment. In ddC treated patients with sub clinical electrophysiologically detectable PNP there is a three times higher risk for clinical manifestation of PNP than in patients with AZT or without treatment.

These results indicate, that ddC seems to promote HIV-1-associated PNP. Therefore we recommend electroneurographic investigation before starting and through the course of therapy with antiretroviral drugs like ddC.

68.11 ACUTE-ETHANOL IMPAIRS NEUROMUSCULAR SYNAPTIC TRANSMISSION BY A DIRECT MECHANISM.

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The effects of acute ethanol (EtOH) administration on neuromuscular transmission have been investigated in vivo in the rat's tail. Extracellular compound muscle action potentials (CMAP) were recorded from dorsal musculature after electrical stimulation of caudal nerve, and latency of appearance, nerve conduction time and residual latency were measured at different time-points after acute ip. administration of ethanol (EtOH; 1-3 g/kg b.w.), tertiary butanol (*t*-But; 0.6 g/kg b.w.), acetaldehyde (20 mg/kg b.w.) or saline (control). Administration of EtOH or *t*-But resulted in increases in both latencies of appearance and residual latencies, while no modifications on these parameters appeared after administration of acetaldehyde. To further elucidate whether synaptic transmission was impaired after administration of both alcohols, in another series of experiments, repetitive stimulation (20 Hz, 60 secs.) was applied to the caudal nerve, resulting in progresive decrease of CMAPs amplitude in control animals (ie. synaptic fatigue), which resulted significantly potentiated in animals treated with either EtOH or *t*-But. Moreover, CMAPs amplitude failed to recover initial values in both EtOH- and *t*-But-treated animals once repetitive stimulation was finished. These results suggest that EtOH impairs synaptic transmission at the neuromuscular junction and that this alteration might be mediated by a direct mechanism, independent of EtOH metabolism.

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68.12 **AN AUTORADIOGRAPHIC ANALYSIS OF BRAIN DOPAMINE D_1 RECEPTORS IN AN ANIMAL MODEL OF ADHD DISORDER.**

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The spontaneously hypertensive (SHR) rats are thought to be a genetic model for studying attention deficit hyperactivity-disorder (ADHD) in children. The aim of this project was to investigate the neural substrates of ADHD by autoradiography using the neurogenetic approach on the brain of the SHR rats and normotensive Wistar-Kyoto (WKY) controls. In a first series of experiments, 4-weeks-old SHR and WKY-rats were either injected with methylphenidate (MP; 3 mg/kg, i.p.) daily during a 15 days period or with vehicle. Rat brains were frozen and stored at -80°C. Twenty-mµ cryostat sections were obtained across the caudate-putamen and accumbal complex to distinguish a frontal, a medial and a dorsal portion. In a saturation analysis (maximal binding capacity and affinity), sections were incubated with 7 concentrations of [^{3}H]-SCH23390 (0.1 - 5.0 nM). To control for non-specific binding D_1 excess cold SCH23390 was used. Slides were apposed to [^{3}H]-sensitive films and exposed for 18 days. Films were developed and optical density (OD) of sections with reference to co-exposed [^{3}H]-microscale standards (calibration curve to convert OD to receptor concentration) were analyzed by a PC-assisted image analysis (M4: MCID). The D_1 receptor binding density was differentially decreased after MP treatment in the anterior portion of the caudate-putamen complex of both SHR and WKY treated rats, and in the anteromedial portion of the n.accumbens of WKY-treated rats only.

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68.13 **A CYTOCHROME OXIDASE HISTOCHEMICAL ANALYSIS OF THE NEURAL SUBSTRATES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN AN ANIMAL MODEL.**

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The spontaneously hypertensive (SHR) rats are thought to be a genetic model for studying attention deficit hyperactivity-disorder (ADHD) in children. The aim of this project was to investigate by neurochemical imaging techniques the neural substrates of ADHD in this genetic model system. Behavioral and histochemical techniques have been employed using the neurogenetic approach on the brain of the SHR-rats and normotensive Wistar-Kyoto (WKY) controls. In a first series of experiments, SHR and WKY-rats were either trained on a multiple fixed interval 120-sec extinction 5-min paradigm or non trained. Rat brains were perfused and analyzed by immunocytochemistry for cytochrome oxidase (CO) histochemistry. Trained WKY-rats showed a marked staining in the striatum, n.accumbens, hippocampal CA1 and dentate gyrus, entorhinal, frontal, pyriform cortices, and amygdaloid nuclei. In the n. accumbens, trained WKY-rats showed a marked CO staining restricted to the anterior portion of the shell, whereas trained SHR-rats showed a diffuse staining along the extension of the shell. In the frontal and pyriform cortices, trained SHR-rats showed a lower staining than WKY-rats. In the amygdala, trained WKY showed a more marked staining in the basal nuclei, whereas trained SHR-rats showed very little staining in the lateral nuclei.

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68.14 CHRONIC MAO-B INHIBITION DOES NOT AFFECT BEHAVIOUR IN AN ANIMAL MODEL OF ATTENTION DEFICIT DISORDER

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Spontaneously Hypertensive Rats (SHR) show a higher response rate than Wistar Kyoto rats (WKY) in a visual discrimination paradigm and are considered a good animal model of Attention Deficit Hyperactivity Disorder (ADHD). SHR and WKY rats were chronically treated for 7 weeks with increasing doses (from 0.25 to 2 mg/kg) of the MAO-B inhibitor l-deprenyl (DEP) or with vehicle. The chronic treatment with DEP did not affect the SHR or the WKY rats' behaviour in this paradigm. Neither in the dorsal nor the ventral striatum nor in the frontal cortex were there any strain differences in tissue concentrations of noradrenaline (NA), dopamine (DA), serotonin (5-HT) or their metabolites, as measured post-mortem. However, SHR showed a lower striatal DA turnover and a higher 5-HT turnover in dorsal striatum and frontal cortex. DEP caused a decrease in DA metabolite levels, DA turnover, and 5-HT turnover in these three areas, as well as an increase in NA levels in ventral striatum and frontal cortex, in both strains of rats, indicating a possible inhibition of both MAO-A and MAO-B after chronic treatment. These results suggest that differences in monoamine neurotransmission in corpus striatum and/or frontal cortex may underlie the behavioural hyperactivity shown by SHR, but they can not be counteracted by MAO inhibition. They also confirm, in an animal model, the negative results obtained with DEP in the treatment of ADHD.

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68.15 DIFFERENTIAL REDUCTION IN HIGH AFFINITY NEUROTROPHIN RECEPTORS IN THE NUCLEUS BASALIS OF MEYNERT OF ALZHEIMER PATIENTS. A. Salehi*, J. Verhaagen and D. F. Swaab Graduate School Neurosciences Amsterdam, Netherlands Institute for Brain Research, Amsterdam, The Netherlands

It has been proposed that the neurodegenerative changes in Alzheimer's disease (AD) are the result of a lack of trophic support. The basis of this idea were i) the ability of cortical neurons to synthesize NGF, ii) the presence of both low (P75) and high (TrkA, B and C) affinity receptors in the nucleus basalis of Meynert (NBM) neurons and iii) the degeneration of both structures in AD. However, the level of NGF in AD was not decreased in the cerebral cortex. In order to study whether AD is associated with alterations in high affinity neurotrophin receptors (NTr) in NBM neurons, we applied three polyclonal antibodies against the external domain of trkA, B and C. Brain material of seven controls (63±4 years old) and seven AD patients (58±3 years old) was obtained at autopsy (7±1 hours post mortem delay), fixed in paraformaldehyde, embedded in paraffine and stained immunocytochemically. TrkA, B and C were present in numerous neurons in the NBM of all controls. However, in AD patients, all three receptors were dramatically reduced, both in number of immunoreactive neurons and in the staining intensity. The most severely affected NTr was trkA, followed by C and B. This decrease was specific for the NBM since immunoreactivity of other hypothalamic nuclei e.g., the supraoptic nucleus which is intensely stained in controls by trkB and C was not reduced in AD brains. Our study shows that the degeneration of NBM neurons is associated with a decreased expression of high affinity NTr.

Antibodies were a generous gift from Dr. D. Kaplan, Frederick Cancer Res. & Dev. Ctr. Frederick, MD, U.S.A. Brain material was obtained from the Netherlands Brain Bank (coordinator Dr. R. Ravid).

68.16 MOTOR NEURONAL ARRAYS IN THE SPINAL CORD OF MUTANT *MDX* AND *MND* MICE. D. Carretta$, M. Santarelli$ (*), R. Carrai$, F. Pinto$, A. Granato#, A. Sbriccoli§, and D. Minciacchi$. Department of Neurological and Psychiatric Sciences$, University of Florence; Institute of Anatomy#, Laboratory of Experimental Neurology§, Catholic University, Rome; Italy.

The mutant *mdx* and *mnd* mice are acknowledged models of human neurological diseases, namely the Duchenne Muscular Dystrophy and the motor neuronal disease-ceroid lipofuscinosis, respectively. We investigated the distribution of spinal motor neuronal populations in *mdx*, *mnd*, and normal C57BL/6 mice. Injections of aqueous solutions of WGA-HRP were performed into the sciatic nerve and retrogradely labeled motor neurons were studied in the spinal cord. In all animals were present distinct populations of large and small sized neurons; no major variations were observed in their laminar distribution. The number of cell labeled in the spinal cord was also similar in the different experimental groups. However, when compared to normal mice, large neurons were less numerous in *mdx* and *mnd* animals whereas small neurons were more numerous. In particular the ratio small *versus* large neurons was 1.4 in normal, and 2.5 and 2.4 in *mdx* and *mnd* mice, respectively.

First, the present data demonstrate that rearrangement strategies are operative for the spinal motor neuronal populations of *mdx* and *mnd* mice, this is particularly interesting in *mdx*, where structural modifications of the cortico-spinal tract have been recently described by our group (Minciacchi et al., Soc. Neurosci. Abstr., Vol. 20, p.3, 1994). Second, two strains which are model of very different neurological diseases display similar strategies of reshaping their motor neuronal pool. The relative increase of the small sized population is comparable in *mdx* and *mnd* and could be thus regarded as a rather stereotyped response of the spinal cord to various supra-spinal and/or peripheral alterations.

68.17 THE MATURATIONAL THEORY OF BRAIN DEVELOPMENT AND KRAEPELIN'S ENDOGENEOUS PSYCHOSES.

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Abstract.
An association has been established between pubertal age - rate of maturation and the final step in brain development when some 40% of synapses are eliminated. The restriction of pre-pubertal pruning to excitatory synapses leaving the number of inhibitory ones fairly constant, implies changes in cerebral excitability as a function of maturational rate.
In early maturation there will be an excess in excitatory drive due to prematurely abridged pruning, which compounds a synchronization tendency inherent in excessive synaptic density. In late maturation a deficit in excitatory drive due to failure to shut down the pruning process, associated with a tendency to the breakdown of circuitry and desynchronization, adds to a similar adversity inherent in reduced density of synapses.
The maturational theory holds that Kraepelin's psychoses are naturally occurring contrasting chemical signaling disorders in the brain at the extremes of the maturational rate continuum. Manic depressive psychosis is a disorder of the early maturer comprising raised cerebral excitability and synaptic density. Schizophrenia is a disorder in late maturation with reduced cerebral excitability and reduced synaptic density.
The conventional effective treatments act on inhibition only by either raising or lowering inhibitory level. By not directly affecting the deviation in excitability this could explain why the drugs do not prevent relapses, they do not cure.

68.18 AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA: A FAILURE OF SENSORY GATING?

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Two well established procedures have repeatedly demonstrated sensory gating deficits in patients with schizophrenia: First, prepulse inhibition (PPI) of the auditory startle (or eye-blink) reflex and second, PPI of the P1 amplitude of the auditory event-related potential (ERP). Both measures of sensory gating apply to automatic or "passive" auditory information processing. Here we report on PPI embedded in an active auditory discrimination task. In healthy subjects the "false alarm rate" was increased when the non-target tone was preceded by a soft acoustic pulse with an interval of 100ms. The response bias (beta) and the sensitivity index (d') correlated significantly with P3b amplitudes in the PPI condition. In schizophrenic patients measures of sensory gating deficits (the startle- and P1-PPI) correlated with their poor discrimination performance and slower reaction times. However, some similar results were also found in patients with obsessive-compulsive disorder. But only in schizophrenic patients an abnormal right-temporal lateralisation of P1-PPI was found. It is concluded that PPI already interferes with early (or pre-attentive) sensory gating mechanisms thus disturbing subsequent active signal vs. noise discrimination of higher cortical centres. This concept is supported by our recent clinical study. Treatment with clozapine seems to improve sensory gating[1] and active auditory information processing as indicated by increasing P3b amplitudes in patients who were prior poor responders to "typical" neuroleptics. Accordingly, positive symptoms like acoustic hallucinations but also complex cognitive functions like strategic thinking capabilities improved.

1) see Freedman et al., Harvard Rev. Psychiatry, 1994, 2:179-192

68.19 PERIPHERAL NERVE STIMULATION IN ALZHEIMER'S DISEASE. THE MORE THE BETTER? E.J.A. Scherder*, A. Bouma and A.M. Steen, Free University, De Boelelaan 1109, 1081 HV Amsterdam, The Netherlands.

In four studies, the effects of a six-week period with peripheral nerve stimulation on memory and affective behaviour of patients with probable Alzheimer's disease (AD) were examined. AD-patients were first treated with transcutaneous electrical nerve stimulation for six hours per day (long-term TENS), subsequently with a 30-minute-a-day application of tactile stimulation and TENS (short-term TENS), and finally with a combination of the latter two types of stimulation. The results of these studies suggest that some aspects of memory and affective behaviour improved, irrespective of the type and nature of the stimulation. However, contrary to our expectation, long-term TENS and combined stimulation yielded less beneficial effects on memory and affective behaviour than those observed after short-term TENS and tactile stimulation applied separately. Underlying theoretical mechanisms will be discussed.

68.20 GENE EXPRESSION OF THE α4 ISOFORM OF THE NICOTINIC ACETYLCHOLINE RECEPTOR IS NOT DECREASED IN THE CEREBRAL CORTEX OF PARKINSON PATIENTS WITH COGNITIVE IMPAIRMENT.

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Cholinergic and cholinoceptive dysfunction are well-known neurochemical features associated with cognitive dysfunction in Parkinson's (PD) and Alzheimer's disease (AD). Nicotinic binding sites have repeatedly been shown to be dcreased in the cerebral cortex of both PD and AD patients. The defect underlying the impaired synthesis of nicotinic acetylcholine receptors (nAChRs) is not well understood.

To start with the gene expression of the widespread α4 subunit, an in situ hybridization approach and a digoxigenin-labeled riboprobe were used to assess the number of α4 transcript-expressing neurons in the frontal cortex of cognitively impaired PD patients (n=4) and controls (n=4). Hybrids were detected by applying an alkaline phosphatase-coupled digoxigenin-antibody and a color substrate reaction.

As shown previously for the normal human cerebral cortex, a rather high number of neurons in layers II-VI expressed the α4 transcript in both groups. The densities of alkaline phosphatase-labeled neurons were not significantly different between control and PD cortices ($p > 0.05$). The same held true for the Nissl-stained neurons.

Disturbances of nAChR synthesis in PD and AD cortices may be located either at (1) the transcriptional or (2) the translational/posttranslational level. The α4 nAChR subunit does not appear to be a likely candidate for the first possibility, although deleterious point mutations may elude in situ hybridization. Mechanisms underlying the cholinoceptive deficit have to be searched for among other neuronal nAChR isoform genes as well as at subsequent stages of nAChR maturation and assembly.

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68.21 FLUPIRTINE HAS ANTIPARKINSONIAN EFFECTS IN MONOAMINE-DEPLETED RATS

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Blockade of glutamate receptors in the output stations of basal ganglia, the internal segment of globus pallidus and the reticular part of the substantia nigra leads to marked suppression of parkinsonian signs in rodent and primate models of Parkinson's disease. Flupirtine which is clinically used as an non-opioid analgesic agent has some NMDA antagonistic properties in different *in vivo* and *in vitro* experiments. We now report that in monoamine depleted rats flupirtine suppressed dose-dependently (1-20 mg/kg i.p.) rigidity, measured as tonic EMG activity in the gastrocnemius muscle, but had no effect on akinesia. In addition, it potentiated the antiparkinsonian effect of L-DOPA on akinesia and rigidity in this rodent model of Parkinson's disease. These effects of flupirtine are of particular clinical relevance, since flupirtine is free of typical side effects of NMDA-receptor antagonists.

68.22 DIASCHISIS, 'ROSSI EFFECT', AND ANTIEPILEPTIC ACTION OF CARBAMAZEPINE.

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Semiquantitative mapping of cerebral blood flow and metabolism, by single photon emission computerized tomography (SPECT), has revealed the occurrence of crossed cerebellar diaschisis (CCD) in epileptic patients following the Wada test with amobarbital (J. Nucl. Med. 28: 1763, 1987). Recently, we observed, by Tc-HMPAO SPECT, the occurrence of CCD following carbamazepine therapy, in two patients with partial epilepsy, and a left fronto-parietal epileptic focus at EEG (Prog. Neuropsychopharmacol. & Biol. Psychiat., in press). A depressant action of these drugs on the predominantly excitatory corticopontine-cerebellar projections, arising mainly from the frontal and parietal regions, is the most likely mechanism involved in this phenomenon. However, the functional significance of CCD remains unknown.

It has been shown that electrical stimulation of neocerebellum results in an increased excitability of the contralateral cerebral motor area (the so-called, 'Rossi effect'), and in a lesser extent of the contralateral parietal and temporal regions. (Arch. Physiol., 10: 389, 1912; J. Neurophysiol., 1: 16, 1938).

We suggest that the depressant action of amobarbital and carbamazepine on the cortico-cerebellar-cortical loop, as evidenced by CCD, may partly explain the antiepileptic effect of these drugs in some partial epileptic seizures, perhaps through a modulation of the 'Rossi effect'.

68.23 EXPRESSION STUDIES OF THE SPINOCEREBELLAR ATAXIA TYPE1 GENE.

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Spinocerebellar ataxia type1 (SCA1) is characterized by progressive neuronal loss chiefly involving the cerebellar Purkinje cells. The molecular basis of the disease is an expansion of a CAG trinucleotide repeat which lies within the coding portion of a novel gene and encodes a polyglutamine stretch. The size of the CAG repeat correlates with the age of onset and severity of disease. Towards understanding the mechanism of the selective neurodegeneration, the present study was initiated with the objective to characterize the expression of SCA1 protein (ataxin-1) in both normal and affected individuals. Earlier work indicated that the *SCA1* gene is transcribed from both the wild type and mutant alleles. To analyze the protein expression, polyclonal antisera were raised to a fusion protein expressed in *E. Coli*. Immunoblot analysis using lymphoblasts extracts from both normal and affected individuals revealed that the antisera recognize a 100kD protein. In addition, in extracts from SCA1 patients a protein of higher molecular mass was detected. The size of the higher band varied according to the size of the CAG repeat expansion. These data unequivocally demonstrate that both wild type and mutant alleles are translated. Expression of both wild type and mutant protein in COS cells transiently transfected with the respective cDNA also confirmed this observation. Expression of the mutant ataxin-1 protein was also studied in cerebellar tissue, the site of neurodegeneration in SCA1 and in parietal tissue which is not affected by the disease. Both the wild type and mutant proteins were expressed similarly in both tissues. These data support the hypothesis that a gain of function or a dominant negative mechanism is involved in SCA1. Immunohistochemical and subcellular localization of ataxin-1 is currently in progress.

68.24 LOCALIZATION OF THE AMYLOID PRECURSOR PROTEIN (APP) AT SYNAPTIC SITES OF THE RAT BRAIN.

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Alzheimer's disease is a progressive neurodegenerative disorder characterized by extracellular amyloid β/A4 protein (Aβ) deposits and the loss of neurons and synapses. Aβ is a 39-42 amino acid peptide derived from the larger membrane-associated glycoprotein, termed amyloid precursor protein (APP). APP is expressed in most mammalian tissues, especially in neurons, and it shows a high degree of evolutionary conservation. But the functional significance of APP has been subject to conjecture. To define the potential role of APP in the brain, we investigated the localization of APP at synaptic sites. We purified synaptic plasma membrane (SPM), synaptic vesicles (SV) and the post synaptic densities (PSD) from Sprague-Dawley rat brain, and examined them by immunoblot analysis using two specific antibodies against N-terminal or C-terminal of APP (gifts from Dr. Yasuo Ihara, the University of Tokyo). We now present that 105kDa full-length APP is localized at SPM, and that PSD contains C-terminal truncated APP. Immunoreactivity of APP was drastically decreased in SV. These data indicate that APP may have roles in physiological synaptic activity.

68.25 VOLUME AND DIMENSIONS OF THE HUMAN HIPPOCAMPAL FORMATION IN NORMAL AGING AND ALZHEIMER'S DISEASE

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Hippocampal atrophy was found as a common feature of advanced Alzheimer's disease (AD) and a good radiographic marker of the disease presence. In order to access aging and AD volumetric changes, 13 normal (ranging from 16 to 99 years) and 11 AD (ranging from 80 to 92 years) postmortem human hippocampi were analyzed. An optimized design for sampling, sectioning and measuring volume of the hippocampal fields using the Cavalieri principle on 50 μm thick cresyl-violet sections was implemented. The measurements were performed on an Olympus Video Stereological Analysis System. The results included shrinkage difference due to tissue processing. Statistically significant age-related reductions in volume of the neuron containing layers were found in the hilus and subiculum, but not in CA1, CA2&3 fields and granule cell layer. The mean total volume of the neuron containing layers of the hippocampus in AD was significantly smaller than in 8 age-matched controls. The most pronounced AD-related volume reductions were found in the subiculum, CA1 field and hilus. The mean values of standard axial length, longitudinal diameter and height through the band of Giacomini were, to a various extent, smaller in AD hippocampi than in normal controls. In addition, an unusual normal hippocampus with 7 internal convolutions was found.

The difference in the pattern of volume reduction associated with normal aging and that associated with AD, supports the hypothesis that AD is not accelerated by aging, but is a distinct pathological process. The data on volumes of the different hippocampal fields and dimensions of the rostral, most variable part of the hippocampus, presented in this study can also serve as highly informative parameters in ontological, phylogenetical, toxicological and radiographic studies. Moreover, the appearance of the hippocampal coronal cross-sections can be used in clinical antemortem radiographic diagnosis of AD.

68.26 EFFECTS OF FELBAMATE ON FIELD POTENTIAL RECORDED FROM RAT NEOCORTICAL SLICES.

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We used field potentials recorded from rat neocortical slices to characterize the electrophysiological effects of the anticonvulsant drug felbamate (FBM). Previous studies have shown that FBM is effective in the treatment of epilepsy. It has been suggested that different mechanisms are involved in the antiepileptic effect of FBM. The aim of the present investigation was to test whether FBM affected cortico-cortical synaptic trasmission whose overactivity has been involved in the pathophysiology of epilepsy. Field potentials were recorded from deep laminae neurons (IV-V layers) of prefontal and frontal cortical slices. Under control condition these potentials were almost completely blocked by 10 μM CNQX, an antagonist of non-NMDA receptors. In control medium (1.2 mM MgCl2 containing solution) stimulus-evoked field potentials were not affected by bath application of 10-100 μM FBM. When magnesium was removed from the bathing medium, we observed a time-dependent increase of field potential amplitude. This effect was reversed by normal magnesium and by bath application of 50 μM APV, an antagonist of NMDA glutamate receptors, suggesting that the removal of external magnesium reveals an NMDA-mediated component in the cortico-cortical field potentials. In the absence of magnesium, 10-100 μM FBM induced a dose-dependent reduction of field potentials amplitude. Our data support the hypothesis that FBM does not alter the release of excitatory amino acids, but reduce the NMDA-mediated component of the cortically evoked synaptic potentials.

68.27 NEUROPROTECTION AGAINST NMDA-INDUCED CELL DEATH IN RAT NUCLEUS BASALIS BY MK-801 AND NIMODIPINE: EVALUATION OF A COMBINED THERAPY AND TIME COURSE OF NEUROPROTECTION.

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Overstimulation of N-methyl-D-aspartate (NMDA) receptors by increased levels of excitatory amino acids is considered to be an important feature in the process of neuronal damage during hypoxia, ischemia and chronic neurodegenerative diseases. NMDA-overexposure leads to massive Ca^{2+} influx mediated primarily by activated NMDA receptor operated ion channels and secondary by voltage dependent Ca^{2+} channels (VDCC). In the present study we evaluated the neuroprotective effects of a combined therapy with a non-competitive NMDA-receptor antagonist (MK-801) and a voltage dependent L-type Ca^{2+} channel blocker (nimodipine) against NMDA-induced neurotoxicity. Most attention was focussed on neuroprotective effects of post-treatment, i.e. administration of the agents after NMDA-exposure.

In the currently used in vivo model 1 µl 0.06M NMDA was unilaterally injected in the nucleus basalis (MBN). Neuronal damage was quantified 12 days after NMDA-injection by measurement of axonal cholinergic fiber reductions in the ipsilateral cortex.

In non-treated controls NMDA-injections damaged MBN-neurons in such way that 66% of cholinergic terminals were lost in the parietal cortex. Pretreatment of a nimodipine diet (860PPM) starting two weeks before NMDA-injection together with MK-801 (5 mg/kg IP) applied 2 hrs before NMDA-exposure provided a neuroprotection of 89%. Combined therapy of MK-801 (5 mg/kg SC) and nimodipine (15 mg/kg IP) 8 min *after* MBN-infusion revealed a 82 % protection while the same combination given 2 hrs *after* NMDA-infusion resulted in still 66% protection against NMDA-neurotoxicity.

In conclusion, the present data show that dual blockade of NMDA-channels and VDCC's even 2 hrs after NMDA-exposure is able to provide a remarkable protection against NMDA induced toxicity.

68.28 C-FOS EXPRESSION IN NEOCORTICAL EPILEPTIC FOCI OF THE RAT: CHARACTERISATION OF THE ACTIVATED NEURONES WITH DOUBLE LABELLING.

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Ictal-like focal epileptiform activity was induced in the neocortex of anaesthetised rats by local application of 3-aminopyridine, and on the identical area of contra lateral hemisphere. After fixation coronal plane vibrotome sections were incubated in the mixture of polyclonal c-fos antibody and monoclonal anti-calbindin. Fluorescence secondary antibodies or avidin-biotin systems were used for detection.

C-fos immunoreactivity was seen in the whole cortical mantle of treated hemisphere: neocortex and allocortex (prepiriform areas) were equally stained. Scattered immunostained nuclei were seen in the contra lateral neocortex in every layers. The reticular nucleus of the thalamus, the claustrum, the amigdaloid nuclei and the media habenula contained c-fos immunostaining. Calbindin-containing neurones in the neocortex, prepiriform cortex, and basolateral amigdaloid nucleus expressed c-fos protein. The calbindin and c-fos expressing neurones of the cerebral cortex were medium-sized, non-pyramidal cells, heaving only a few but long dendrite-like processes. These preliminary results prove that focal neocortical epileptiform activity is activating large neuronal populations in the neocortex. Some of the should be inhibitory. The activated subcortical neural circuits may have excitatory connections with the cerebral cortex; and these synaptic connections have to be very effective, probably they induce gene expression and long-term changes. Obviously, we need more immunohistochemical data from further colocalisation experiments, in order to delineate the neuronal circuits which are sensitive to convulsant stimulation.

68.29 NEUROPHARMACOLOGICAL PROFILES OF SELEGILINE AND NIMODIPINE IN MODEL EXPERIMENTS WITH OLD RATS.

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Two nootropic drugs with different mode of action were studied in animal model experiments: selegiline, selective irreversible inhibitor of MAO-B, and nimodipine, Ca channel blocker. The experimental protocol simulated as close as possible the clinical situation in senile dementia treatment (i.e. *longterm peroral drug administration in aging rats*). Experiments were carried out in rats, strain Wistar, aged 12-22 months, treated for 10 weeks with selegiline (0.5 mg/kg/day) or nimodipine (10 mg/kg/day), mixed in standard pellet diet. Several behavioral tests as well as brain biochemical analysis were performed at the end of the experiment. In comparison with age-matched controls, treated rats of both groups improved some features of cognitive behaviour. Neurobiochemical effect of selegiline was characterized by decreased lipid peroxidation in the cortex, whereas in nimodipine by enhancement of cholinergic activity in the hippocampus. These results may be interpreted as a deceleration of aging processes.

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68.30 LEVEL OF DOPAMINE AND SEROTONINE IN EXPERIMENTAL MODEL OF ALZHEIMER'S DISEASE

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Update studies show that apart from deficiency of cholinergic system characteristic for Alzheimer's disease, there is deficiency of seretonergic system, while data showing disorders of dopaminergic system are less persuading. Many literature data show significant role of aluminum in pathogenesis of A.D., so treatment of experimental animals with aluminum has been proposed as a model for Alzheimer's disease. The purpose of our study was to examine changes of levels of dopamine and serotonine in cerebral cortex, hippocampus and nucleus caudate of Mongolian gerbils treated once with aluminum chloride *per os* in LD 25 dose (experimental model for A.D.) Animals were killed 24, 48, 72 and 96 hours after acute poisoning and levels of dopamine and serotonine were determinate by reversed phase liquid chromatography with electrochemical detection (HPLC-ED).

Significant decrease ($p < 0.01$) of level of serotonine in cerebral cortex and nucleus caudate of treated animals compared to the levels in control animals, was observed within first 24 hours after application of aluminum chloride (18.2±2.9 vs. 34.1±2.4 pmol/mg prot. for cortex and 19.9±2.5 vs. 49.4±4.2 pmol/mg prot. for n. caudate). During further investigated period level of serotonin continued to decrease reaching after 96 hours in cortex 8.7±0.6 pmol/mg prot. and 14.8±4.6 pmol/mg prot. in n. caudate. Level of serotonin in hippocampus also decreased after 24 hours, but statistically significant difference was observed after 72 hours (6.0±1.4 vs. 19.8±2.5 pmol/mg prot.).

Level of dopamine in cerebral cortex and hippocampus during first 24 hours decreased significantly ($p < 0.05$) compared to the levels in control animals (5.95±0.97 vs. 11.45±2.06 pmol/mg prot. in cortex and 1.45±0.55 vs. 4.13±0.63 pmol/mg prot. in hippocampus), but during further investigated period it reached levels similar to those in control group (after already 48 hours there was no statistically significant difference). Statistically significant differences of changes of levels in dopamine were not observed in nucleus caudate, compared to the levels in control animals (455.7±56.6 pmol/mg prot.), although there is some decrease in concentration of this parameter in animals killed after 48, 72 and 96 hours.

Changes of levels of dopamine and serotonine in this experimental model show changes similar to those observed in patients with Alzheimer's disease.

68.31 STUDIES ON THE PATHOLOGICAL EFFECTS OF BRAIN MICRO DIALYSIS IMPLANTATION ON THE SMALL BRAIN NUCLEI

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Brain micro dialysis probes have frequently been used for investigation of the brain neurotransmitter systems by sampling and monitoring from certain brain area (During, 1991; Vahabzadeh and Fillenz, 1992). They can be also used for therapeutic propose by the mean of the psycho surgical techniques. The present studies aimed to examine the pathological effects of micro dialysis probe implantation.

Rats (250-300 g) were implanted with micro dialysis probes in the ventral Tegmental Area (VTA), raphe nuclei (RN) and locus coeruleus (LC) under chloral hydrate anaesthesia (500 mg/kg i.p.) and perfused with artificial CSF. Then rats were scarified immediately, 12, 48, 72 hours after probe implantation and 7 (a week), 30 (a month), 356 (a year) days after removal of the implanted probe. Both Y and U shape probes with an outer diameters of 300 and 700 µm were used. For pathological examinations formaldehyde technique was used.

Microscopic examination of all given brain areas showed deformation and damage of the fibber together with capillary rupture along the passage of the implanted probe immediately after probe implantation. Deformation of the neuronal pattern was also present within 12 to 72 hours. However, this accompanied by the gathering of the glial cell within 72 hours along the passage of the probe. Glial gathering and deformation of neuronal pattern decreased but formation of fibrous tissue enhanced within 7 days after removal of the implanted probe. Within 30 days the fibrous tissue begun to shrank to about half an original size. 356 days after removal of the implanted probe the fibrous tissue disappeared along the passage of the implanted probe and no major behavioural, somatosensory and/or motor impairments were observed. Dispute of the larger diameter of the U shape probe the amplitude of the pathologic damage was close to the Y shape probe within loner period. However, short term deformation was greater with U shape probe. This probably is due to the elastic nature of the tip of the U shape probe.

The present studies suggest that probe related damage and functional impairments are negligible. Particularly this can be true in man with relatively greater brain and constant size of the probe. The result provide some supportive data for the use of brain micro dialysis technique in psycho surgery for local application of drugs.

References:

During, M. J. (1991). In vivo neurochemistry of the conscios human brain: Intrahippocampal microdialysis in epilepsy. In: *Microdialysis in the neurosciences*. T. E. Robinson and B. V. Justice (eds). 425-442, Elsevier Science Publishers B. V.,

Vahabzadeh, A. and Fillenz, M. (1992). Studies on the origin of hippocampal dihydroxyphenylacetic acid using microdialysis. *Neuroscience Letters* **136**: 51-55

68.32 NORADRENERGIC MODULATION OF KAINIĆ ACID-INDUCED GENERALIZED CONVULSIONS IN RATS.

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Noradrenergic system has been demonstrated to regulate seizure threshold in several models of epilepsy. We have tested the effect of several selective compounds intefering with the brain noradrenergic system on kainic acid-induced limbic seizures in rats. Rats were pretreated with one or with combinations of the following combounds: α_2-adrenoceptor agonist, dexmedetomidine (2.5, 5, 10, 20 µg/kg, s.c.), α_2-adrenoceptor antagonist, atipamezole (0.1, 0.3 mg/kg, s.c.), α_1-adrenoceptor antagonist, prazosin (0.1, 0.3 mg/kg, s.c.), β-adrenoceptor antagonist, propranolol (1, 5 mg/kg, s.c.). Kainic acid (7 mg/kg, i.p.) was injected 15 or 30 min after the injection of noradrenergic drug(s). Dexmedetomidine with the dose of 5 µg/kg was the most effective against generalized convulsions. Prazosin and propranolol did not markedly modulate the anticonvulsant effect of dexmedetomidine. Atipamezole (0.3 mg/kg) potentiated the kainic acid-induced convulsions, and the convulsions were further potentiated by the pretreatment with propranolol. On the contrary, prazosin antagonized the proconvulsant effect of atipamezole, indicating possible effect through postsynaptic α_1-adrenoceptor stimulation due to enhanced release of noradrenaline.

The results indicate that α_1- and β-adrenergic antagonism have limited effect on the anticonvulsant activity of α_2-agonist, dexmedetomidine but can modulate the proconvulsant effect of α_2-antagonist, atipamezole.

68.33 Abstract withdrawn

68.34 EFFECT OF K^+, HYPOTONIC SOLUTION AND EXCITATORY AMINO ACIDS ON DIFFUSION PARAMATERS IN THE ISOLATED RAT SPINAL CORD.

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Extracellular space (ECS) volume fraction (α) and ECS tortuosity (λ) - the parameters affecting diffusion of substances in the CNS - were studied in developing rat spinal cord. Changes in ECS diffusion parameters were measured using the real-time iontophoretic method (Nicholson and Phillips, J. Physiol. 321:225-257, 1981). Superfusion of isolated spinal cords with solution containing 50 mM K^+ induced a decrease of α from 0.18-0.27 to 0.08-0.15 and an increase of λ from 1.4-1.68 to 1.78-2.13. Hypotonic solutions produced similar decrases in α and small increases of λ . There were no significant differences in the peak values among age groups (P5, P10 and P20) but the time course was significantly slower in younger animals. Application of NMDA or AMPA resulted in a decrease in α up to 0.04. A larger change in λ was produced by AMPA (10^{-5}M), while NMDA ($5x10^{-5}$M) resulted in little or no increase in λ. The effect of NMDA was blocked by MK-801 and in Ca^{2+} free solutions, but not in solutions with 2-5 mM Ba^{2+}, and it was not observed at P10 and older animals. These differences can be explained by maturation of glia. Our results suggest that decreasing ECS volume is due to swelling of neurons and glial cells, while tortuosity might be related particulary to glial cells swelling. Funded by GAČR grant 309/94/1107 and U.S.- CZ S&T grant 920 48.

68.35 EFFECT OF ACUTE BENZENE ADMINISTRATION ON SOLUBLE AND MEMBRANE-BOUND TYR-AMINOPEPTIDASE ACTIVITIES IN SEVERAL AREAS OF THE RAT BRAIN.

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Benzene is an aromatic hydrocarbon, a petroleum by-product, a component of unleaded gas, and thus an ubiquitous environmental pollutant. Because of its physical properties, it is widely used in the chemical industry. It is well established that this organic solvent possesses neurotoxic and behavioural effects. However, the neurochemical mechanism of this solvent action on the central nervous system is relatively unknown. It has been recently described that subacute and subchronic exposure to benzene generates a reduction in immunostaining for met-enkephalin in several areas of the rat brain. In this communication, the effect of acute administration of the toxicant on Tyr-aminopeptidase activities in different brain regions of the rat is described. These enzymes have been suggested as the principal regulators of enkephalins in the neuron. The brain areas (taken by dissection) under study were the frontal and parietal cortices, the striatum, the hypothalamus, the hippocampus, the amygdala, the medulla and the globus pallidus. Acute treatment with benzene generates a reduction in membrane-bound puromycin sensitive (aminopeptidase MII) and insensitive (aminopeptidase M) enzyme activities in the hypothalamus and the medulla. Aminopeptidase M also decreases in the thalamus after benzene treatment. It could be suggested that membrane-bound Tyr-aminopeptidase activities could play a role in benzene neurotoxicity.

68.36 PREDICTIVE VALUE OF MEMORY SCORES IN PATIENTS WITHOUT DEMENTIA REFERRED TO A MEMORY CLINIC

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It is difficult to assess whether cognitive complaints in elderly are the first manifestions of dementia. To investigate this problem a follow-up study has been set-up with patients without dementia referred to a memory clinic. As memory is one of the first cognitive functions that deteriorates in dementia, it was supposed that patients who become demented during the follow-up had lower memory scores on the first visit compared to patients who did not decline. Not eligible were patients with age <40 years, MMSE<25, and patients with organic or systemic disorders that were a likely cause for the cognitive complaints. Initial assessment included a dementia screening, and a neuropsychological test battery. The Auditory Verbal Learning Test was used to assess memory. Outcome measures were total number of words remembered, delayed recall and delayed recognition. After 2.5 years the patients were seen again. They were screened for dementia with dementia rating scales and with the same neuro-psychological test battery.

Of the 111 patients who entered the study, 76 got the second evaluation (68%). Nine of these patients had become demented. This subgroup had been on average 10 years older (66 vs 55 years) than the group of non-decliners at the first assessment. They had performed significantly worse with respect to the total number of remembered words and delayed recall, compared to the non-decliners. However, when the scores were corrected for age, these differences were not significant anymore.

It is concluded that memory assessment alone can not identify the patients who are at risk for dementia.

68.37 PROBLEMS AND PITFALLS IN CULTURING RAT MOTOR NEURONS

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of unknown origin, characterized by progressive degeneration of spinal cord motor neurons (MN). MN enriched cultures obtained from rat embryos are frequently used to study the pathogenesis of ALS. Primary MN cultures were prepared from ventral spinal cord of E15 rat embryos using a metrizamide gradient (9.2%) and plated on PLL-coated chamber slides (Labtek, 100.000/cm^2). Chicken muscle extract was added to the cultures. The MN enriched fraction contained 52% MN (large multipolar cells, cell diameter $\geq$15 μm) after 15 h, 50% MN after 24 h and 48% after 48 h in culture. At these time points 66%, 81% and 86% stained positive for the low affinity NGF-receptor using the antibody 192-IgG. With an antibody against the homeobox protein Islet-1 (2D6 Islet-1 diluted 1:2-500), suggested to be MN specific, 100% of cells stained at 15, 24 and 48 h after plating. Incubation with propidium iodine revealed 39%, 31% and 33% dead cells after 15, 24 and 48 h resp. Apoptosis was visualised in situ as well. Usually MN are characterized on morphological and immunostaining characteristics.We conclude that in the evaluation of MN enriched cultures immunostaining properties (NGF, Islet-1, CAT) alone are not suitable to evaluate MN purity, because the antibodies are not MN specific. Morphometry and cell death evaluation are equally important to describe the cultures in detail.

68.38 MODULATION OF SODIUM CURRENTS BY VALPROIC ACID IN ACUTELY ISOLATED CA1 NEURONS FROM HUMAN AND RAT HIPPOCAMPUS

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The effect of valproic acid (VPA, 2 mM) on sodium current (I_{Na}) was studied in cells dissociated from the hippocampal formation resected from drugresistant epileptic patients and from rats. CA1 pyramidal neurons are enzymatically isolated and sodium currents were measured at room temperature, under whole-cell voltage-clamp conditions.

Voltage steps from -120 mV to -20 mV evoked maximal I_{Na} with a peak of -230 $\pm$ 50 A/F (n= 17) in neurons from patients and of -439 $\pm$ 44 A/F (n= 15) in neurons from rat. The time constant of current inactivation was -2.3 $\pm$ 0.2 ms in human cells and -2.1 $\pm$ 0.1 ms for rat cells. The half maximal activation potential ($V_{h,a}$) was -26 $\pm$ 1 mV for human and -28 $\pm$ 1 mV for rat. Half maximal steady-state inactivation potential ($V_{h,i}$) was -61 $\pm$ 2 mV for human and -63 $\pm$ 2 mV for rat. Recovery from inactivation at -70 mV had a time constant of -16 $\pm$ 2 ms for human and -15 $\pm$ 1 ms for rat.

Apart from the current density the basic properties of I_{Na} in CA1 neurons were comparable for human and rat.

Maximal I_{Na} was not reduced by VPA. Under VPA the current inactivation time constant was reduced by 0.2 ms in human and rat; $V_{h,a}$ was shifted by -4 mV in humans, $V_{h,i}$ was shifted by -4 mV, in human and rat; the time constant of recovery from inactivation was changed by -6 ms for human and by -3 ms for rat. Trains of ten depolarizations from -70 mV with an interval of 10 ms showed the accumelative effect of VPA on repetitively activated I_{Na}. Under VPA I_{Na} evoked at the first depolarization was reduced by 14% for human and by 11% for rat; the steady state level of activation, reached after five depolarizations, was reduced by 29% for humans and 19% for rat.

The reduction of sodium current by 2 mM valproic acid becomes especially apparent at high frequency activation in cells from human and rat.

68.39 ELECTROPHYSIOLOGICAL AND CLINICAL OBSERVATIONS IN MOUNTAINEERS DURING SHORT TERM EXPOSURE TO 3,050 AND 4,559 METERS. G. Riedmann and R. Waanders*, Ludwig-Boltzmann Institut für Neurorehabilitation und Prophylaxe, A-6830 Rankweil, AUSTRIA.

In two field studies in the Alps we examined the impact on EEG parameters of 1 to 5 h of exposure to moderately hypoxic altitudes of 3,050 and 4,559 m (ascent from 500 m within 24 h), where the pO_2 of the ambient air is ± 25-40% lower compared with sea level. At 3,050 m 54 volunteers and at 4,559 m 22 subjects participated.

Severity of Acute Mountain Sickness (AMS) was determined too using a clinical list of symptoms (Lake Louise, 1993).

After puncture of the radial arteria arterial blood oxygen pressure paO_2 was measured with AVL 912. The hemoglobin in the arterial blood was about 90% oxygen saturated at 3,050 m, whereas at 4,559 m it was about 70% oxygen saturated.

EEG spectral analysis was first performed at a base-line altitude of 500 m. Now, base-line data will be compared with measurements of absolute and relative alpha power, of increase in beta and theta power and of paroxismal theta activity at 3,050 and 4,559 m (NEUROFILE 2: Nihon Kohden). Also, EEG parameters will be compared between subjects showing signs of AMS (AMS+) and healthy mountaineers (AMS-). Next, values in spectral EEG bands will be correlated with paO_2.

We expect altitude dependent clinical scores of AMS as well as changes in EEG bands related to hypoxic conditions (lowered paO_2) at 3,050 and 4,559 meters.

68.40 ADDITIVE EFFECTS OF LAMOTRIGINE WITH AN ORGANIC CALCIUM ANTAGONIST IN IN VITRO EPILEPTOGENESIS
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It is assumed that the antiepileptic action of lamotrigine (LTG) may be due principally to inhibition of glutamate release through blockade of voltage dependent sodium channels (Leach et al., Epilepsia 27, 490-497, 1986). Since epileptic activity can be blocked by organic calcium channel blockers, the aim of the present investigation was to compare the action of LTG with the organic calcium antagonist verapamil (VERA).
Experiments were carried out in hippocampal slice preparations of guinea pigs. Extracellular field potentials (EFP) were induced by omission of the extracellular Mg^{2+} and augmentation of the K^+ of the extracellular fluid. LTG reduced in a dose-dependent manner the frequency of occurrence of EFP in areas CA1 and CA3. The threshold concentration which did not decrease EFP repetition rate was about 1 µmol/l. A combination of this subthreshold concentration with a subthreshold concentration of VERA (2 µmol/l) decreased the repetition rate to 33.5 ± 11.4 % of the initial value (n=6) after 34 ± 7.7.min. A combination of LTG with a subthreshold concentration of the NMDA antagonist APV was without effect.
The results suggest that LTG may have besides the action on sodium channel also an effect on voltage dependent calcium channels which recently was shown in glial cells (Lees and Leach, Brain Res. 612, 190-199, 1993).

68.41 RELATION BETWEEN Ca^{2+} HOMEOSTASIS AND EXCITABILITY OF CULTURED MYOTONIC DYSTROPHIC SKELETAL MUSCLE CELLS.
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The neuromuscular disease myotonic dystrophy (MyD) is characterized by increased excitability, delayed relaxation, weakness and wasting of muscle and abnormalities of various non-muscle systems. Defective regulation of ion homeostasis may explain the pathophysiology in MyD.

The effects of repeated 125 mM K^+ stimulation on the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) were measured in cultured skeletal muscle cells of controls and MyD patients using the fluorescent probe Fura-2. This study was approved by the Ethical Committee of the University of Nijmegen.

The basal $[Ca^{2+}]_i$ in control cells is about 130 nM. During repeated K^+ stimulation the characteristics of a Ca^{2+} response, *i.e.* the amplitude ($[Ca^{2+}]_{i,max}$), $[Ca^{2+}]_i$ at the end of a repolarisation period ($[Ca^{2+}]_{i,rest}$) and the halflife time of the increasing (τ_i) or decaying phase (τ_d), depend on the repolarisation time between two successive K^+ stimulations. When the repolarisation time decreases the Ca^{2+} responses become smaller and slower. As result $[Ca^{2+}]_{i,rest}$ raises, $[Ca^{2+}]_{i,max}$ declines and τ_i as well as τ_d increase. When $[Ca^{2+}]_{i,rest}$ equals the basal $[Ca^{2+}]_i$ the inital Ca^{2+} response can be recovered. In MyD muscle cells the basal $[Ca^{2+}]_i$ is significantly higher. In all experimental settings their Ca^{2+} transients are smaller and slower compared to the corresponding Ca^{2+}responses of control cells.

In conclusion: there is a high correlation between $[Ca^{2+}]_{i,rest}$ and both τ_i and $[Ca^{2+}]_{i,max}$ and between $[Ca^{2+}]_{i,max}$ and τ_d. These correlations are the same in muscle cells of controls and MyD patients. MyD muscle cells are, however, less excitable due to their elevated basal $[Ca^{2+}]_i$. This phenomenon would oppose myotonia but it could explain the muscle weakness in MyD.

68.42 COEXPRESSION OF α4-SUBUNIT NICOTINIC ACETYLCHOLINE RECEPTOR mRNA AND TAU PROTEIN IN THE CORTEX OF ALZHEIMER PATIENTS.
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Changes in pharmacology and expression of the nicotinic acetylcholine receptor (nAChR) have been among the first reported neurochemical landmarks of Alzheimer's disease (AD). The availability of nAChR subunit specific nucleic acid probes allows us to investigate possible changes in subunit gene expression and resulting different receptor subtypes and its relation with pathological intracellular changes.

In situ hybridizations were carried out on autopsy samples of the superior frontal gyrus of AD brains (n=6) and age-matched controls (n=5) using digoxigenin-labeled riboprobes specific for the α4 nAChR subunit. Hybridized probes were visualized by an alkaline phosphatase coupled-digoxigenin antibody and incubation with BCIP/NBT. Simultaneous detection of tau-protein was achieved after hybridization by applying a monoclonal anti-tau antibody and an indirect immunoperoxidase protocol.

As reported earlier, α4 subunit mRNA was expressed in various neurons of all cortical layers. There were no overall alterations in the distribution of α4 subunit nAChR expressing neurons in AD as compared to controls. Corresponding to the density of structures expressing tau protein, the number ofα4 mRNA-bearing apical dendrites was decreased in AD, especially in layer II/III pyramidal cells. Neurons heavily labeled for the tau-protein displayed only a weak α4 mRNA signal.

The present results underline the importantrelation between the expression of pathologic filaments and nAChR mRNA. Additional mRNA distribution studies on the EM level will render further informations on nAChR mRNA transport.

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68.43 MORPHOLOGY OF NEURONS AFTER EPILEPTIC ACTIVITY: FINE STRUCTURE AFTER APPLICATION OF A CALCIUM IONOPHORE (BUCCAL GANGLIA, HELIX POMATIA).
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Epileptic activity leads to an increase of intracellular calcium ($(Ca^{++})_i$) and also to alterations of neuronal fine structure. Causal relationships between both phenomena are unknown. Presently it is studied whether non-epileptic increases in $(Ca^{++})_i$ can change the neuronal fine structure in a way comparable to that observed after epileptic activity.
For experiments the identified neuron B3 in the buccal ganglia of *Helix pomatia* was treated for 5 h with a snail "Ringer" solution containing 100 µg/ml of the calcium ionophore A23187. Tissue was processed for electron microscopy (n=6). The treated ganglia were compared to ganglia in which epileptic activity was induced with pentylenetetrazol (40 mmol/l, 5 h, n=6) and to non-treated ganglia (controls, 5 h, n=6). Changes in $(Ca^{++})_i$ were monitored in neurons injected with fura 2.
Application of pentyleneterazol induced alterations in neuronal fine structure compared to controls. The alterations after epileptic activity were comparable to those after application of the ionophore. After both treatments, there was a condensation of the fine granular chromatin, which tended to aggregate with heterochromatic islets. The number of clear vesicles profiles (diameter up to 0.3 µm) was significantly increased compared to controls and especially small vesicles (diameter below 100 nm) were most frequent. Dictyosomes were often filled with electron dense materials and/or showed a reduced number of vesicles in the trans-golgi region. The rough endoplasmic reticulum (rER) tended to aggregate. After ionophore treatment, however, meander-like structures of the rER occurred and the rER appeared widened and electron-lucent in some regions.
Since fine structural alterations after epileptic and non-epileptic increase of $(Ca^{++})_i$ share common characteristics, it can be speculated that epileptic activity evokes fine structural changes via an increased $(Ca^{++})_i$.

68.44 ON THE MECHANISM OF EXCITATORY AMINO ACID RELEASE DURING ISCHEMIA - LIKE CONDITIONS IN RAT HIPPOCAMPAL SLICES.
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Ischemic neuronal injury is caused in part by the accumulation of excitatory amino acids (EAA) in synaptic cleft. EAAs are released into extracellular space from synaptic vesicles, metabolic pool of neurones and from cytoplasm of glial cells. The importance of these particular sources in ischemia - stimulated release is still under discussion. In this studies the release of non metabolised analogue of glutamate: [^{3}H] D-aspartate ([^{3}H]D-asp.), loaded into 500 µm slices of rat's hippocampus was investigated. The efflux of EAA was measured during anoxic - aglicemic incubation and stimulation with 65 mM KCl. To determine the pool from which [^{3}H] D-asp. is released we used inhibitors of Na^+-dependent transporter of aminoacids: L-trans-pyrrolidine-2,4-dicarboxylic acid (PDC) and sodium channel bloker tetrodotoxin (TTX). It is shown, that, upon KCl stimulation in normoxic condition, about 40% of the aminoacids is released from synaptic vesicles (TTX and sodium dependency). Additional 40% is transferred to the extracellular space from the cytosol of neighbour cells propably by the reversion of Na^+-dependent transporter situated in the membranes of both neuronal and glial cells. This last component is preferentially stimulated during ischemia. Thus, application of PDC during ischemia *in vitro* significantly decreased the massive influx of EAA into synaptic cleft. The additional experiments strongly suggested, that the increase in extracellular EAA during ischemia is also mediated through stretch activated channels localised in the membrane of astrocytes. Swelling of these cells during and after ischemia could be the additonal driving force for their opening.
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68.45 SYNAPTIC ALTERATIONS ON LUMBOSACRAL MOTONEURONS AFTER LOW THORACIC SPINAL CORD HEMISECTION IN THE ADULT RAT.

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Synaptic changes on lumbosacral motoneurons (MN) were studied between 3 and 90 days after low thoracic spinal cord hemisection in adult rats by light microscopic immunohistochemistry for synaptophysin (SYN) and also by electron microscopy (EM). In all segments caudal and ipsilateral to the lesion, there was a transient loss of SYN-immunoreactivity at the somal and proximal dendritic surfaces of MN, which extended caudally, from the side of injury, over a postopertive (p.o) period of 42 days and returned to close to normal levels by 90 days p.o.. Coincidentally, EM revealed phagocytosis of early degenerating axo-somatic boutons by activated microglia. However, numerous boutons which persisted at the perikaryal surface of MN underwent complex non-degenerative changes which were resolved by 90 days p.o.. From 42 days p.o., somal surfaces of MN were partially covered by processes of reactive astrocytes and occasionally degenerating motoneurons were detected. This apparent preferential disturbance of predominantly inhibitory axo-somatic synapses may alter the normal excitatory/inhibitory balance of synaptic input at the MN level and contribute to the well-established increase of motoneuronal excitability after spinal cord injury.

69. Poster Session: Behaviour III

69.01 A DOPAMINE ANTAGONIST BLOCKS ENHANCED DISTRACTIBILITY PRODUCED BY FOOTSHOCK OR EXCITOTOXIC LESION OF THE PREFRONTAL CORTEX.

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We have previously established an animal model of cognitive distractibility. After being trained to traverse a straight runway in order to receive reinforcement rats are exposed to an additional runway ending in an empty box. In this procedure, dopaminergic stimulants increase the time spent in the additional runway. Visits to this runway interfere with goal directed behavior and are therefore considered as distraction. These visits are different from exploration, because dopaminergic stimulation reduces exploration of an unknown environment. There is evidence that enhanced dopaminergic transmission impairs selective attention and augments sensitivity to distractors. It seems, then, that the procedure is an adequate model of distractibility. Using this model, we have found that footshock and excitotoxic lesions of the prefrontal cortex increased distractibility. Both these events stimulate dopamine release in the nucleus accumbens. The role of dopamine, however, was not evaluated in that study. The purpose of the present work was to determine if a dopamine antagonist could block the increase in distractibility produced by footshock or cortical lesion.

Six groups of rats were used. One received a saline injection before the distractometer test. The second was shocked for 100 sec 10 min before the distractometer test. The third was shocked after injection of 0.25 mg/kg of cis(Z)-flupentixol, the fourth was prefrontally lesioned with kainic acid, the fifth was lesioned and injected with flupentixol before the test; and the last group was left intact and injected with flupentixol in the absence of shock. The results showed that footshock and lesion enhanced distractibility. This effect was blocked by flupentixol. The drug had no effect by itself. It is concluded that the procedure may be a useful model of schizophrenic attention disorder.

69.02 IMPAIRED PERFORMANCE ON A SPATIAL CONSTANCY TASK FOLLOWING DORSO-MEDIAL (DM) AND DORSO-LATERAL (DL) TELENCEPHALIC LESIONS IN GOLDFISH.

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Fish spatial abilities have been widely described. Recently, fish telencephalon involvement in spatial learning and memory has been suggested. Telencephalic ablation in teleost fishes produces impairment on tasks in which place strategies are required. In land vertebrates, similar spatial learning deficits have been found after hippocampal formation lesions. Embriological, citoarchitectural, histochemical and electrophysiological data have led to discrepant hypothesis on the limits of the pallium in teleost fishes, as different structures have been proposed as homologous to the hippocampus of land vertebrates. The present work studies the effects of DM and DL telencephalic lesions on the performance of goldfish in a task with spatial memory requirements. Goldfish were trained to solve a "spatial constancy" task (Ingle & Sahagian, 1973). Once criterion was reached, animals received one of these surgery treatments: bilateral DM, DL or Anterior ablation, olfactory tract transection, sham operation or intact. Following surgery recovery, DM and DL animals showed significant impairments in the solution of the spatial task. Nevertheless, the DM group improved performance with retraining. In contrast, the effects of the ablation of the DL nucleus persisted by the end of the experiment. Neither of the other groups showed significant differences after surgery. The resuts are discussed in regard to similar data found in reptilians, birds and mammals following medial pallium or hippocampal formation lesions. Finally, implications for possible hippocampal homologies are suggested.

69.03 ARE NEURASTHENIC SYMPTOMS CAUSED BY IMPAIRMENT OF ASTROGLIAL K^+ AND GLUTAMATE UPTAKE?
An hypothesis that link astroglia to behaviour

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Asteno-emotional (AE or neurasthenic) symptoms with stress intolerance, decreased simultaneous capacity, fatigue upon mental activity, lability and decreased concentration capacity are common in organic brain processess. The symptoms often precede degenerative brain diseases such as dementias, or inflammatory diseases such as multiple sclerosis or can accompany a focal brain lesion such as a focal trauma or a stroke. The symptoms may appear even in the absence of a focal tissue destruction, *e.g.* after a concussion or after a virus meningitis with no other neurological symptoms. In fact, the AE symptoms can develop even in situations of massive anxiety and stress and can thus be induced by psychological mechanisms. The AE symptoms may persist for long periods of time and may impair the patient's possibilities to work and thus make rehabilitation more difficult.

The underlying cause of the symptoms seems to be a decreased capacity for fast and distinct activation of many neuronal pathways in parallell and during longer time periods. The pathogenetic mechanisms might be a disturbance in the glutamate (Glu) transmission with a decreased signal to noise ratio for the transmitter.

We here present data that the astroglial syncytium by modulating the neuronal extracellular miliue, can regulate the excitability of many neuronal systems in parallell. Furthermore, we present evidence that a dysfunction of these cells, concerning extracellular clearance of K^+ and Glu, might be one pathogenetic factor in the development of the AE symptoms.

69.04 SEVERAL REPRESENTATIONS FOR A SINGLE POINTING ACTION.

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There are neuropsychological evidences for separate systems involved in visual perception and movement production toward visual goal. This work was aimed at investigating such a dissociation for proprioception in normals. Subjects were asked to point with their right arm in the sagittal plane toward unseen proprioceptive target. Target locations were demonstrated by a passive positioning of the left hand. Two different target arrays were used (arc or line). When pointing movements were made immediately after target demonstration (delay 0), the confidence elipses of the endpoints tended to be slightly elongated toward the starting point. When pointings were made after an 8 seconds delay, the elipses were larger and elongated along a major axis aligned with the target array. Interestingly, requiring the subjects to point with a 0 second delay while verbalizing target position produced pointing distributions which major axes were also aligned with the target array. This did not occur when subjects had to verbalize another word during their movement. These results show that building up a verbal representation of the stimulus or memorizing its location alters the nature of the errors made by movements aimed at this stimulus. These data support the idea that two different systems can be responsible for goal directed movement generation. These data support the existence of two visual systems devoted respectively to action (pragmatic or "How" system) and to perception (semantic or "What" system).

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69.05 AN IMAGE-PROCESSING SYSTEM TO DISTINGUISH DIFFERENT RESIDENT-INTRUDER INTERACTIONS IN A COLONY OF RATS.
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An video tracking and motion analysis system was developed which is able to track 4 rats living in a colony situation. The system the individually identifies the rats by means of a colour mark applied to their dorsal fur. A female and a male intruder were introduced into the colony and observed by the automated system for a period of 45 minutes. The X,Y-coordinates corresponding to the spatial locations of the rats were stored on file and used to quantify the temporal and spatial characteristics of the interactions between the residents and female or male intruder. Human observations, conducted over a period of 10 minutes, were compared to parameters calculated from the X,Y-coordinates. These parameters are: travelled distance, average distance between rats, dyadic net movement-towards/movement-from and the frequency with which the distance between members of a dyad fell within a certain range. The relative hierarchical position of residents and behavioural differences as determined by the human observer, were replicated by the automated system.

69.06 STUDIES ON THE ROLE OF THE SEROTONERGIC SYSTEM AND ITS INTERACTION WITH THE CHOLINERGIC SYSTEM IN THE MODULATION OF WORKING MEMORY IN RATS .
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The present study compared the effects of muscarinic antagonists (scopolamine, N-methylscopolamine) and nicotinic antagonists (mecamylamine, hexamethonium) on working memory between the rats with a serotonergic lesion (5,7-DHT icv or pCA ip) and their controls. Working memory was assessed using the delay non-matching to position task. 5,7-DHT group had a more profound decrease of serotonin in the hippocampus (90%) than pCA group (65%). The choice accuracy did not differ between control group and pCA group, but 5,7-DHT group chose more poorly than their controls. The difference in choice accuracy was apparent at the longest delays (8 and 16 secs) which favors for the impairment of working memory. Scopolamine (75 and 150 µg/kg) reduced choice accuracy, and pCA group, but not 5,7-DHT group, tended to be more sensitive to scopolamine-induced impairment of choice accuracy than their controls. Mecamylamine (3 mg/kg) slightly impaired choice accuracy, but this effect did not differ between serotonin-lesioned and control rats. However, the reduction of choice accuracy which was induced by cholinolytics was apparent even at the shortest possible delay which suggest that it is non-mnemonic deficit rather than the impairment of working memory *per se*. In addition, scopolamine and mecamylamine also impaired performance of rats (e.g. a marked reduction of completed trials). Furthermore, N-methylscopolamine (150 µg/kg), a peripheral antagonist, impaired the performance and choice accuracy of rats. Thus, those results do not indicate that the central serotonergic and cholinergic systems interact in the modulation of working memory processes.

69.07 BEHAVIORAL AND HIPPOCAMPAL EVOKED RESPONSES IN AN AUDITORY ODDBALL SITUATION WHEN AN UNCONDITIONED STIMULUS IS PAIRED WITH DEVIANT TONES IN CATS.
T. Ruusuvirta*, T. Korhonen, M. Penttonen, J. Arikoski, and K. Kivirikko. Dept. of Psychol., Univ. of Jyväskylä, Finland.

An acceleration of head movements and hippocampal event-related potentials (ERP) were measured in an oddball situation in freely moving cats. An electrical stimulation of the lateral hypothalamus (US) was paired with pitch deviant tones. In addition to the developing conditioned orienting head turns (orienting response, OR) towards the deviant stimuli, an amplitude increase of the parallelly elicited hippocampal ERPs was found. In fact, the changes in the ERP amplitude preceded the changes in the behavioral level. Both the behavioral and neural responses appeared not until the 50 ms latency range. Furthermore, time-amplitude characteristics of the ERPs corresponded to time-acceleration characteristics of the conditioned behavioral ORs indicating a close functional connection between the ERPs and the behavioral OR. The observed ERPs that were elicited at the latency range following the typical latency range of a hippocampal mismatch-like negativity in cats (30-50 ms) may represent a cat analogy of ERPs following a mismatch negativity (MMN) in humans (N2b, P3).

69.08 GLUCOCORTICOID FACILITATION OF LONG-TERM MEMORY FORMATION: THE INVOLVEMENT OF GLYCOPROTEINS
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Only a fraction of novel information is enduringly stored in the brain. Long-term memory formation for the one-trial passive avoidance task in the day-old chick requires a late phase of neuronal membrane glycoprotein synthesis occurring around 5.5-8.5 h posttraing. However, that enhancement on glycoprotein synthesis did not occur in chicks trained on a weak paradigm, which memory decays a few hours (<10) after training. Intracerebral administration of corticosterone around the time of training (up to 1 h posttraining) facilitates long-term memory formation in weakly trained chicks. When injected to undisturbed chicks, corticosterone was able to induce an increase in glycoprotein synthesis comparable to that induced by the strong aversant training. The facilitation of long-term storage that corticosterone induces in the weak training task, was prevented by injecting chicks intracerebrally with antibodies to the neural cell adhesion molecule (NCAM) at 5.5 h posttraining. These findings highlight the adrenal steroid hormone corticosterone, which is released during learning situations, as an important signal for the establishement of the strenght of a memory, through its ability to modulate mechanisms underlying long-term memory representation.

69.09 INITIAL COMBINATION OF VISUAL AND KINESTHETIC INFORMATION IS REQUIRED FOR ACTIVATION OF PATH-INTEGRATION BASED REPRESENTATION.
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Previous studies have suggested that during navigation, rats form both visual and path-integration representations of space. Use of path-integration orientation from different starting points probably requires that animals "know" their initial and final positions. This experiment was aimed at testing accuracy of path-integration (swim in darkness) after rats were allowed to have only visual information or to combine visual and kinesthetic information from their initial position. In the Morris water maze, rats were trained to reach a submerged platform 1) in the standard conditions of the navigation task in order to allow them to form a spatial representation (light condition), and 2) when starting in light, swimming in darkness and getting light on target (light/dark condition). In this latter condition, one group (n=5) was allowed to have only a brief view of the environment from the starting point and the other (n=5) was allowed to swim the first 30 cm towards goal in light. Six trials in light and in light/dark conditions were given per rat and per day, from three starting points (S, W, N). The platform was always located in the NW quadrant. At the end of training, rats received a transfer test from a new starting point (E). Escape latency improved over days for the two groups in both conditions. However, rats which had brief visual information displayed longer latencies in light/dark than in light condition (45 and 35 sec on first day, 10 and 6 sec on last day, respectively). By contrast, rats which had the opportunity to combine visual and swimming experience did not display such difference. The former rats were also impaired in the transfer test. These results suggest that initial combination of visual and kinesthetic information is necessary to properly activate path-integration representation. Supported by fellowship from the "Programme Cognisciences du CNRS", France and grant IGA AVCR 711401.

69.10 RECOGNITION MEMORY WITH AND WITHOUT RETRIEVAL OF THE ENCODING EPISODE: A STUDY WITH EVENT-RELATED BRAIN POTENTIALS.
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Event-related brain potentials (ERPs) were used to dissociate stimulus-locked brain activity linked to recognition memory associated with successful or unsuccessful retrieval of the study episode. In the study phase of the experiment, subjects viewed a succession of word pairs. For each pair, they were required to generate a short sentence that incorporated both of the words. In the test phase, a series of single words was presented, half of which had appeared at study (old words), and half of which were new to the experiment (new words). For each word, subjects were required to judge whether it was old or new, or to indicate they were unable to decide. For each item judged old, they were further required to attempt to recall the word with which it had been paired at study.

ERPs were recorded from 13 scalp sites, and were formed from artefact-free trials associated with items correctly judged new, items correctly judged old and for which their associates were successfully recalled (old+), and items correctly judged old but for which the associate failed to be recalled (old-). Compared to the ERPs evoked by the new and the old- words, ERPs evoked by old+ words showed a sustained positive-going shift from around 500 msec post-stimulus. This effect was strongly lateralized to electrodes over the left hemisphere.

Together with previous findings, these results indicate that ERPs dissociate recognition memory associated with recollection of details of the learning episode from recognition based on acontextual sources of information, such as a general feeling of familiarity.

69.11 **SPATIAL LEARNING IN RATS WITH LIMITED GRANULE CELL DEGENERATION IN THE DENTATE GYRUS IS DISRUPTED BY A SUBAMNESTIC DOSE OF MK-801 (DIZOCILPINE)** G.Schuster*, J-C Cassel and B.E. Will - LN2C, URA 1939 CNRS, ULP, 67000 Strasbourg, France

Rats receiving injections of large amounts of saline into the dentate gyrus (2µl/site; 5 sites/hippocampus) exhibit complete granule cell degeneration in the vicinity of the injection sites (Vietje B.P. & Wells J., Exp. Neurol. 106: 275-282, 1989; Cassel et al., Neurosci. Lett. 150: 89-94 , 1993).

Two weeks after surgeries, rats sustaining sham-operations or intragyral saline injections were tested in an eight-arm radial maze using a place learning protocol (4 arms baited). Half the sham-operated and saline-injected rats were given a subamnestic dose of MK-801 (0.08 mg/kg, i.p.) 30 min before testing. The other half of each group received i.p. vehicle control injections.

In rats with granule cell degenerations, the number of working memory correct errors (*i.e.*, reentry into a baited arm within a given trial) tended to be increased in absence of any drug treatment. In sham-operated rats, MK-801 had no effect. Conversely, in rats with granule cell degenerations, MK-801 induced a significant impairment of the spatial working memory performances.

These findings indicate that a topographically-limited degeneration of the dentate granule cells does not significantly alter spatial learning processes but produces an increased sensitivity to systemic blockade of NMDA receptors.

69.12 PROTECTIVE AND RECOVERY-PROMOTING EFFECTS OF SUBSTANCE P IN AN ANIMAL MODEL OF HEMI-PARKINSONISM

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The neuropeptide substance P (SP) is known to act as a neurotransmitter and -modulator in various parts of the nervous system. Apart from its enhancing effects on reinforcement and memory, found after central and peripheral administration, there is evidence that SP can also have neurotrophic effects. Since SP is anatomically and functionally related with the nigrostriatal dopamine (DA) system, such neurotrophic effects of SP may play a role in cases of experimental damage of DA neurons, and in relevant neurodegenerative disorders, especially in Parkinson's disease. Thus, in a previous experiment (Mattioli et al., Neuroscience 48'92, 595-605), we administered SP daily (50µg/kg, ip) starting with the day after unilateral 6-OHDA injection into the rat substantia nigra and found that such post-lesion treatment with SP not only promoted recovery from the lesion-dependent deficit in thigmotactic scanning, but also prevented the ipsiversive asymmetry in turning in animals with subtotal depletions of neostriatal DA. These results indicated that SP might have acted also in a protective way. Thus, a subsequent experiment was conducted where rats received the unilateral 6-OHDA injection after 1 week of daily treatment with SP (50µg/kg, ip). An additional group was treated with cholecystokinin (CCK, 1µg/kg, ip), another neuropeptide also closely associated to DA in the forebrain. The analysis of behavioral asymmetries during 2 weeks after 6-OHDA injection showed that animals with pre-lesion SP treatment showed less behavioral asymmetry than vehicle- or non-treated controls, whereas the asymmetries were even stronger in CCK-treated animals. Thus, these results strengthen our hypothesis that SP can act in a protective way.

69.13 **THE STIMULATION OF CCK_B RECEPTORS IN THE ROSTRAL NUCLEUS ACCUMBENS ANTAGONIZED PCP-INDUCED EEG AND BEHAVIOURAL EFFECTS IN RATS.**

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The influence of cholecystokinin (CCK), bilaterally injected into the rostral nucleus accumbens, was studied towards the EEG and behavioural effects induced by phencyclidine (PCP) in rats. CCK (10 ng) significantly inhibited both the EEG (increase of spectral power with respect to pre-drug tracing; increase of relative power distribution into the slowest frequency bands), and the behavioural (number of circling/60 min; highest intensity of ataxia reached) effects induced by PCP. The inhibitory effects of CCK were completely antagonized by PD 135-158 (1 ng) a selective CCK_B receptor antagonist, but not by lorglumide (1 µg), a selective CCK_A receptor antagonist. Since the effects induced by PCP in rodents may be regarded as experimental correlates of the psychotic symptoms it induces in humans, these results confirm that CCK may act as a neuroleptic. They also suggest that CCK_B receptors located at the level of rostral nucleus accumbens may be greatly involved in the neuroleptic-like activity of CCK.

Animal care and use followed the directives of the Council of the European Communities.

69.14 **IN VITRO** EFFECT OF LITHIUM CARBONATE ON CEREBELLAR NUCLEI AND SYNAPSES

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Previous experiments have shown that renal toxicity of lithium carbonate is associated with changes in the conformation of rat kidney chromatin (Sidiropoulou & Issidorides, 1983). In order to investigate whether this action of lithium on chromatin is also associated with the cerebellar syndrome caused by lithium intoxication (Manto et al., 1994) we repeated the above experiments using rat cerebellum. Alternate slices of cerebellar cortex were incubated in saline containing 1.1 mEq/lt Li_2CO_3 and in plain saline to serve as controls. All tissues were fixed in cacodylate-buffered glutaraldehyde, stained en-block with the anionic phosphotungstic acid hematoxylin (PTAH) reagent (Issidorides et al., 1975) and processed for electron microscopy (EM). This method was developed for the study of chromatin ultrastructure based on the affinity of phosphotungstic acid for histones (Sheridan & Barrnett, 1969) and basic amino acids in synaptic junctions (Bloom & Aghajanian, 1968). The study of thin sections with the EM showed changes, under the influence of lithium, in the chromatin of granule cells and at synaptic sites in the glomeruli. The masses of chromatin in the control granule cells were electron-dense, indicating strong binding of the reagent, while in the equivalent cells of the lithium treated slice, they were electron-lucent, indicating compaction of the chromatin. In the control glomeruli we observed the typical parallel pre- and post-synaptic densities through binding of the PTAH. In the lithium treated slice, these densities presented gaps in the staining of PTAH as well as changes in length . These results indicate that lithium causes changes in the conformation of chromatin also in cerebellar nuclei with possible repercussions on genomic expression ,and, in addition, affects the basic protein elements of the synapses presumably affecting transmission.

69.15 COMPENSATORY EFFECTS OF ACOUSTIC DEPRIVATION IN VISUAL SEARCH TASKS? R. Sireteanu* and R. Rettenbach, Max-Planck-Institute for Brain Research, Deutschordenstr. 46, 60528 Frankfurt, FRG

Do deaf people develop capacities of their remaining senses that exceed those of hearing individuals? Are the compensatory effects due to attention-dependent strategies? We examined these questions by testing 98 deaf and hearing subjects aged 6 to 20 years with visual search tasks: Subjects searched for a target item among a number of distracting items. Dependent on search time per item it is possible to distinguish parallel from serial search. We used four types of salient stimuli. The subjects's task was to press a button and to indicate whether and where the target had been. Each subject performed 896 trials, grouped in two experimental sessions. Statistical comparisons (α = .05) do not indicate compensatory effects of acoustic deprivation in visual search tasks: For all age groups the reaction times of the deaf subjects were statistically significantly worse than those of the hearing subjects. That was the case for both serial and parallel components of the tasks. The effect of age was similar in both groups and concerned both task components in the same way. These results suggest deficiencies in visual processing capacity of deaf children both in tasks with and without attentional load.

69.16 GENETIC CORRELATION BETWEEN AGGRESSION AND HIPPOCAMPAL INTRA- AND INFRAPYRAMIDAL MOSSY FIBERS IN MICE. F. Sluyter[1*], P-V. Guillot[1], R.A. Hensbroek[2], P.L. Roubertoux[1], G.A. Van Oortmerssen[2] and W.E. Crusio[1].
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Male mice selected for Short Attack Latency (SAL) show smaller sizes of the intra- and infrapyramidal hippocampal mossy fiber (IIPMF) terminal fields than those selected for Long Attack Latency (LAL). This genetic correlation is supported by a strong correlation between aggression and the sizes of the IIPMF in seven inbred strains. A more detailed genetic analysis, which makes use of congenic lines, demonstrates an effect of the non-pseudoautosomal part of the Y chromosome (Y^{NPAR}) in the SAL and LAL lines. The "slow attacking" LAL Y^{NPAR} has an incremental effect on the sizes of the IIPMF. Furthermore, an additive effect of the LAL background (which includes the pairing part of the Y chromosome, the X chromosome, the autosomes, mitochondrial DNA and the maternal environment) is observed. This background effect is also found in two inbred strains with the "less aggressive" CBA/H males showing larger sizes of IIPMF terminal fields than the "more aggressive" NZB/B1N ones. However, no effect of Y^{NPAR} is observed in these strains.

69.17 LEARNING-SPECIFIC INCREASES IN THE AMOUNT OF NEURAL CELL ADHESION MOLECULES (NCAMs) IN THE CHICK FOREBRAIN AFTER VISUAL IMPRINTING. R O Solomonia*, B J McCabe and G Horn
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A restricted part of the chick forebrain, the left intermediate and medial hyperstriatum ventrale (IMHV), is a site of recognition memory for the learning process of filial imprinting. The amounts of 3 major NCAM isoforms (180,140 and 120 kDa) in P_2 fractions of IMHV, hyperstriatum accessorium (HA) and posterior neostriatum (PNS) in the left and right cerebral hemispheres were measured 10 and 24 h after training using SDS electrophoresis-immunoblotting methods. Trained birds were classified as "good learners" or "poor learners" according to the strength of their preference ("preference score") for the training object. One group of chicks was untrained ("dark-reared"). There was significantly more NCAM (for each isoform) in the left IMHV of good learners as compared to poor learners or dark-reared chicks 24 h after imprinting. There was also in this region a significant positive correlation between the amounts of NCAMs 180 and 120 kDa and the preference score. These effects were not attributable to locomotor activity or sensory stimulation per se. No significant learning-specific changes were found in the right IMHV, HA (a visual projection area) or in PNS. The results show that in the left IMHV learning is associated with increased expressions of NCAMs, implicating enhanced cell-to-cell adhesion in long-term memory.

69.18 LESIONED SUBSTANTIA NIGRA AFFECT HUMORAL AND CELLULAR IMMUNE RESPONSE AND MOTOR PERFORMANCE IN THE OPEN FIELD BEHAVIOUR

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It is well documented that 6-hydroxydopamine (6-OHDA) injected in rostromedial substantia nigra (rmSN) destructs A9 and A10 neurons and induces parkinsonism-like abnormalities. In order to characterize humoral and cell-mediated immune response and behavioral locomotor disorders in animal hemiparkinsonism, male Wistar rats (250-300g) received an unilateral microinjection of 6-OHDA (20µg) into the rmSN. Sham-lesioned (Sh) rats were treated in an identical manner with saline. Two weeks after the operation locomotor activity of lesioned, Sh-lesioned and intact rats were tested in the open field (OF) for three consecutive days before and after the immunization. A part of animals of all groups was immunized with sheep erythocytes (SE) for plaque-forming cell response, while a second part of animals was immunized with bovine serum albumin (BSA) for hypersensitivity skin raections and antibody production to BSA. Lesiones of rmSN significantly decreased PFC-response to SE, Arthus reaction to BSA on day 20 in comparison to both control's (intact and sham-operated), delayed hypersensitivity on day 10 and on day 21 in comparison with intact control and anti-BSA antibody production on day 14 after the immunization in comparison with intact control. Horizontal and vertical locomotor activity in the OF were significantly decreased in rmSN-lesioned rats on day 2 before and on day 2 after the immunization with SE in comparison with both controls. Decreased horizontal locomotor activity was obseved in rmSN-lesioned rats on day 9, 18 and 19 after the immunization with BSA. Vertical locomotor activity was decreased on day 8, 9, 17, 18 and 19 after the immunization with BSA. It appears, therefore, that lesions of substantia nigra cause impairment of both humoral and cell-mediated immune response to SE and to BSA and decrease locomotor activity in the open field test in the rat. (Supported by Ministry of Sciences and Technology of Serbia)

69.19 **ETHOANALYSIS OF THE NALOXONE-PRECIPITATED MORPHINE WITHDRAWAL SYNDROME IN RATS**

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Physical signs during opiate withdrawal syndrome in rats are usually evaluated by selected physical signs or global scores. However, the selection criteria of signs and scores have not been subjected to an ethological discussion. The objectives of this study were thus: i) to analyse the rat's behavior during the naloxone-precipitated morphine withdrawal syndrome, ii) to evaluate the validity of classic methods, and iii) to design a new "etho-score". Rats were implanted with morphine pellets (75 mg x 2, s.c.), and assigned to six groups (n=10 each) all receiving naloxone following a within design (0, 0.01, 0.05, 0.1, 0.5, 1 mg/kg s.c.). Naive groups were also tested (saline, n=10; 1 mg/kg naloxone, n=10) to determine learning effects. Behavior was videotaped and later analyzed by ethological techniques. The ethogram was composed of 15 patterns such as exploratory and self-care responses, wet-dog shakes, writhing posture, mastication, jumping, etc. Descriptive pattern parameters were measured, and a cluster analysis allowed to discern the behavior structure. Number of defecations and micturitions, presence of diarrhea, weight loss and the Gellert-Holtzman (GH) score were also evaluated. The data revealed that writhing posture and mastication changed in a linearly dose-related fashion, even though writhing was highly affected by learning. Wet-dog shakes and jumping changed following an U-shaped curve. Significant changes in weight loss were found to be dose-dependent, and correlated to diarrhea. The GH score, highly influenced by learning, was gradually enhanced after naloxone. In conclusion: i) classic signs and the GH score are useful, but they appear to be affected by learning and "ceiling" effects, and ii) mastication and weight loss are the best indicators of the naloxone-precipitated morphine withdrawal syndrome, representing the basis of a new "etho-score". *Supported by a grant to E.F.E from Junta de Andalucía, Spain.*

69.20 EGOCENTRIC SPATIAL LEARNING OF RATS IN THE MORRIS WATER MAZE: INVOLVEMENT OF MEDIAL PREFRONTAL CORTEX. W.A.M. Swinkels*, J.M. de Brabander and J.P.C. de Bruin, Graduate School of Neurosciences Amsterdam, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands

An animal can use various strategies to orientate in space. It was examined whether the capacity to use a praxis strategy (egocentric orientation) depends on the integrity of the medial prefrontal cortex (mPFC).

In a first experiment it was investigated whether intact male Wistar rats can learn an egocentric spatial learning task in the Morris water maze, and, if so, how the learning of this task compares with the learning of the allocentric Morris water maze task. The data illustrate that rats can indeed learn and remember the egocentric task, but also demonstrate that this task is more difficult to learn than the allocentric task. This is evidenced by a slower and more capricious acquisition. Based on these findings a second experiment was conducted, in which the performance of sham-operated and mPFC-damaged rats were compared in the egocentric spatial task in the Morris water maze. The results show that both escape latency and path length of the mPFC-damaged animals were significantly higher than those of the sham-operated animals. A behavioural analysis of the swimming patterns demonstrated that the mPFC-damaged rats were more persistent in their use of an allocentric orientation, while the sham-operated animals were better able to switch to the more successful egocentric orientation. These data support the hypothesis of a functional dissociation of the mPFC with regard to its involvement in these two different types of spatial learning.

69.21 THE EFFECT OF SMALL AND LARGE TEMPORAL LOBE LESIONS ON THE SENSORY STORAGE OF VISUAL INFORMATION.

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We examined the effect of small focal hippocampal lesions as compared to large temporal lobe lesions on a time limited sensory storage of visual information. Eleven normal control subjects, 8 patients with focal damage to the anterior part of the hippocampus, and 20 patients with unilateral temporal lobectomy participated in the experiment. They were presented with geometrical shapes exposed in pairs, each for 100 ms, one after another. Two interstimulus intervals (ISI), 50 ms and 500 ms, were used. The subjects judged (by pressing one of three buttons), whether the second stimulus was the same as, smaller or bigger than the first one. The first stimulus in each pair was exposed unilaterally (randomly in the left or right visual field), and the second one in the centre of the screen. The number of errors was analyzed. Neither patients with focal hippocampal lesion nor patients with left temporal lobectomy differed from controls. Patients with right temporal lobectomy performed worse than both the control group and the left temporal lobectomy group. The differences were mainly due to their lower scores in the left visual field presentation condition. Moreover the data showed an interesting visual field asymmetry effect: the left visual field presentations yielded higher performance than the right visual field presentations. This effect was present in all groups but right temporal lobectomy group. Our results indicate that right temporal lobe structures (probably temporal neocortex) are involved in time limited sensory storage of visual information.

69.22 THE IMPACT OF PUBLICATIONS IN NEUROSCIENCE FROM AUSTRALIA AND HUNGARY. Eva Tarjan* and Andras Schubert.
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The impact of publications by authors from two comparable countries with a tradition of excellence in neuroscience was analyzed. The list of journals analyzed included all the journals listed in the Current Contents under the heading Neurosciences and Behavior. This journal list during the period 1985-1995 expanded from 89 to over 220 journals. The quantity and quality of contributions from scientists of Australia and Hungary to publications in neuroscience during the period 1991-1993 was investigated in detail. Between 1991 and 1993 over 21000 papers were published annually in journals listed under the heading Neuroscience. Of these over 600 were produced annually by Australian authors, which is more than 4 % of the total Australian publication output in the field of life sciences. Similar ratio was obtained in relation to Hungarian scientists. The following further studies are reported:

the actual impact of publications by Australian and Hungarian neuroscientists, as compared to the expected impact of publications;

the effect of mother tongue (English and non-English) on the number and impact of publications;

the influence of professional affiliation to scientists from another country on the publication number and publication impact;

the influence of home-country based journal on the quantity and quality of publications in the field of neuroscience.

69.23 THE ROLE OF EARLY VISUAL EXPERIENCE IN EXPLORATORY PATTERNS AND REACTIONS TO SPATIAL CHANGES IN THE HUMAN SUBJECT.

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Assessing the means that are implemented to get acquainted with the experimental situation and solve spatial tasks provides a suitable means of gaining some insight into the abilities of the subjects to integrate and set up spatial representations.
We have examined the effects of early visual deprivation on 1) the reaction to a spatial change following locomotor exploration of an environment which contained a set of objects at fixed locations and 2) the spontaneous patterns of exploration.
The level of performance of the early blind group was significantly inferior to that of the late blind and blindfolded groups, which did not differ.It was also evidenced that the early blind group used exploratory patterns which were different from those observed in both visually experienced groups. Finally, each specific pattern of exploration was related to a specific level of performance.
We confirm the quantitive deficits classicaly found after early onset of blindness and, in addition, we demonstrate a qualitative effect of early visual privation on spatial processing during exploration.

69.24 **RETENTION OF A BRIGHTNESS DISCRIMINATION IS IMPAIRED BY INTRAHIPPOCAMPALLY APPLIED c-*fos* ANTISENSE OLIGODEOXY-NUCLEOTIDES.**

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Long-term plastic changes of the brain are assumed to depend on a sequential induction of regulatory and functional target proteins. As one of the earliest responses after training of rats on a foot-shock motivated brightness discrimination, a differential induction of immediate early genes like *c-fos, c-jun, jun-B* and *zif/268* in hippocampal and cortical structures of rat brain is observed. Introducing the antisense technology as a tool to study the functional significance of gene expression in the rat brain during processes of neuronal plasticity *in vivo*, experiments assaying the effects of inhibition of c-*jun*, *jun*-B and c-*fos* expression by intrahippocampally applied antisense phosphorothioate oligodeoxynucleotides (S-ODN) on the acquisition and the retention of brightness discrimination were performed. We have shown previously (NeuroReport **5**, 1501, 1994) that the suppression of c-*jun* expression influences chiefly the acquisition of brightness discrimination. This is documented by a significantly increased number of errors during the first training session compared with control animals, whereas activity in an open field test was not affected. Inhibition of *jun-B* expression did not impair the brightness discrimination score. After intrahippocampal injection of anti-c-*fos* S-ODN the number of errors during the first training session was not impaired, whereas retention performance estimated by a relearning test 24 hours later had significantly deteriorated compared with control-S-ODN treated rats. Our results suggest a functional importance of c-Fos-containing transcription factors such as AP-1 for mechanisms involved in consolidation and/or retrieval of the discrimination reaction.

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69.25 INVOLVEMENT OF INTERHEMISPHERIC GABA-ergic TRANSMISSION IN SENSITISATION OF VTA FUNCTION AFTER UNILATERAL VTA LESION.

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In our previous works we found that unilateral electrolytic lesions of VTA sensitised behaviours (feeding and forward locomotion) evoked by electrical stimulation of the contralateral VTA. In the present study we investigated a possible mechanism responsible for such a "contralateral facilitation" of function. A hypothesis was tested that unilateral lesion destroys interhemispheric GABA-ergic projections which normally inhibit VTA functions thus leading to their disinhibition.

In male Wistar rats implanted with unilateral VTA cannula and contralateral VTA stimulating electrode a latency to initiate locomotion in response to stimulation was measured in a latency to move-stimulation frequency paradigm. Then, GABA-ergic transmission was blocked contralaterally by VTA injections of 0.5 or 5.0 ng of bicuculline, and latency-frequency functions were determined postinjection. It was found that unilateral bicuculline mimicked the effect of unilateral VTA electrocoagulation and sensitised locomotor activity elicited from VTA electrodes located in the other hemisphere. This sensitisation manifested as a decrease of frequency threshold by mean 25.5% after 0.5 ng, and by mean 5.2% after 5.0 ng of bicuculline, which was accompanied by a leftward shift of the latency-frequency function. The results indicate an important impact of interhemispheric GABA-ergic transmission in the phenomenon of "contralateral facilitation" of function after acute, unilateral brain injury.

69.26 IMMEDIATE EARLY GENE (IEG) EXPRESSION DURING A DISCRIMINATION TASK IN ADULT CAT VISUAL CORTEX : AN IMMUNOCYTOCHEMICAL STUDY.

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Using immunocytochemical methods we investigated the influence of a visual learning process on the expression of two IEGs, c-fos and zif-268, in the primary visual cortex of the adult cat. We compared the expression levels of both IEGs in the visual cortex and somatosensory cortex (SII) from different cats before and after being trained in a bar orientation discrimination task at different performance levels. In the visual areas 17 and 18, but not in SII, we detected different degrees of c-fos and zif-268 labeling depending on the experimental conditions. The expression level of c-fos and zif-268 was elevated in the bar orientation discrimination cat after five days of training, during which the cat really learns to distinguish between two bars of different orientation. In contrast the expression levels of both IEGs in the brains, i.e. before orientation discrimination training, or after completion of the training (75% correct for an orientation difference of 5°) in bar orientation discrimination revealed a basal level of c-fos positive nuclei in the supra- and infragranular layers, while the expression of zif-268 immunoreactive neurons even was below basal level in layers II, III, IVc and VI of area 17 and 18 in a full-trained cat. Our results show that a discriminative learning process induces c-fos and zif-268 expression in areas 17 and 18 of the cat visual cortex.

69.27 FLESINOXAN-INDUCED NEUROENDOCRINE CHANGES AND SEROTONIN SYNDROME ARE MEDIATED POSTSYNAPTICALLY.

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The 5-HT1A receptor agonist flesinoxan induces changes in hypothalamus-pituitary- adrenal (HPA) activity as well as the so-called serotonin syndrome in rats. Since 5-HT1A receptors are located both pre- and postsynaptically in rat brain, we investigated the mechanism of hormonal and behavioral actions of flesinoxan by depleting the serotonin system with p-chlorophenylalanine (PCPA). Male Wistar rats were treated with PCPA (300 mg/kg i.p.) or vehicle on two successive days. On the third day, flat body posture and lower lip retraction were observed after administration of flesinoxan (0, 3 or 10 mg/kg s.c.). The animals were decapitated 60 min after flesinoxan in order to dissect brains and collect trunk blood. Forebrain 5-HT and 5-HIAA levels were below detection limits in PCPA-treated rats. PCPA pretreatment did not attenuate the flesinoxan-induced behavioral syndrome nor did it diminish plasma ACTH, corticosterone, prolactin or glucose responses to the flesinoxan challenge. This indicates that the respective behavioral and neuroendocrine effects have a postsynaptic origin. PCPA treatment might even result in postsynaptic supersensitivity reflected by a tendency to an exaggerated corticosterone response and a higher lower lip retraction score. The localisation of the 5-HT1A receptors involved remains to be elucidated.

69.28 ESTROGEN INCREASES THE STRENGTH OF A MEDULLARY-LUMBOSACRAL MOTONEURONAL PROJECTION, POSSIBLY INVOLVED IN LORDOSIS BEHAVIOR IN THE CAT.

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The nucleus retroambiguus (NRA) is a compact group of interneurons located in the caudal medullary tegmentum. The NRA forms a relay between the periaqueductal gray (PAG) and motoneuronal cellgroups involved in vocalization and possibly lordosis behavior. NRA interneurons have recently been shown to project directly to distinct motoneuronal cellgroups in the lumbosacral cord innervating hindlimb muscles such as iliopsoas, adductor and hamstring muscles, as well as proximal tail and pelvic floor muscles. This set of muscles is involved in lordosis behavior in the cat, which is typically displayed in the presence of elevated levels of estrogen. Estrogen is known to induce plastic changes in hypothalamic pathways which play a role in lordosis behavior. The question arises whether estrogen induced changes are also present in the NRA-motoneuronal pathway. Therefore, the density of the NRA-lumbosacral projection was studied in six estrus and eleven non-estrus cats at the light and electron microscopical level. The NRA was injected with WGA-HRP and light microscopically, the density and arborization pattern of anterogradely labeled axons in their target motoneuronal cell columns was studied. At the ultrastructural level, the number of labeled and unlabeled terminals was counted in the semimembranosus motoneuronal cell group. The results show marked differences in the NRA-lumbosacral projection in estrus versus non-estrus cats. Light microscopically, the density of labeled NRA axons was much higher in estrus than in non-estrus cats. At the ultrastructural level, the number of labeled NRA terminals increased significantly in estrus cats. The results suggest that estrogen induces axonal outgrowth and synaps formation in the NRA-lumbosacral motoneuronal pathway. Periodical, estrogen related changes in the density of the NRA-lumbosacral motoneuronal pathway might be one of the factors responsible for lordosis to occur.

69.29 EFFECT OF TRANSIENT INACTIVATION OF THE ANTERIOR PART OF THE DORSAL STRIATUM ON THE REVERSAL OF A DISCRIMINATION IN JUST TRAINED OR OVERTRAINED RATS.

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One possible neural substrate of learning stimulus-response (S-R) associations is the dorsal striatum. This is particularly evidenced through experiments from McDonald and White (1993) or Packard et al. (1989) in different experimental situations such as Morris water maze or radial maze. In a recent experiment, we showed that NMDA lesions of the dorsal striatum in rats lead to an important impairment in the acquisition of an avoidance response to a tone in a two-way shuttle box, but that once acquired this response became unchanged when the experimental context was modified (Van Golf-Racht et al., 1995). These results confirm the role of the striatum in the acquisition and retention of a strong S-R association and lead us to test such a functional perturbation of the dorsal striatum in a situation where the S-R strength was increased by using an extended training.

In the present experiments, animals were trained to discriminate between two different stimuli (a light and a tone) either to a criterion of learning (40% of difference between responses to S+ and S-)or overtrained (420 more trials than criterion group). Both groups were then tested in a reversal of discrimination. Our results exhibited a more rapid reversal in overtrained animals than in criterion animals. This effect is known as the overtraining reversal effect (ORE; Reid, 1954). To study the possible implication of dorsal striatum in the associations established by overtrained animals as compared to criterion animals, a transient blockade of this structure was tested, by local injection of lidocaine, just before each reversal session. From the resultas obtained with both groups compared to control groups (saline injection), the validity of the hypothesis involving the antero-dorsal striatum in the specific establishment of the S-R associations will be discussed.

69.30 ON THE USE OF NEUROPSYCHOLOGICAL RISK INDICATORS IN SCHIZOPHRENIA RESEARCH.

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The etiology of schizophrenia is still unclear. A familial component in schizophrenia has long been recognized. Twin studies have addressed the question of whether the familial risk of schziophrenia is due to genetic factors. The study of twins offers the possibility to seperate genetic and environmental factors in the etiology of schizophrenia by comparing monozygotic twins with dizygotic twins.

In discordant monozygotic twins impairments in learning and memory were found in both twins[1], which suggest that these impairments can be used to assess the genetic component in schizophrenia.

In our study the performance of identical and fraternal twins on neuropsychological tests of frontal lobe functions are evaluated in a standardized way. Estimates of the strength of these neuropsychological risk indicators are obtained by comparing monozygotic twins to dizygotic twins and will be presented.

[1] H.E. Goldberg et al., Psychological Medicine, 1993, 23, 71-85.

69.31 THE EFFECT OF DIAZEPAM ON AUDITORY EVOKED POTENTIALS OF RATS.

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Electrophysiological studies utilizing event related potentials (ERPs) have provided important brain measures for the study of cognitive processes such as selective attention, classification of stimuli and memory. We evaluated the effects of diazepam on auditory evoked potentials (AEPs) generated by a passive oddball paradigm.

Male WAG/Rij rats were implanted with electrodes over the auditory and frontal cortex. They subcutaneously received silastic tubes either empty or filled with diazepam (50 mg/kg/day resulting in constant blood concentrations of ± 200 ng/ml). We presented a frequent occurring stimulus (90 %, 8 kHz, 95 dB) randomly altered with an infrequent occurring stimulus (10 %, 12 kHz, 102 dB) each with a duration of 20 ms and a 2.5-3.5 s random intertrial interval. Trials during locomotion and slow wave sleep were excluded.

A series of large amplitude potentials in the 20-200 ms range could be identified. For both frequent and infrequent stimuli diazepam caused an increase in the amplitude of the P66 and a right shift of the second negative component (N102 shifted to N120). No differences in early components (P32 and N45) were found between groups. With respect to the infrequent stimulus diazepam caused an increase in amplitude of the P137, the third positive peak, and a larger negativity in the mean value of the afterdischarges (300-500 ms).

We showed that diazepam only modulates the later components of the AEPs. justifying the conclusion that diazepam has an effect on cognitive processes.

69.32 AGING, DOMINANCE POSITION AND SOCIAL BEHAVIOUR IN SOCIALLY HOUSED MONKEYS (MACACA FASCICULARIS).

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Researchers studying the effects of aging on learning and memory in monkeys have shown that aged monkeys are impaired on several learning tasks, such as the delayed response (DR) task and the delayed non-matching to sample (DNMS) task. However, these impairments were not distributed equally among aged animals; instead a large individual variation was observed.

Although the exact cause of this variation is not known, there are indications that life-history (e.g. stress) influences age-related deterioration of cognitive capacities. Several studies have shown, for example, that glucocorticoids can have important effects on the survival of neurons in the hippocampus, important for learning and memory processes.

In monkeys the amount of stress an animal experiences is to a large extent determined by social background. Lower ranking monkeys are more frequently attacked, have less opportunity to redirect the aggression and have more difficulty in obtaining access to resources such as food or mating partners.

Until now no study on the effects of aging on memory has been able to relate cognitive capacity of aged monkeys to their social history, either because the social history was not known, or because the monkeys were housed solitarily or in pairs.

The aim of this study was to assess whether there is an effect of dominance position on age-related changes in social behaviour in three large groups (totalling around 150 individuals) of socially housed monkeys (Macaca fascicularis). In this species members of the same family have similar rank position. Thus, to exclude general effects of family and rank, we compared old animals with their younger relatives for the occurrence of certain social and stress-related behaviours.

The results, namely a correlation between age and stress-related behaviours and an influence of rank position on age-related changes in social interactions are discussed.

69.33 CHRONIC ADMINISTRATION OF PIRACETAM IMPROVES PERFORMANCE AND INDUCES SCOPOLAMINE RESISTANCE IN A SPATIAL DELAYED RESPONSE TASK FOR RATS.

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Piracetam has been reported to improve memory functions in a wide range of experimentally induced amnesias. Most of these investigations have been carried out in reflexive memory tests. The reports on cognitive short-term memory (working-memory) tests are sparse and somewhat contradictory.

In the present study a 3-hole spatial delayed response test, recently developed in our laboratory, was used to examine the spontaneous effects of piracetam and its ability to revert a scopolamine-amnesia in PVG rats (2-3 months old). The test is a delayed-match-to-sample task, testing cognitive short-term memory. Results were obtained after acute drug administration and after two weeks of chronic piracetam treatment. Scopolamine (0.6 mg/kg), piracetam (250 mg/kg) and NaCl (0.9%, control) were administered s.c. one hour before testing.

The results showed a significant ($p=0.001$) 35.7% reduction in performance of acutely scopolamine treated animals compared to NaCl-treated ones. This was associated with an increase ($p=0.003$) in erroneously repeated visits to the same hole. Concomittant injections of scopolamine and piracetam did not improve performance compared to that of scopolamine treated animals. After two weeks of chronic piracetam administration the scopolamine affected performance was only reduced by 10.1%, which is significantly ($p=0.005$) less than the performance of acutely scopolamine-treated animals. The repetitive errors were also significantly ($p=0.04$) reduced. There was no acute effect of piracetam on non-amnesic animals, but after chronic administration, performance was significantly improved ($p=0.01$).

In conclusion, chronic piracetam administration lead to a significant improvement of performance in young non-amnesic rats, and induced resistance against scopolamine-amnesia. There were no effects of piracetam after acute administration.

69.34 "INSIGHT" PHENOMENON: NEUROPHYSIOLOGICAL AND PSYCHOLOGICAL CHARACTERISTICS.

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We have studied the so-called "insight" in experiments with visual identification of slides with double pattern. At the first stage systemic organization of the human brain processes was studied at identification of visual pictures by the data of interconnections mapping. At the second stage the possibility of reflection of the processes of visual thinking was revealed in the systemic organization of the brain electric activity (model of logic and non-logic form of making decision - phenomenon of insight). At the third stage the role of emotional-motivational processes in the mechanism of non-logic form of making decision was studied. The data-processing method consisted in three-dimensional mapping of so-called "community coefficient" which described each EEG-process in its recording point through its partial correlation with the other processes. The difference of our technique consists in possibility to present all interconnections in one map. The results of the experiments show that the phenomenon of insight has its systemic manifestation in the electric processes of the human brain. Topomaps of the electrical processes of the human brain are highly individual, but each subject has its own distribution of the cerebral cortex potentials. The subjects experienced the phenomenon of insight at conscious level as "instantaneous", "sudden" process, at subconscious level the insight is somewhat dragged out in time. The character of potentials distribution testifies to insight preparation by the brain. All subjects were tested by R.Cattell method. The best result in non-logic identification was demonstrated by the subjects with intermediate characteristics of emotional stability at general identification and at estimation of correct slides identification as well. High of motivation promotes greater number of the identified slides, but accuracy of correct identification is better at the mean level of motivation.

69.35 MEMORY DISORDERS IN APHASIC PATIENTS

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Verbal memory in 52 aphasic patients /30 with traumatic and 22 with vascular etiology/ was examined by Rey Auditory Verbal Learning Test. The main goal of this examination was to discover the relationship between disorders of verbal memory and language functions in aphasia. Our results showed that aphasics have great disorders of verbal memory.The more severe disorders of verbal memory was found in acute phase and in patients with aphasia of vascular etiology.By examining the relationship between verbal memory and specific language functions we discovered significant difference between memory disorders and auditory language comprehension, and memory disorders and naming.We discovered better recovery of memory in patients with traumatic aphasia.It was concluded that the severity of verbal memory disorders is closely connected with severity of disorders of language functions and the type of aphasia.

69.36 DEVELOPMENT OF COGNITIVE FUNCTION IN THE PRESENCE OF A DISCRETE LEFT BASAL GANGLIA LESION ACQUIRED IN UTERO

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JCP, a young man of 15 years, presented with a history of learning difficulties, affecting reading, spelling and writing, and evidence of clumsiness and motor incoordination. There were no neurological deficits, but an MRI scan showed a discrete triangular-shaped lesion of the left lentiform nucleus, and general abnormality in the area of the left caudate nucleus and anterior limb of the internal capsule. Neuropsychological examinations showed average intelligence, but selective deficits in spelling, arithmetic, writing and verbal fluency. Measures of executive function demonstrated impairments in category sorting, self-ordering, and an impaired performance on the Stroop test. Novel motor and perceptual learning were also impaired. Discrete congenital lesions of the basal ganglia are rare. Documented cases with impairments due to such lesions usually have had normal development prior to acquiring the pathology in adulthood. JCP therefore presents the opportunity to study the effects of basal ganglia pathology on the development of selective aspects of cognitive function.

69.37 COGNITIVE FUNCTIONING IN CALLOSAL AGENESIS.

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Experimental studies in patients with agenesis of the corpus callosum present a unique opportunity to explore interhemispheric integration and the development of functional lateralization in humans. The ongoing study assesses language mediation, interhemispheric transfer and cross integration in subjects with callosal agenesis. At present, two male subjects, one (WC) with complete and one (HO) with partial callosal agenesis have been studied. Both subjects have several MR-documented brain abnormalities (heterotopies, hypoplasies) and a subnormal IQ in addition to their callosal anomaly. Neuropsychological investigations showed equal performance of both hands in tactile naming, object use and finger identification tasks. A dichotic listening procedure revealed a strong left ear advantage in HO and a right ear advantage in WC. Both subjects performed astonishingly well in tasks requiring the judgement of nonidentical shapes which were presented simultaneously in both hemifields. Our results indicate that subjects with callosal agenesis have inconsistent patterns of functional lateralization and that they can integrate visual and tactile information from both hemispheres, probably via the anterior commisure or other residual interhemispheric connections. Correlations between cognitive functions and CT, and MR-imaging will be discussed.

69.38 PARAMETERS AFFECTING CONSCIOUS VERSUS UNCONSCIOUS VISUAL DISCRIMINATION WITH DAMAGE TO V1.

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The object of the present study was to determine whether there were conditions under which a subject, G.Y., had "blindsight", i.e. could discriminate between different directions and orientations of motion in the absence of awareness, and if so, to compare the stimulus parameters which define both the conscious and unconscious modes of discrimination. A key question is whether the two modes of discrimination are just different portions of the same psychometric function, or whether they reflect different and possibly independent processes. We investigated how stimulus parameters such as speed, stimulus contrast, orientation of motion trajectory and length of excursion affected the subject's conscious awareness of the visual stimulus and also the probability of correct discrimination.

69.39 ANXIETY BEHAVIOR IN DSP-4 TREATED RATS.

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In the present paper we introduced the photo-phobic test with the light - danger and dark - safe parts of experimental chamber to search the participation of the dorsal noradrenergic system in the control of anxiety. The experiment was carried out on the 12 male Wistar rats divided into 2 groups: control and DSP-4 treated. We measured the time of activity in the light and dark parts of experimental chamber, time of escape reaction and the latency of escape reaction from the light to dark part of experimental chamber. Next we injected saline or DSP-4 (50mg/kg i.p.) respectively preceded with zimelidine, and repeated our behavioral observation. Ten days after saline treated rats we did not observe any changes in all parameters of reaction. In the DSP-4 treated animals, latency of escape was elevated 6 times, time of escape was elevated 3 times, time spent in light part of experimental chamber was elevated 3 times and time spent in dark part of this chamber was reduced 3 times. This results suggested that after reduction of NE with DSP-4, the rats indicated decrease level of anxiety. The biochemical analysis of the concentration of monoamines and their main metabolites are in progress (using Hewlett-Packard HPLC-ED system).

69.40 MISMATCH NEGATIVITY IN DICHOTIC LISTENING CONDITION. POSSIBLE EVIDENCE FOR HEMISPHERIC LATERALIZATION ?

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Dichotic stimulation represents a procedure intended to present an auditory stimulus primary to a single hemisphere. Hence, this technique may be useful for the study of hemispheric lateralization of various cognitive functions. In this context, possible lateralization of automatic auditory attention was explored through ERP recording in a "Mismatch" paradigm using dichotic pairs of pure tones as stimuli. Twelve normal right handed volunteers were presented (while playing word quizz) with eight different auditory sequences: in four sequences all stimuli were dichotically presented and included 80% standard pairs (800 hz/1200 hz) and 20% deviant pairs, with the deviant at the left (840/1200 hz, 10%) or at the right ear (800/1260 hz, 10%). For comparison, four paradigms using monaural stimuli were applied (at the left or at the right ear with the standard tone at 800 or at 1200 hz). ERPs were recorded at Fz, Cz, C3 and C4, separately for each category of standard and dichotic pair. Searching for the existence of either "ear advantage" or hemispheric asymetry of ERP components, the voltage of N1 and P2 components as well the area of the mismatch negative component of the difference waye were measured. No significant asymetry was found with monaurally presented stimuli. In dichotic condition, in some subjects the MMN was either very small or symetrically distributed according to the recording electrode and to the ear at which the deviant was presented. In other subjects, the MMN was significantly larger over both hemispheres when the deviant was at the right ear than when it was at the left ear. This would be in favor of a left hemisphere lateralization of the automatic attentional switch produced by an auditory stimulus deviating from the background ones which is supposed to underlie the MMN component.

69.41 EMOTIONAL AND PHYSICAL STRESS DIFFERENTIALLY AFFECT THE BEHAVIOURAL RESPONSE TO NOVELTY

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Animals were exposed for 5 consecutive days to either physical stress (PS, repeated footshocks) or emotional stress (ES, forced perception of another rat receiving footshocks). When exposed to a novel environment (small open field) 5 days after the last stress session ES rats showed more ambulation, rearing and sniffing activity as compared to control rats while PS rats showed a decrease in these behaviours. Naloxone (1 mg/kg sc) pretreatment antagonized the increase in the behavioural activity of ES rats whereas the activity of control animals and PS animals was not affected, suggesting an involvement of opioid systems in the behavioural changes observed in ES rats. No relationship was found between the behavioural activity and the changes in corticosterone, ACTH and prolactin levels induced by exposure to the small open field, indicating that the behavioural and neuroendocrine response are regulated by separate mechanisms.

69.42 HEMISPHERIC ASYMMETRY OF BIOELECTRICAL HUMAN BRAIN ACTIVITY DURING SOLVING THE INTELLECTUAL AND EMOTIONAL TASKS.

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This work was devoted to investigation of the dynamic of the interhemispheric relations of the spatio-temporal organization of the brain potentials in healthy subjects during wakefulness and some kind of activities. The method of the quantitative evaluation of successive topograms (relieves) of the brain potentials was used. Significant role in description of higher psychological (mental) functions of a human being and of the behavior of animals in parameters of bioelectrical activity belongs to rapid changes (momentary) in brain states. These important rapid changes states were named as topograms. A topogram is a momentary value of potentials under the electrodes which form a relief of potentials. The relieves can be shown as maps. Quantitative evaluation of changing topograms were fulfilled in regard to the topograms with sagittal gradient of potentials in each hemisphere. Dynamic of relieves of potentials can be different under various psychic conditions of a man, for instance under emotional processes and his intellectual activity. It has been established that the states of human neocortex are determined both by interhemispheric characteristics of the cortical potentials and intrahemispheric ones. It was ascertained that all kind of activities resulted in stabilization of the level of hemisphere asymmetry. This level did not depend on the intrahemisphere changing of the relief of the brain potentials. Optimal ratio of the intra- and interhemispheric characteristics of the spatio-temporal reorganization of the brain potentials is the neurophysiological base of the mental activity of man.

69.43 INFLUENCE OF MELATONIN ON AVP VIP PEPTIDERGIC NEURON

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Previous work has confirmed that melatonin (MLT) inhibit discharge and D-2-glucose uptake of neurons in SCN, but SCN contains many types of neurons. Its peptidergic neurons include AVP VIP SOM and other neurons.Our research aims at influence of MLT on dif ferent peptidergic neuron in rat hypothalamic SCN.

METHODS:Wistar male rats were divided into experimental and control groups.The experimental groups contain pinealectomy group and MLT injection group. Rats of MLT injection were injected subcutaneously with MLT at 10:00,or 17:00,or 24:00 daily for 30 days.They were anesthetized and perfused with fixative.Brain sections were cut with freezing microtome, stained with ABC immunohistochemistry and measured with MIAS for semiquantitive analysis.

RESULTS:The results show that MLT(17:00) does'nt affect AVP,but increases VIP quantity in SCN neuron.

DISCUSSION:That MLT has selective effect on AVP and VIP peptidergic neuron in SCN may result from different distribution of MLT receptor.Increase of SCN VIP may have relation with sleep. MLT and VIP possess strong hypogenic effect. We think that MLT exerts its effect on sleep by increase of VIP quantity and that VIP may be a circadian pacemaker.

69.44 CONDITIONS INTERFERING WITH PLACE NAVIGATION DO NOT DISRUPT ACTIVITY OF HIPPOCAMPAL PLACE CELLS (PCs) IN RATS.

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The role of hippocampal PCs in spatial behavior was tested by plotting their firing fields (FFs) in states supporting or blocking navigation. A computerized tracking and unit sorting system was used to plot the firing maps of PCs recorded in rats searching food pellets in a 2m arena. Out of 32 PCs with clear cut FFs in light, 13 retained the same FF location in darkness, while 19 were lost or clearly displaced. In 3 PCs FFs stayed unchanged under scopolamine (1mg/kg). Thirteen PCs were tested after dividing the arena by a transparent partition. In the half containing the original FF, FFs did stay in 10 and disappeared in 3 PCs, in the other half no FFs were found in 5 and new FFs appeared in 8 PCs. While these findings are consonant with preserved navigation in restricted environment, disruption of place navigation by darkness or scopolamine is not due to blockade of PC activity but to interference with post-PC processing of spatial information.

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69.45 DETECTING CHANGES IN THE DIRECTION OF SIMULATED EGO-MOTION.

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When moving through our surrounding, we seldom maintain fixation on a single static structure for a long period of time. Nevertheless this is the condition studied in most experiments on the accuracy of perceived heading. In the present study we examined how the position one is fixating influences detection thresholds for perceiving changes in the direction of simulated ego-translation. We simulated ego-translation across a horizontal surface with 200-250 visible points that were perceived to be at ground level (large screen; binocular stereopsis using LCD spectacles). We examined whether displacing the fixation point (at the moment at which the direction of heading could change) results in higher thresholds (while average heading eccentricity was kept constant). When maintaining fixation on a distant point (which hardly requires pursuit eye movements), thresholds were not influenced by the displacement (despite the saccade that is required to retain fixation). When fixating a nearer point (which requires pursuit eye movements), thresholds were higher when the fixation point was displaced. Theoretically, this is what we would expect if subjects had mainly been attending to the motion of the fixation point itself. Indeed, when we only presented the (near) fixation point, performance was almost identical to performance when the whole ground surface was visible. Thus, during eye movements, information from the structure we are attending to determines how sensitive we are to changes in the direction of heading. Subjects' performance in a similar task did not even deteriorate when a sole fixation point was shown to one eye only. This suggests that subjects do not only use the available visual information, but are also strongly influenced by the knowledge that they are moving across a simulated ground plane.

69.46 THE DEVELOPMENT OF NEWBORN INFANT'S CRY(-ING) FROM BIRTH UNTIL THE END OF THE FIRST MONTH

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This work represents one part of the results obtained in the project "Speech development in the prelingval stage" that is being realized at the Institute for Experimental Phonetics and Speech Pathology after the concept of Prof. Djordje Kostic.

In studying speech and language development, one of the aims is to detect the very beginning of speech communication in the prelingval period. That is why we analyzed the development of speech and language starting with the first cry(-ing) from birth until the end of the first month.

The research results proved the existence of stages in cry(-ing) development that are very important in following the hearing development and future speech and language as well as in the development of methodological procedures of early detection of hearing impairment and speech habilitation of the hearing impaired children with the aim of disability prevention.

69.47 SPATIAL DATA PROCESSING AND VERBAL ABILITIES IN PATIENTS WITH RIGHT OR LEFT CEREBELLAR LESIONS.

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Emerging evidence suggests that Cerebellar computational properties may be important for cognitive functions. Aim of the present study was to investigate the effect of circumscribed cerebellar lesions upon different cognitive functions. Patients (n= 15) with focal cerebellar lesions, grouped according to the side of the lesion (left n= 10; right n= 5) and 30 control subjects were submitted to an extensive neuropsychological battery. Results demonstrated that cerebellar patients present significant impairments in selective verbal and spatial tasks. Although the side of the lesions affected only slightly the verbal performances, a clear lateralization effect for the spatial abilities has been observed. In a timed verbal task requiring naming production under forced (phonemic or semantic) condition patients produced significantly less words than controls with the lowest production rate in the right lesioned group. In timed tasks exploring complex spatial operations such as mental object construction and rotation a clear effect of the side of the lesion on performances was observed. Only left lesioned cerebellar patients scored significantly lower than control. Qualitative analysis of the performances demonstrated clear differences in the strategies used by left and right cerebellar groups. While, left focal cerebellar patients performed very slowly scoring significantly lower than controls especially because of the low number of items executed, patients with right focal cerebellar lesion were able to complete the most part of test with high production of errors and a characteristic error distribution. The present data demonstrate that circumscribed cerebellar lesions can affect in a lateralized manner high order cognitive functions.

70. Poster Session: Development and plasticity III

70.01 REGIONAL INTEGRATION OF NEURAL PRECURSORS DERIVED FROM SELECTED REGIONS OF THE FETAL MOUSE BRAIN AFTER GRAFTING INTO THE EMBRYONIC RAT FOREBRAIN

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The ability of neuronal precursors to integrate and develop in a site-specific manner in the developing brain was studied in an *in utero* transplantation model using a cross-species grafting tecnique. Precursors derived from the mouse embryonic day (E) 11.5-12 or 13.5-14 lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE), cortical ventricular zone (CVZ) were injected into the E15, E17 or E19 rat cerebral ventricle. At 0 to 42 days posnatal age, brains were fixed and processed for M6 (a mouse-specific neuronal marker) immunoreactivity and regional brain markers. M6-positive cellular profiles were observed in numerous forebrain nuclei after grafts of either E13.5-14 LGE, MGE or CVZ tissue. The most consistent site of M6 integration after LGE grafts was the striatum where M6-positive profiles were observed to form clusters around myelin bundles and send fibers to the globus pallidus and substantia nigra. Many of the striatal M6-positive cellular profiles expressed DARPP-32 (a marker for striatal neurons) while those observed in adjacent telencephalic structures (i.e. the septum and cortex) and also in distinct periventricular nuclei of the diencephalon were DARPP-32 negative. Grafts derived from the MGE and CVZ contributed less frequently to the striatum but displayed distinct patterns of incorporation within the forebrain. The degree of parenchymal integration appeared to be less extensive in older recipients (E17 and E19), with a larger proportion of M6-positive clusters in the ventricular walls. However, the specificity of the projection patterns was maintained. Furthermore, progenitors derived from E11.5-12 appear to follow similar patterns as those from the E13.5-14 brains. Preliminary results indicate that mouse progenitors derived from mid- and hindbrain regions such as the ventral mesencephalon and rhombencephalic lip also display distinct patterns of integration and axonal projections after grafting into the forebrain ventricle. These results suggest that certain neuronal progenitors possess the ability to incorporate into homotypic brain regions and undergo site-specific differentiation. The grafting model presented her may, thus, provide a useful tool to investigate the developmental potential of neuronal precursors from different brain regions at various stages of development.

70.02 GENE EXPRESSION OF THE α4 SUBUNIT OF THE NICOTINIC ACETYLCHOLINE RECEPTOR IN THE DEVELOPING RAT CEREBRAL CORTEX

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Nicotinic acetylcholine receptors (nAChR) play an important role in cholinergic transmission in the adult cerebral cortex. While nAChR subunit expression has been studied in adult rats, little is known on the ontogeny of this system, which may contribute to a better understanding of degenerative and regenerative mechanisms.

By means of a digoxigenin-labeled riboprobe, the expression of the mRNA for the α4 subunit - the most widespread subunit in adult rat brain - has been studied in the developing rat cerebral cortex between embryonic day 14 [E14] and postnatal day 60 [P60]. Hybridization was visualized by applying an alkaline phosphatase-coupled digoxigenin-antibody, followed by incubation with BCIP/NBT.

At E14 nearly all ventricular zone (VZ) cells were labeled. In the area of the primordial plexiform layer hardly any positive cells were detected. At E20, all cells of the VZ were still labeled. In the intermediate zone, many α4 mRNA expressing cells were seen. In the cortical plate (CP), in particular in the frontal region, prospective layer V neurons were stained. Positive CP neurons of the occipital regions were localized more superficially, while those of the frontal cortex were found at deeper levels. At day P0, there was a strong labeling of neurons in layer VIb. The distinctly positive layer V was moved to deeper levels of the cortex by late-developing, weakly stained layer II and IV neurons. Similarly to the adult cortex, layers VIb and Vb could be distinguished, while the other layers did not contain labeled neurons.

Thus, a transient expression of α4 mRNA in other parts of the cerebral cortex than those expressing α4 transcripts in adult brain was not detected. Development of cholinergic innervation and α4 gene expression, however, run asynchronously. The functional meaning of the prenatal α4 mRNA expression has to be elucidated.

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70.03 MORPHOLOGICAL PRINCIPLES OF ABNORMAL HUMAN NEOCORTEX FORMATION IN THE PRENATAL ONTOGENESIS

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Development of human fetal telencephalon of 7 to 11 weeks of gestation grafted into different areas of nervous system and anterior eye chamber of adult rats was studied. In cases of either immunosuppression or non-conflict survival without immunotherapy a reorganization of germinative layer, changing of both proliferative activity and direction of postmitotic cell migration as well as differentiation delay were evident 2 to 3 weeks following grafting. Cytoarchitectonics, stratification, cell types relation, their density and orientation typical for normal neocortex were never seen. Observed features in general resemble the structure of schizophrenia patients neocortex. It is suggested that the model used allows to study mechanisms of prenatal abnormal development.

70.04 N-TYPE CALCIUM CHANNELS MEDIATE THE *IN VIVO* RELEASE OF GLUTAMATE IN THE FRONTAL CORTEX OF THE RAT. EFFECTS OF AGING.

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The influx of Ca^{2+} into the nerve terminal is generally accepted as the trigger mechanism for transmitter exocytosis. However, the type of Ca^{2+} channel involved, as well as the conditions --basal or evoked release-- vary according to the neurotransmitter studied. Contrary to other neurotransmitters such as DA, NA, Ach or 5-HT, the basal release of glutamate seems to be independent of neuronal activity, and has no vesicular origen. Glutamate has been implicated in the neurodegeneration underlying aging processes.

We used microdialysis to analyze the effects of age on the basal and 100 mM K^+-evoked release of glutamate in the frontal cortex of the awake, freely moving rat. The effects of ω-conotoxin GVIA (ω-CTX) and aminoglycosides (neomycin and kanamycin) as VDCC blockers, and tetrodotoxin (TTX) as a Na^+ channel blocker, were determined in two groups of rats aged 3 and 24 months. The glutamate content of the dialysates was determined as OPA-derivative by HPLC with fluorescence detection.

TTX, ω-CTX (an N-type specific VDCC blocker), neomycin or kanamycin had no effects on the basal release of glutamate in young or aging rats. The K^+-evoked release was higher in young than in aged animals. Neomycin, kanamycin, ω-CTX and TTX completely abolished the evoked release in both age groups.

We conclude that K^+-evoked glutamate release is diminished in the aging frontal cortex, probably as a consequence of loss of the functional capacity of the neurons. On the other hand, N-type VDCC mediates the *in vivo* evoked glutamate release in both age groups. (Supported by DGICYT 90-0146 and Junta de Andalucía).

70.05 POSTNATAL DEVELOPMENT OF LAYER V PYRAMIDAL NEURONS IN THE HUMAN PREFRONTAL CORTEX: A RAPID GOLGI STUDY. Z. Petanjek* (1,2), H.B.M. Uylings (2), I. Kostović (1). (1) Croatian Institute for Brain Research, Zagreb, Croatia, (2) Netherlands Institute for Brain Research, Amsterdam, The Netherlands.

We studied the dendritic development of layer V pyramidal neurons in the region of Brodmann's area 9 of the human prefrontal cortex (PFC) in rapid Golgi stained sections using the 3-dimensional semiautomatic dendrite measuring system developed at the Netherlands Institute for Brain Research. Sections were 150-200 μm thick. The quantitative analysis was performed on basal dendrites of 17 subjects ranging from newborn up to 86 years. Research questions are (a) which developmental phase can be detected, (b) can silver rapid Golgi data be compared with our previous study using the mercury Golgi-Cox staining and (c) are there any differences in the development of layers IIIC and V pyramidal neurons. The results show a rapid elongation of dendritic tree in the first two years of life. This increase is explained by a large increase of terminal segment length and a small increase of intermediate segment length. Adult number of dendritic branches and soma surface size had already been reached in the first postnatal month. Overgrowth in size of soma was only visible at the age of 5 years. These results show that the developmental curve for layer V pyramidal neurons in human PFC is similar in rapid Golgi and Golgi-Cox stained sections. However, differences were present in absolute values of some measured variables and in dendritic regression during aging. The development of layer V pyramidal neurons did not last longer than that of layer IIIC neurons. Is is concluded that major growth takes place during the first and second postnatal years and that postnatal maturation of layer V neurons dendritic tree has ended at 5 years of age.

Supported by the Ministry of Science, Croatia, and the Van den Houten Foundation, The Netherlands.

70.06 ALLOTRANSPLANTATION OF FETAL RAT NEOCORTEX INTO THE BRAIN AND INJURED SCIATIC NERVE: COMPARATIVE STUDY

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Fragments of fetal neocortex from 14-15-day-old Wistar rat embryo were grafted into neocortex and crushed sciatic nerve of adult Wistar rats. Electron microscopic study 30 d later showed that grafts contain differentiated neurons, glial cells, matured neuropile, many vessels. Histological investigation with toluidin blue showed that grafts in the brain and nerve are different. The former contain about 40% of neurons, while the latter only 16% neurons. Few layers of glial cells on periphery of grafts in the nerve were seen. Electron microscopy revealed that these cells are ependymocytes with cilia.

It is suggested that microenvironment das influence on grafted neuroepithelial cells development and differentiation.

70.07 CELL-ADHESION FACTORS AND LONG-TERM MEMORY IN ADULT RATS.

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At present the similarity of the molecular mechanisms underlying neural plasticity in developing and adult brain is widely assumed. Accordingly, we studied a role of the lectins -cell adhesion and recognition factors, named CSL and Rl,- in the mechanisms of habituation of the acoustic startle response in adult rats. Applications of the antibodies (ABs) to the lectins 1 h before training at the vermis impaired long-term but did not short-term habituation of the acoustic startle, whereas the ABs injected 1 h before testing did not affect expression of acquired long-term habituation of the reflex. The level of CSL in the vermis increased first during a consolidation of long-term habituation (on 3th-6th day), and then returned by the initial value (on 14th day). The level of Rl in the vermis started to rise only 9 days after training and was the most high on 14th day.

The present results suggest the involvement of the lectins in the molecular mechanisms underlying the long-term memory in adult animals.

70.08 AN ANIMAL MODEL FOR NEURODEVELOPMENTAL DISORDERS; BEHAVIOURAL EVALUATION.

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A number of brain malfunctions, amongst others certain psychiatric disorders such as schizophrenia, are possibly related to a disturbance of prenatal brain development. A model was, therefore, construed to investigate abnormal limbic- and early neocortical development in the rat.

Four groups of female rats were injected with methylazoxy methanol acetate (MAM), which destroys cells undergoing mitosis, on E9 (group1), E10 (group 2), E11 (group 3) or E12 (group 4). A control group was injected on E11 with saline. Postpartum, a number of male siblings was randomly selected for evaluation tests, including neurological reflexes, habituation and prepulse inhibition, working and reference memory, and social behaviour.

Results indicate memory abnormalities in groups 1 and 2, deficits in habituation and prepulse inhibition in groups 2 and 3, and certain neurological deficits in groups 3 and 4. Social behaviour was differently affected in the various groups. It can be generally concluded that the same pathogenic factor can result in different behavioural syndromes, depending on the precise time at which it impinges on development. Also, within the gestational time span tested here, a later disturbance of development (groups 3 and 4) correlated with progressively more obvious phenotypical abnormalities. This possibly reflects a diminished adaptive plasticity of various structures with progressing development. Finally, it appears that a relatively subtle disturbance of early cortical development, can result in neurological behavioural and electrophysiological abnormalities that are, in some cases reminiscent of certain psychiatric and personality disorders.

70.09 OLFACTORY FUNCTION OF ECTOPICALLY LOCALIZED GLOMERULI IN BULBECTOMIZED RATS.

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In this experiment neonatal rats (P3-P5) were subjected to the removal of the right olfactory bulb (OB). At the age of 90 days the rats were tested in simple and unambiguous food finding task and then the intact OB of these trained animals was ablated. After 6 days of postoperative recovery the rats were retested in the same task. The significant failure to retrieve the food has been observed in 14 animals out of 20. When opening the skull we ascertained that these anosmic rats had both their OB completely removed, it means that the lesion involved at least the anterior third of the olfactory peduncle. Glomerular-like structures were formed in the frontal neocortex on the neonatally operated side. The results of the behavioral tests of these rats have indicated that reconstituted olfactory projections, which terminate in the forebrain, do not support olfaction. In the remaining 6 animals we found macroscopically visible OB remnants, which could mediate smell.

70.10 PHOTOPERIOD AND TEMPERATURE EFFECTS ON THE "REACTIVE NEUROGENESIS" PERIOD THAT PRECEDES REGENERATION OF THE LIZARD CEREBRAL CORTEX

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The lizard medial cortex (=lizard fascia dentata) shows delayed postnatal neurogenesis. It may regenerate after being lesioned using the neurotoxin 3-acetylpiridine. Regeneration is always preceded by a short and intensive period of cell proliferation activity ("reactive neurogenesis") in the subjacent ependyma. Then, the just generated neurocytes migrate along radial glia reaching the cell layer where they replace the killed neuronal somata.

This regenerative potentiality is different when the experiments are carried out in different seasons (summer-winter). This study was aimed to check the differential effects of the two main ambient components: temperature and photoperiod. Four colonies of lizards were maintained at cold/warm (10°C/25°C) temperatures and short/long (8h/day; 16h/day) light periods simulating winter/summer ambient conditions. After 3AP lesion, cell proliferation was detected using immunodetection of proliferating cell nuclear antigen as well as pulses of tritiated thymidine and 5-bromodéoxiuridine delivered at different times after lesion.

Labelled cell counts reveal that a long photoperiod enhances proliferation activity and that temperature is mainly concerned with the migratory activity of new-immature neurons. Animal maintained in non-natural conditions (i.e., animals maintained in warm+short photoperiod or cold+long photoperiod) suffered the higher mortality after 3AP lesion.

70.11 DIFFERENTIAL EXPRESSION OF MAP1B ISOFORMS IN THE ADULT RAT NERVOUS SYSTEM. Ramón-Cueto, A.* and Avila, J. Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), Cantoblanco, 28049 Madrid, Spain.

Axonal growh and subsequent maintainance of axons depend on the assembly and stability of neuronal microtubules. Microtubule-associated proteins (MAPs) and their phosphorylation govern microtubule dynamics and hence, neuronal morphological plasticity. Specifically, a phosphorylated MAP1B isoform (MAP1B)* is related to the growth of neurites *in vitro* and is expressed in high amounts in the developing brain. We aim to establish the possible differences in the phosphorylation of MAP1B in the adult nervous system depending on neuronal type, function, plasticity or region. Thus, we performed Western-blot and immunohistochemistry from several areas of the adult rat peripheral and central nervous systems (PNS and CNS, respectively), using a set of antibodies that specifically recognize phosphorylated and dephosphorylated MAP 1B epitopes.

We observed that MAP1B* isoform was very abundant in the axons and cell bodies of all PNS neurons. However, in the CNS this phosphorylated isoform was only detected in retinal ganglion cells and their central projections, the hippocampus, and in some hypothalamic nuclei. Although MAP1B* was also found in the spinal cord, brainstem and olfactory bulb, this molecule was exclusively located at axons from PNS sensitive neurons (central path of spinal, cranial and olfactory nerves). In addition, MAP1B* was absent from other CNS regions. In summary, MAP1B* isoform was exclusively expressed by sensory neurons from both the adult PNS and CNS (retinal ganglion cells). Moreover, it was detected in either peripheral neurons, known to retain their regenerative ability in the adult, or those CNS regions where synaptic plasticity persits throughout adulthood.

70.12 CONGENITAL ESOTROPIA. S.RETHY,D-46535DINSLAKEN Kreuzstr. 39.

Infantile strabismus is a series of rapid steps of adaptations in brain program, provoked by initially intermittent esodeviation, not a single inherited conglomerate.Early onset from 2nd-3rd m of age is followed by rapid adaptations as a cascade ,when left untreated. At 6th m of age intially intermittent on/off effort of the near reaction (accomm + converg) is constantly active,automatically programmed and latent (not-relaxing with glasses). The "incurable" disease and "unknown" origin could be prevented before stabilization by adaptations occurs.Early diagnosis at 2nd-3rd m of age is needed to be causal,in order to provide secure causal prevention with glasses for baby born with connatal blur owing to frequently inherited refractive errors in the family.

70.13 LARGE SCALE PRODUCTION OF RECOMBINANT HUMAN NERVE GROWTH FACTOR, EXPRESSED BY BACULOVIRUS IN INSECT CELLS. Robertson AGS*, MacGowan SH, Holden PH, Allen SJ, Drake T, and Dawbarn D. Molecular Neurobiology Group, Department of Medicine (Care of the Elderly), University of Bristol, Bristol BS2 8HW UK.

One of the earliest stages in Alzheimer's disease is the loss of cholinergic function in the basal forebrain. Nerve growth factor (NGF) is a potent neurotrophic factor for forebrain cholinergic neurons and promotes the survival and differentiation of sympathetic and sensory neurons during development. In animal models it has been shown that administration of NGF to animals corrects the effects of cholinergic atrophy in aged or lesioned animals. It is therefore thought that administration of NGF may be beneficial to patients suffering from Alzheimer's disease. The gene encoding human NGF has been cloned and engineered into the Baculovirus expression system using the insect host SF9 cells. The insect cells express and process the pre-pro NGF and secrete the mature protein into the culture media. The insect cells are grown in serum-free media and yield approximately 0.5 to 1mg of NGF per litre of culture. The mature NGF is then purified from the culture media in a three step process, ion exchange on an expanded bed column, Streamline SP (Pharmacia), then hydrophobic interaction chromatography, phenyl sepharose, and finally ion exchange, Resource S (Pharmacia). The resulting protein is homogeneous as judged by SDS PAGE and resolves at a Mr of approximately 13,000. The protein is recognized by an ELISA and promotes neurite outgrowth of PC12 cells. After toxicity tests, the NGF will be used in a clinical trial to treat Alzheimer's patients.

70.14 EXPERIMENTAL MODEL OF THE SPINAL CORD INJURE IN CATS.
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The effect of mechanical lesion of the lumbar region of cat spinal cord on morpho-biochemical parameters was studied.The observations were performed 1,2 or 4 weeks after traumatic or shame operation. One week after the transversal lesion (crush) of the lumbar spinal cord (L_2) necrotic and degenerative tissue changes were spread approximately 30mm to both sites from the lesion. The extent of altered spinal cord corresponded to almost 5 spinal segments after 14 days. Changes in the activity of glutamyl transpeptidase (GGT) were used as biochemical marker of cell destruction.A week after the mechanical lesion GGT activity was increased in all samples below the lesion.Two weeks after the transversal spinal cord lesion the activity of GGT decreased in all regions of the lumbar spinal cord,with the exception of tissue samples dissected 30mm distally from the injury.Further analysis showed that the changes in the GGT activity are localized preferentially to the funiculus lateralis and posterior.

70.15 INDUCTION OF FOS DURING THE POSTNATAL DEVELOPMENT OF THE VISUAL SYSTEM OF THE RAT. G. Ruiz* and X. Rojas. Facultad de Medicina, U. de Valparaíso, Chile.

It has been suggested that immediate-early genes, such as Fos, Junb, and NGF-IA, are involved in the plastic response of neurons and in its response to novel stimuli. To investigate such possibilities, we have studied the expression and pattern of distribution of the Fos protein in the visual system of young rats (8,15,30 & 60 days old), during a period known for its anatomical and physiological development and susceptibility to plastic changes. Both the basal Fos immunoreactivity (ir) and after non-invasive physiological stimulation with flashing light were studied.

Our results show that the basal level of Fos ir was restricted to faintly labeled nuclei in the visual cortex (VC) up to 15 days of age. There was no basal Fos ir in the VC of older rats, nor in the superior colliculus (SC) at any age tested. In contrast, visual stimulation resulted in numerous darkly labeled nuclei, and its distribution was also affected by age. In the SC, Fos ir changed from none at day 15 to heavy label at day 30. In the VC, changes with age involved differential Fos ir laminar distribution. These results are discussed in the context of visual system maturation and of each area's response to the model used.

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70.16 DIRECT CURRENT STIMULATION OF THE TRANSECTED RABBIT SCIATIC NERVE.
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Presented study tested the implanted 5uA stimulators in a transcected and sutured sciatic nerves in rabbits.

In respect to the rules of the European Communities Council Directive(86/609/EEC) 15 experimental animals were subject of the double blind study.In 5 animals active 5uA stimulator was implanted, another 5 had inactive,last 5 served as controls.The length of survival was 3 month.For the evaluation clinical test, nerve conduction velocity and morphological studies were used.

In both stimulator groups no regeneration was proved in contrary to the good results of regeneration in the controls.

The failure of axons to cross the transection site in both stimulator groups was likely caused by permanent micromovements of nerve stumps generated by the stimulator and electrodes movement whenever the animal moved. The implantation of stimulators is an invasive method,which does not seem to be appropriate for the enhancement of regeneration of the transected peripheral nerve.

70.17 EFFETS OF AN UNILATERAL LABYRINTHECTOMY ON NMDA SUBUNITS mRNA EXPRESSION IN THE VESTIBULAR NUCLEI OF THE GUINEA PIG.
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In adult guinea pig, the localization of neurons expressing the different subunits of the NMDA glutamate receptor was examined throughout the vestibular nuclei (VNs) by non-radioactive in situ hybridization (ISH), using alkaline phosphatase labeled oligonucleotide probes.

Our study identified the topographical patterns and the cellular distribution of expression of the mRNAs encoding NR1, NR2A, NR2B, NR2C and NR2D subunits in the VNs. Constitutive expression of NR1 mRNA was evidenced in large- to small-sized neurons of the median vestibular nucleus (MVN). The NR2A, NR2B, NR2C and NR2D subunits had a restricted distribution in the VNs.

As neuronal plasticity is controlled in part by NMDA receptors, the molecular implication of the different subunits was assessed by analyzing the effects of hemilabyrinthectomy (UL) at various times post lesion, from 10 hours to 30 days, and comparing their expression patterns in the ipsi- and contra-lateral VNs. Changes in the ISH colorimetric signal were quantified by image analysis. In the MVN ipsilateral to the lesion, UL induced a remarkable 16% increase of NR1 mRNA in neurons after 20 hours and a 20% decrease 48 hours post-UL. Concomitantly, at this 48 hours delay, a light increase in NR2C mRNA was observed in the ipsilateral MVN, whereas the very low basal expressions of NR2A, NR2B and NR2D remained unchanged.

These findings suggest that changes in the subunit composition of the NMDA receptor channel take place during the early stages of the vestibular compensatory process. The timing of these transient changes in NMDA receptor channel composition indicates that they may play a important role in the reorganization mediating the delayed modifications in the vestibular network linked to vestibular compensation.

70.18 TRANSIENT LHRH CELLS AND FIBERS IN THE CEREBRAL CORTEX OF EMBRYONIC AND YOUNG RATS.
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In previous experiments we have shown by using DiI that at early embryonic stages (E13) axons arising in the olfactory placode enter the olfactory bulb anlage, some of them coursing over the telencephalic vesicle (Dev. Brain Res. 70 213-222). DiI did not allow us to find out the nature of this last set of axons. In the present study we have found that from E17 until P7 LHRH immunoreactive fibers can be found coursing mainly in the marginal layer of the prospective cingulate gyrus, into the prospective somatosensorial cortex and other cortical areas. At postnatal stages immunoreactive fibers were observed in layer I of the cingulate gyrus and the somatosensorial cortex. LHRH containing cells were located in different parts of the cerebral cortex, but they were more frequently found into the cingulate girus (or its anlage), and the nearby cortex. They were more abundant from E17 to E20. The number of LHRH ir cells decreased according to the age of the animals. Some cells were seen at postnatal P11. No fibers or cells were observed in adult animals at this location. We suggest that besides the well known olfacto/vomeronasal and nervus terminalis fibers, there exists a third set of fibers having their origin in the olfactory placode. This last set of fibers also carries LHRH immunoreactive elements. They course over the telencephalic vesicle and are prominent at E13 but they are transitory and do not last to adulthood. The early axons of this system could be detected as LHRH fibers at later embryonic stages and could serve as a guide for the neuronal LHRH cells found in the telencephalic vesicle at embryonic and young postnatal stages.

70.19 CONTEXT EFFECTS IN THE CHICK'S POSTDISCRIMINATION GENERALIZATION GRADIENTS: PSYCHOPHYSICAL SHIFT DATA FROM TWO VISUAL DISCRIMINATION TASKS.
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A successive discrimination procedure was applied with subsequent stimulus-generalization testing under different asymmetrical context-test conditions. One subgroup of chicks learned to discriminate between a "blue" and a "green" training square, the other one between a "small" and a "large" object. After reaching the 90 percent criterion of correct responding, for each psychophysical dimension the test phase started, with two asymmetrical test-series and one symmetrical series as the control. All stimuli were produced by a touch-screen device. The generalization tests with the respective asymmetrical versus symmetrical stimulus-series resulted in systematic context shifts, as predicted from earlier psychophysical research with humans (perceptual *relativity*); i.e. stimulus-response shifts were found as a function of either the color or the size of the contextual test-series used (Sarris, *BBS* 1994).

70.20 **USE OF GAD-LAC Z TRANSGENIC MOUSE LINES IN TRANSPLANTATION EXPERIMENTS.**
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Three constructs, carrying different, progressively longer regions of the GAD (67 kDa) promoter linked to LacZ reporter-gene, were used to obtain GAD-LacZ transgenic mice. Ten mouse lines expressed the transgene in the CNS, detected by X-gal histochemistry. Animals carrying the longest construct showed almost correct expression of the transgene in the GABA-ergic structures. Some ectopic expression was found in not typically GABA-ergic neuronal populations, but their incidence was more frequent in the animals carrying the shorter constructs. Besides studying regulation of the GAD gene these lines appear to be very useful for studying development, neuronal survival and plasticity in the CNS. The transgene was found to behave as an intrinsic cellular marker even when expressed at ectopic sites, which prompted us to use the GAD-LacZ transgenic mice in different transplantation paradigms. We transplanted i/embryonic olfactory bulb of TgGAD1 line homotopically; ii/embryonic cerebellum of TgGAD9a line and iii/adult dorsal root ganglia of TgGAD9a line heterotopically into olfactory bulb of neonatal (B57Bl6xCBA)F1 mice. In all cases the transplant was clearly identified by X-gal staining. The expression of the transgene within the transplanted tissue showed the same neuronal expression pattern as the control material. Moreover, the staining of individual neurons was similar to Golgi impregnation, so we could follow their processes and the newly formed connections between the transplant and host neurons. Using tissue from GAD-LacZ transgenic mice as graft, allowed us to follow the fate of intrinsically labeled neurons months after transplantation.

70.21 EFFECTS OF THE NEUROTROPHIC ACTH(4-9) ANALOGUE ON MICROGLIAL CELLS IN THE VISUAL SYSTEM OF NORMAL AND DYSTROPHIC RATS.
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Rats of the RCS-strain (Royal College of Surgeons) suffer from a hereditary photo-receptor dystrophy which results in a nearly 90% loss of photoreceptor cells (PRs) during the first two postnatal months. The present study revealed that an intravitreously injected fragment of adrenocorticotrope hormone (ACTH4-9) and the antiinflammatory tuftsin fragment macrophage/microglia inhibiting factor (MIF) prevent this de-gradation. ACTH4-9 was injected three times and MIF two times between the second and eighth postnatal week into the left vitreous body of animals of both sexes. The numbers of PRs in two months old animals were morphometrically determined on histological sections. The application of the antiinflammatory MIF resulted in a 2.5 fold rescuing effect in the injected eye, whereas the neurotrophic ACTH4-9 preserved a 2.6 fold population of PRs, interestingly in both eyes of male but not in female animals. In order to investigate the influence of both substances on different cell types in the retina of normal and dystrophic rats, the fluorescent dye 4Di-10Asp was applied on the transected optic nerve, which results in a fluorescent staining of ganglion cells and phagocytosing microglial cells. Both cell types were evaluated at day 12 after surgery. An additional injection of either ACTH4-9 or MIF at day 9 after surgery revealed an obviously blocking effect of MIF on microglial cells, their number was reduced and their typical ramified shape transformed into a rounded type. The application of ACTH4-9 did not change the shape of microglial cells but their number was slightly decreased whereas the number of ganglion cells was significantly increased on a twofold level in comparison to untreated controls. These results indicate a primary protecting effect of ACTH4-9 on neuronal cells which results in a secondarily diminished activation of microglial cells. The results on MIF suggest that this factor has got primarily deactivating qualities which lead secondarily to surviving neuronal cells.

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70.22 IMMUNOHISTOCHEMICAL STUDY ON THE DEVELOPMENT OF CATECHOLAMINERGIC (CA) NERVE STRUCTURES IN THE PORCINE NUCLEUS PARAVENTRICULARIS (PVN).
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Although the ontogeny of catecholaminergic system in the hypothalamus of rats and mice was described, nothing is known about the ontogeny of the catecholaminergic system in the porcine hypothalamus. Therefore, the present study was aimed at investigating the development of tyrosine hydroxylase (TH), dopamine ß-hydroxylase (DßH) and phenyl N-methyl transferase-immunoreactive (PNMT-IR) hypothalamic nerve structures in the pig. Investigations were performed in brains of female porcine foetuses at different age (10, 14, 16 weeks old) collected during the caesarean section. Anaesthetised foetuses were transcardially perfused with 4% paraformaldehyde in phosophate buffer. Collected hypothalami were postfixed and transferred into 30% sucrose solution. In addition, hypothalami from female pigs at different ages (1 day, 10 weeks. 7-8 months) were studied. The animals were transcardially perfused with 4% para-formaldehyde in PB. In case of the oldest pigs only their separated heads were perfused through the common carotid arteries. Hypothalami were cut with a cryostat. Single- and double-labelling immunohistochemistry was applied using antisera raised in mice and rabbits against TH and DßH and PNMT. In the porcine PVN of 10-week-old foetuses, only singular CA neurons and nerve fibres were present. Number of CA structures increased in 14- and 16-week-old foetuses, and in 1 day-old piglets. In 10-week-old pigs still greater number of CA structures were observed, but in sexually mature sows the number of CA structures was smaller than in 10-week-old pigs.

Conclusions: Number of CA structures in porcine PVN increased with advancing age of animals, but decreased between 10 weeks and 7-8 months of life.

70.23 3 DAYS OF APPETITIVE CLASSICAL CONDITIONING TRAINING CHANGES CORTICAL BODY MAPS IN THE BARREL FIELD OF ADULT MICE, A 2DG STUDY.

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Changes in topographical maps in the first somatosensory cortex were visualized with 2-deoxyglucose (2DG) autoradiography after appetitive sensory conditioning training. In this study we used paradigms of classical conditioning involving stimulation of mystacial vibrissae row B. Row B of vibrissae on one side of the snout was stroked immediately before delivery of sweet water to the mouth. The pairings were repeated 4/min for 10 min. Training lasted 3 days. 2DG experiments were done after the last training session. Following injections of [^{14}C]2DG rows B of vibrissae were stimulated on both sides of the snout. Stimulation of "trained" row resulted in labeling of a larger area of the barrel field than stimulation of the "untrained" row on the other side of the snout. Enlargement of row B representation was visible in layers II/III 27% and layer V 28%. The labeling was centered on row B of barrels and overlapped neighboring rows. The results demonstrate a learning induced changes in cortico-cortical and cortico-subcortical connections.

70.24 EXPERIENCES IN EARLY LIFE: DETERMINANTS FOR ADULT SOCIAL BEHAVIOR

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The reaction of an organism to environmental challenges depends on the properties of the situation, genetic composition of the individual and experiences in "critical periods" during development. In this study we have altered the adult social behavior of male Wistar rats by interefering with their social experience in the first three weeks of during week 4 and 5 of age. Pups demonstrated preference for their "own" nest during the first three weeks of life. During week 4 and 5 young rats are motivated to frequently display play behavior. To study the long-term function of this preference and play behavior pups have been changed from one nest to another in order te prevent bonding to their "own" nest. In week 4 and 5 young rats have been isolated in order to prevent the display of play behavior. Pups who had been daily changed from one nest to another showed a delay in copulatory behavior, an alterd performance (gender dependent) in the elevated plus maze and increased alterness in a shock prod-burying task. Young animals deprived of the possibility to play had severe problems with coping with the offensive behavior of another dominant male. Both a decrease in freezing behavior and an increase in plasma corticosterone levels have been observed in these animals. Apparently, the nature of social experience of young rats has far reaching consequences for their social behavior in adulthood.

70.25 AXONAL OUTGROWTH ON RETINAL CRYOSTAT SECTIONS

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The formation of neuronal networks during development is one of the elementary steps for stucturing the nervous system. In order to elucidate the axonal guiding mechanism during retinal pattern formation, chicken retina explants were cultured on unfixed retinal cryostat sections. Like in vivo retina ganglion cells extend their axon into the innermost layer whereas outer tissue layers were avoided.

(1) Stereotropism (mechanical guidance) along the edges of the cryosection could be excluded by analogy with a novel explant culture system using three-dimensional micro structured silicon chips.

(2) Laminin of the basement membrane did not affect the oriented axonal outgrowth. Even in the absence of nature laminin (inactivated by UV-irradiation) the axons grew preferentially on the innermost retina layer.

(3) However, retina ganglion cell axons did not grew on cryosections with prior removal of the inner limiting membrane (including basement membrane and glial endfeet). In addition purified glial endfeet provide an excellent substratum.

(4) In contrast, cells of the outer retina were inhibitory for outgrowing ganglion cell axons. This could be shown by cultivating retina explants on "delayered" living retina tissue (the three innermost layers of the retina were removed by mechnical detachment) and by using membranfractions which cause collapse of growth cones in vitro.

Taken together the data substantiate the hypothesis that within the retina, ganglion cell axons are guided by a dual mechnism based on a permissive zone (glial endfeet) and an inhibitory zone (outer retina layers).

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70.26 AN ANIMAL MODEL FOR NEURODEVELOPMENTAL DISORDERS; MORPHOLOGICAL EVALUATION.

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A number of brain malfunctions, amongst others certain psychiatric disorders, are possibly related to a disturbance of prenatal brain development. In this light a model was developed to investigate possible causes and consequences of abnormal development in the rat. As our main interest was on disorders involving cognitive deficit, the model focusses on the period of limbic- and early neocortical development.

Four groups of female rats were injected with methylazoxy methanol acetate (MAM), which destroys cell undergoing mitosis, on E9, E10, E11 or E12. A control group was injected on E11 with saline. A number of male siblings was randomly selected for histological evaluation: Brain slices were processed for immunohistochemistry against proteine kinase C-gamma (PKC), which, in the cortex, is mainly present in pyramidal cells, or parvalbumine, which is found in interneurons. Both procedures highlight the layered organization of cortical structures, which facilitates the detection of possibly occuring aberrations of cytoarchitecture.

The material was quantitatively assessed through cell counts in various limbic and neocortical regions, namely the entorhinal cortex, the anterior and posterior cingulate cortex, the associational prefrontal cortex and a segment of parietal cortex. Differences in hippocampal staining were quantitatively determined through computerized densitometric measurements.

Preliminary results suggests reductions in basal, subcortical and limbic structures in the earlier treated groups, and reductions in limbic and neocortical cortical structures in the groups treated later in development. Reduction of the neocortex is particularly pronounced in group 4.

70.27 SHORT STRESSORS CAN INDUCE ADAPTIVE CHANGES IN HYPOTHALAMIC CRH-NEURONS THAT LAST FOR WEEKS

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Hypothalamic CRH neurons that project to the external zone of the median eminence (ZEME) control the secretion of ACTH from the pituitary gland. These CRH neurons have the potency to co-produce vasopressin (AVP). In adult male rats 25-50% of the CRH-neurons show co-production, co-storage and co-secretion of AVP. Single administration of interleukin-1 (IL-1) markedly increases the fraction of AVP co-producing neurons 2 weeks later. In addition to IL-1, also single session of electric footshocks (15 min) induces long-lasting (weeks) increase of AVP but not of CRH in the ZEME. This is associated with an increased AVP/CRH ratio of the hypothalamic signal controlling ACTH secretion and results in increased ACTH-responses to stressors 2 weeks later. In order to study whether all stressors induce such long lasting changes in hypothalamic CRH neurons, groups of rats were exposed to one of various stressors including ether, insuline, footshocks, IL-1 and endotoxin. Rats were placed back in their home cages and CRH and AVP stores in the ZEME were studied 7 and 11 days afterwards. In separate groups ACTH and corticosterone responses to these various stressors were studied. Most stressors increased AVP in the ZEME, whereas CRH remained unaffected. This delayed increase in AVP correlated (r 0.89) with the initial ACTH response to the stimulus (area under the curve). These observations lead us to conclude that long-lasting hyper-expression of AVP in CRH neurons is induced by stress-induced activation of these neurons.

70.28 STIMULATION OF AXONAL GROWTH FROM PERIPHERAL NERVES OF ADULT MICE BY SEGMENTS OF LESIONED NERVE AND NGF IN VITRO

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The factors determining the success of peripheral nerve regeneration are poorly understood. Nerve Growth Factor (NGF) has been shown to promote neurite outgrowth from dissociated adult sensory neurons in vitro and its synthesis is increased in lesioned nerves. However, the role of NGF during peripheral nerve regeneration is uncertain since antisera to NGF do not inhibit regeneration of sensory nerve axons in vivo and furthermore, expression of receptors for NGF on sensory neurons is reduced after axotomy.

In the present study, intercostal nerves with attached dorsal root ganglia of adult mice were cultured in collagen gels. In control preparations, only a few axons grew out of the ends of the intercostal nerves but both the numbers of axons and their lengths were markedly increased by addition of NGF. Preparations incubated together with segments of lesioned sciatic nerve also showed significant increases in numbers and lengths of axons within 1 day in vitro. The stimulatory effects of the lesioned nerve segments on axonal growth were blocked by antibodies to NGF. The results indicate the release NGF or an immunologically related substance from lesioned peripheral nerves can stimulate axonal growth of adult sensory neurons.

This work was supported by Start-Up funds from King's Collge London.

70.29 **Targeted inactivation of the Fibroblast Growth Factor-5 gene by replacement with the E.coli LacZ gene**

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Fibroblast growth factor-5 (FGF-5), a member of the FGF gene family, was originally identified as the product of a human oncogene. Unlike the prototypical FGFs, aFGF and bFGF, FGF-5 contains a hydrophobic leader sequence typical of a secreted protein. FGF-5 is expressed during embryogenesis in a time- and tissue-specific manner suggesting that this factor might play an important role during the embryonic development. In adult, the FGF-5 expression is prominent in the central nervous system, and thus FGF-5 might serve as a trophic factor for neurons and glia. FGF-5 is known to support the survival of cultured motoneurons and to promote the differentiation of rat septal cholinergic and raphe seretonergic neurons, but the natural targets for FGF-5 action *in vivo* remain unclear.

To elucidate the biological function of FGF-5 *in vivo*, we have used the gene targeting approach to mutate the FGF-5 gene in mice. For this, we constructed a targeting replacement vector in which a part of the FGF-5 gene was replaced with the E. coli LacZ gene. This approach will give us the opportunity not only to study consequences of FGF-5 disruption, but also to determine the expression profile of FGF-5, since the β-galactosidase activity will be driven by the endogenous FGF-5 promoter. After selection of ES cells transfected with the targeting vector, resistant clones were analysed by Southern blot for the indentification of homologous recombination events in the FGF-5 gene. 15 clones were indentified carrying the desired mutation. Injection of several of these clones into mouse blastocysts, resulted in chimeric animals which have been used to generate FGF-5 mutant mice. The mutant mice are viable and fertile, and appeared phenotypically normal untill ~2 weeks after birth when their hair starts to grow abnormally long. Results from the ongoing analysis in the nervous system of the mutant mice as well as a detailed mapping of the expression profile of the FGF-5 gene during the development will be presented.

70.30 MELANOCORTIN RECEPTORS MEDIATE α-MSH INDUCED NEURITE OUTGROWTH IN NEURO2A CELLS

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Melanocortins stimulate nerve regeneration in various models via a yet unknown mechanism. The recent cloning of neural melanocortin (MC) receptors opened new avenues to clarify the mechanism underlying the neurotrophic effects of these neuropeptides. Neuro2A cells form longer neurites when incubated with 10 nM α-melanocyte stimulating hormone (α-MSH) as compared to control cells. The pattern of melanocortin peptides able to promote neuritogenesis in Neuro2A cells was similar to the pattern of these peptides able to increase cAMP levels in 293 HEK cells stably expressing the MC4 receptor. α-MSH induced neurite outgrowth could be blocked by the MC receptor antagonist [D-Arg8]ACTH(4-10). By RNAase protection assays it was shown that Neuro2A cells express low levels of MC4 receptors. These data suggest that the stimulatory effect of melanocortins on neuritogenesis in Neuro2A cells is mediated by MC4 receptors. Which MC receptor mediates the effect of melanocortins on nerve regeneration *in vivo* is topic of current research.

70.31 **Consequences of neonatal and adult lesions of the medial prefrontal cortex (mPFC) on DMTP behavior and the effects of local infusion of dopaminergic and cholinergic drugs.**

C.G. van Eden, R.N.J.M.A.Joosten, and L.M. Broersen

T-maze delayed alternation performance is disrupted by lesions of the dorso-medial prefrontal cortex in the adult rat. On the other hand, it has been shown that neonatal mPFC lesioned rats (P6) can recover and perform as good as controle animals on this task. This recovery has been shown to be accompanied by an extention and activation of the mesocortical dopaminergic system in the remaining ventromedial parts of the mPFC. The present study was performed to further investigate the recovery of function in an operant delayed matching to position task and to explore the effects of dopaminergic and cholinergic a- and antagonists infused into the remaining ventral mPFC.

The results showed that DMTP behavior (with delays of 1.5, 5, 15 and 30 s) is significantly impaired by adult mPFC lesions, albeit not in a delay-dependent manner. As before, the rats with neonatal mPFC lesions performed at the same level as their control-operated littermates also at trials with long delay intervals. Local infusions into the ventromedial PFC in adult rats of flupenthixol (10, 30, 45 μg/site), apomorphine (3 and 9μg/site) and physostigmine (1 and 3μg/site) did not have significant effects on DMTP behavior. Scopolamine infusions (5 and 15μg/site) resulted in a significant deterioration of DMTP behavior. In contrast to earlier findings in intact (non-lesioned) rats this effect is not delay-dependent.

70.32 EXPRESSION OF ß-GALACTOSIDASE IN SUPRACHIASMATIC NUCLEUS TRANSPLANTS UPON ADENOVIRUS-MEDIATED TRANSFER OF THE BACTERIAL MARKER GENE Lac-Z.

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Lesioning of the suprachiasmatic nucleus (SCN) results in a disturbance of the circadian drinking rhythm in rats. We have shown before that transplantation of a rat fetal SCN can restore the drinking rhythm in about 40% of arhythmic SCN-lesioned adult rats. The recovery of drinking rhythm was suggested to be mediated by sparse outgrowth from the transplant into the host brain of fibers containing vasopressin and vasoactive intestinal polypeptide. We hypothesized that enhancement of the amount and extent of outgrowth of these fibers should result in an increase in the percentage of rats recovering their circadian drinking rhythm. Gene transfer mediated by a replication-defective adenovirus can provide the transplant with increased levels or prolonged expression of either growth factors or growth-associated proteins. This could promote the fiber outgrowth from the transplant into the host brain. In the present experiment, we describe gene transfer of the reporter gene Lac-Z encoding for ß-galactosidase into fetal SCN explants prior to grafting. In vitro, explants placed for 2-18 h in culture medium containing the viral vector expressed the gene in the following 8 days. Intracranial placement of such explants 24 h after onset of gene transfection also revealed a clear and extensive expression of ß-galactosidase on day 8, which was present both in neural and non-neural cells. These preliminary results show that it is indeed possible to provide fetal grafts with an additional gene, which is expressed for at least 8 days.

70.33 GROWTH CONE COLLAPSE OF IDENTIFIED *LYMNAEA* NEURONS INVOLVES SIGNALING BY G PROTEINS OF THE Gq CLASS

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Growth cone collapse is a neuronal avoidance behavior implicated in pathfinding and target selection. The intracellular signal transduction pathways that mediate collapse-inducing signaling are largely unknown. Recently, evidence has been presented suggesting the involvement of pertussis toxin-sensitive G proteins (Igarashi et al., (1993) Science 259: 77-79). Here we report the involvement of a specific G protein (subclass) in growth cone collapse of identified neurons from the mollusc *Lymnaea stagnalis*.

In cell cultures of identified *Lymnaea* neurons, dopamine secreted by the Right Pedal Dorsal 1 interneuron (RPeD1) induces target neurons (synaptic partners *in vivo*) to form synapses, whereas non-targets (not synaptic partners *in vivo*) exhibit growth cone collapse. In this study an antibody specific for the α subunit of Gq/11 proteins recognized a single protein band of approximately 42 kDa on Western blots of *Lymnaea* brain extracts. The apparent molecular weight of this band corresponds well with the theoretical value for a Gαq/11 subunit which was recently cloned by us. In immunofluorescence experiments with the identified non-targets Visceral F (VF) and Right Parietal Dorsal 1 (RPD1), the antibody stained varicosities and growth cone regions, organelles involved in neuronal communication. Upon micro-injection of the antibody into non-targets, dopamine-induced growth cone collapse was prevented. These results suggest, for the first time, a coupling of dopamine receptors to G proteins of the Gq family. Moreover, they implicate pertussis toxin-insensitive G proteins of the Gq class in signaling pathways that govern growth cone collapse of identified snail neurons.

70.34 OPEN FIELD AMBULATION: A PREDICTIVE INDICATOR FOR THE RATE OF FUNCTIONAL RECOVERY AFTER SCIATIC NERVE CRUSH LESION IN THE RAT ?

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Recently we have shown that chronic stress impedes sensorimotor recovery following a sciatic nerve crush lesion in the rat and that the degree of recovery was individually determined. In this study the relation between functional recovery from a sciatic nerve crush lesion and a behavioural characteristic, the locomotor response in a novel environment, was investigated in young male rats.

Ten high-active (HIGH) and ten low-active (LOW) rats were selected from a stock of sixty rats, on the basis of the distance (m) they travelled when exploring a novel open field, during four consecutive daily trails of 4 min each. Both HIGH and LOW rats underwent a unilateral sciatic nerve crush. Subsequently, the recovery of motor and sensory function was monitored, by evaluation of the free walking pattern and the foot withdrawal reflex.

Recovery of motor function revealed no significant differences between both groups. A significant negative correlation between open field ambulation and the quality of motor function at the end of the experiment was found ($p<0.05$). Recovery of sensory function in HIGH rats was significantly more rapid than in the LOW rats ($p<0.01$). A strong negative correlation between open field ambulation and the day of complete sensory recovery was found ($p<0.01$).

These observations indicate the existence of a relationship between inherited activity, as measured by the behavioural locomotor response to a novel environment, and the recovery of nerve function following crush lesion in individual rats.

70.35 EFFICIENT ADENOVIRAL VECTOR DIRECTED EXPRESSION OF A REPORTER GENE TO NEURONS AND SUSTENTACULAR CELLS IN THE MOUSE OLFACTORY NEUROEPITHELIUM. A.J.G.D. Holtmaat[1,2], W.T.J.M.C. Hermens[1,2], M.G. Kaplitt[3], A.B. Oestreicher[2], W.H. Gispen[2], J. Verhaagen[*1,2]. [1]Neth. Inst. Brain. Res., A'dam, NL; [2]Rudolf Magnus Inst., Utrecht, NL; [3]The Rockefeller University, New York, USA.

The mammalian olfactory neuroepithelium is an unique neural tissue since it exhibits continual replacement of receptor neurons. Although the expression of various molecules in subpopulations of olfactory cells has been characterized in great detail, the precise molecular regulation of neurogenesis, maturation, neuron death and odor detection has not been elucidated. Adenoviral vectors have been shown to be highly efficient gene transfer vehicles for neural cells *in-vivo*. In future experiments we want to use adenoviral gene transfer to investigate the effect of specific gene products on olfactory neuron turnover and regeneration. As a first necessary step to explore the performance of adenoviral vectors in the olfactory neuroepithelium, 1.25 x 10^7 and 1.25 x 10^8 viral particles in 50 μl of an adenovirus vector for LacZ (Ad-CMV-lacZ) were infused in the nostrils of mice. At 3 and 8 days after infusion this resulted in numerous ß-galactosidase (ß-gal) expressing OMP-positive olfactory neurons and sustentacular cells. Immunocytochemical analysis with anti-B-50/GAP-43 antibodies revealed that only a few immature neurons did express lacZ. This, together with the observation that many sustentacular cells are ß-gal-positive, suggests that the viral vector is taken up most efficiently by cells that are in direct contact with the mucus membrane. In numerous neurons the synthesized ß-gal was transported through primary olfactory axons to the olfactory bulb. These results indicate that adenoviral genetransfer in the olfactory neuroepithelium is a feasible approach towards efficient *in-vivo* genetic intervention in the olfactory neuro-epithelium and may be instrumental to elucidate molecular mechanisms that govern olfactory neuron turnover, regeneration and function.

70.36 IN VIVO QUANTIFICATION OF PATHOLOGICALLY (EAE) INDUCED ALTERATIONS IN WATER DIFFUSION IN THE RAT BRAIN BY NMR IMAGING. M.R. Verhoye*[1,2], E.J.'s-Gravenmade[3], E.R. Raman[2], J. Van Reempts[4] and A. Van der Linden[1]; [1]Bio Imaging Lab, [2]BIMEF: University of Antwerp, Belgium; [3]Dept. of Neurology: Univ. Hosp. Groningen, The Netherlands; [4] Dept. Life Sciences, Janssen RF, Beerse, Belgium.

In vivo NMR Images of the rat brain were obtained on an NMR microscope (7 Tesla) from S.M.I.S. (England). Four animals were imaged every 3 to 4 days during a pathological cycle (starting after induction and up to 37 days) of EAE (experimental allergic encephalomyelitis), an animal model for multiple sclerosis. The EAE rats were weighted and clinically scored daily. • A multi slice spin echo NMR sequence was used with diffusion sensitizing gradients in the X, Y and Z direction with equal strength and at the same time which ensured an intersection of all nerve fiber directions. Sets of five diffusion-weighted images were used to calculate diffusion maps at different time intervals of the pathology. The grey level in these maps represents the Apparent Diffusion Coefficient (ADC). • For the control rats, we obtained <ADC> values of (474 ± 15) 10^{-12} m²/s for grey matter and (920 ± 30) 10^{-12} m²/s for white matter, measured in the external capsule. • There were no alterations in ADC values of the grey matter with increasing clinical scores. Concerning the white matter, as determined in the external capsule, there were no significant differences in ADC values between controls and EAE rats before clinical signs occurred. However as soon as clinical signs were observed, we could demonstrate a significant positive correlation between the clinical score and the ADC values in the external capsule. As the clinical signs became more severe, we measured a rise in water diffusion (increase in ADC) in the external capsule which was accompanied by the occurrence of interstitial edema as revealed by a complementary histological study.

70.37 INFLUENCE OF INTERLEUKIN-1ß ON REVASCULARIZATION AND VASCULAR PERMEABILITY IN RAT PINEAL AUTOGRAFTS. J. Villegas*, A. Villegas, C. Fernández-Vjadero, R. García-Rivas & D. Crespo. Dpt. Anatomy & Cell Biology, School of Medicine, University of Cantabria, 39011-Santander (SPAIN).

Interleukin-1ß (IL-1ß), an immunomodulator produced by mononuclear phagocytes, has been reported to stimulate blood vessel growth when injected into the brain (Giulian et al., 1988). We studied the effects of IL-1ß on revascularization time course and permeability of blood vessels in rat pineal autografts. Pineal grafts immersed in 3 μl of recombinant human IL-1ß were stereotaxically injected into the striatum of female Sprague-Dawley rats with the aid of a Hamilton syringe. Post-grafting survival times were 1 day through 3 months. Several animals having grafts without IL-1ß were used as controls. Time course and developing vasculature within the grafts were studied at light microscopic level in sections from immersion-fixed brains incubated to demonstrate the endogenous peroxidase activity of red cells trapped within the vascular lumen. Vascular permeability in graft blood vessels was assessed by injecting horseradish peroxidase (HRP) intravenously into the grafted animals. The pineal grafts injected together with IL-1ß showed vascularization by 3-4 days post-transplantation; progressive development of the vascular network was observed primarily during the first two weeks after grafting. Control animals, on the other hand, showed no evidence of angiogenesis before 10 days post-transplantation. Extravasation of HRP from blood vessels vascularizing the grafts, was evident in both grafted animals injected with IL-1ß and control animals, with both groups of animals showing fenestrated capillaries under ultrastructural inspection.

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70.38 THE HYPERPOLARIZATION-ACTIVATED CURRENT IN RAT DORSAL ROOT GANGLION NEURON SOMAS AND GROWTH CONES Z. WANG*, R.J. VAN DEN BERG and D.L. YPEY Laboratory of Physiology, University of Leiden, The Netherlands.

Hyperpolarization-activated currents I_h were investigated at two regions of cultured dorsal root ganglion (DRG) neurons: the soma without processes and the isolated growth cone. The DRG neurons were obtained from neonatal 1-day old rats. After mechanical dissociation, the cells were cultured in F14 medium enriched with 10% of horse serum. The patch-clamp technique was used in the perforated-patch configuration. A series of hyperpolarizing voltage pulses from -80 mV to -120 mV was used to activate I_h. At the soma 81% of the cells tested (n=26) possessed I_h, while at the growth cone (n=18) 22% of them showed I_h. The activation midpoint potential at the soma was found to be -92 ± 1 mV (n=9), which was significantly different from that -98 ± 4 mV (n=4) at the growth cone. The activation time constants at the soma were faster than those at the growth cone at all the tested voltages. Thus, there were distinct differences in I_h channel expression and properties at the soma and at the growth cone. These differences may be important for neuron regeneration.

70.39 THE SYMPATHIC INNERVATION OF THE PINEAL GLAND SAMPLED BY MICRODIALYSIS IN FREELY MOVING RATS: VISUALIZATION OF THE ON/OFF SWITCH OF THE BIOLOGICAL CLOCK W.J. Drijfhout and B.H.C. Westerink (*) University Center for Pharmacy, Deusinglaan 2, 9713AW, Groningen, The Netherlands

A method was developed to sample extracellular noradrenaline in the pineal gland of rats by the microdialysis technique. A transpineal cannula was implanted and 24 h later, when the animals were recovered, the output of noradrenaline was estimated. To quantify noradrenaline in dialysates an alternative HPLC-method based on fluorescence detecion of a diphenylethylenediamine derivative, was necessary (detection limit 0.5 fmol/injection). Extracellular noradrenaline in the pineal gland expressed an extreme day-night rhythm. This rhythm resembled clearly an on-off switch. During the light-period virtually no noradrenaline was detected. We used intrapineal and intracerebral infusions, light pulses and behavioural paradigms (mild stress) to study the properties of the noradrenergic innervation of the gland. In addition the rhythm in noradrenaline release was compared to the secretion of melatonin that was similarly recorded by microdialysis. It is concluded that the microdialysis model is very useful to further analyse the interactions between the biological clock and the pineal gland.

To the best of our knowledge this is the first time that the sympathic nervous system is directly sampled by microdialysis in conscious animals.

70.40 REGENERATION IN VITRO OF ADULT MOUSE SCIATIC SENSORY NEURONS IS NOT SENSITIVE TO INHIBITION OF PROTEIN KINASE C. Peter Wiklund*, Per A.R. Ekström and Anders Edström, Department of Animal Physiology, University of Lund, Helgonavägen 3B, S-223 62 LUND, SWEDEN

Protein kinase C (PKC) is regarded to be of importance for neuronal plasticity and outgrowth. It is also possible that PKC has a role in the regeneration of peripheral nerves. In the present study we have addressed this question by using the adult mouse sciatic nerve, which regenerates readily under serum-free conditions in vitro.

By the use of immunohistochemistry we show that PKCß, an isoform that is highly expressed in the nervous system, is rapidly upregulated in cultured dorsal root ganglia neurons. This suggests that PKC is involved in the regenerative events taking place during culturing. However, the specific PKC inhibitor chelerythine did not affect the regeneration of cultured mouse sciatic nerves. Chelerythrine at 5 µM, a concentration well above its IC50 value for PKC, failed to reduce the outgrowth distance of new axons. This was not due to impermeability of the drug, since the same concentration caused a clear reduction of the injury-induced proliferation of Schwann cells in the crush region. Likewise, an inhibitor of cyclic nucleotide-dependent protein kinases, HA-1004, lacked effect on outgrowth , even at very high concentrations (100 µM). In contrast, outgrowth was significantly reduced when 5µM chelerythrine and 5 µM HA-1004 were used in combination.

The lack of effect of PKC-inhibition on axonal outgrowth could mean that PKC is not important in nerve regeneration. On the other hand, inhibited PKC-phosphorylation of certain substrates involved in the outgrowth could be compensated by phosphorylation by other kinases. The latter seems to be supported by the effects of the combination of inhibitors.

70.41 MAGNETIC RESONANCE IMAGING (MRI) APPLIED FOR THE IN VIVO FOLLOW-UP OF EMBRYONIC NEURAL TRANSPLANTS IN ADULT SPINAL RATS.

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After intraspinal neural transplantation, morphological studies require the use of immunocytochemical techniques in order to determine whether the transplanted cells survive or not, and how they develop close contacts within the host spinal cord. Unfortunately, these are post-mortem studies. The aim of this study was to use MRI in order to obtain in vivo morphological data for the follow-up of these neural transplants. Two month old adult rats underwent complete spinalisation at T8-T9 level. One week later, they were injected with a cell suspension containing embryonic monoaminergic neurons into the spinal cord beneath the transection at T12 level. A series of MR images was obtained 2 to 12 weeks post-transplantation in both spinal control and spinal transplanted rats. The animals were anaesthaetised with equitesine (0.3 ml/100g). They were placed in the supine position on their back and centered over a surface coil. Imaging was performed with a 1.5-tesla magnet system by acquiring multislice 3 dimensional spin-echo images (TR=300 ms, TE=30 ms) in both transverse and sagittal planes with a surface coil. Good differentiation of gray and white matter was obtained. The transplants showed hypointense zones relative to the host spinal cord. These MR images will be compared to post-mortem histological pictures. We conclude that MRI techniques could provide promissing morphological data for the follow-up of our transplanted rats, especially if the animals modify their functional capacities.

70.42 **EFFECTS OF ESTROGEN ON THE HYPOTHALAMIC NEURON IN VITRO---SCANNING ELECTRON MICROSCOPIC OBSERVATION.**

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Estrogen has an ability to masculinize the nuclei of the hypothalamus in the critical period. In this study, to clarify the mechanisms of the masculinization, the ultrastructure of the developing processes of the hypothalamic neurons were investigated.

Hypothalami were obtained from day 18 of gestation of female rats. Low-density cultures were prepared and maintained in Eagle's MEM containing dextran-treated 10% fetal calf serum. Experimental groups were treated with estradiol-17β(E_2, 100ng/ml). Cells were fixed with 4% paraformaldehyde and 0.1% glutaraldehyde on 6,12,24,48 and 72hr after plating and freeze-dried using t-butanol.

The fine structure of the hypothalamic neuron showed no difference between control and E_2-treated group before 12hr *in vitro*. However, after 24hr of culture, processes began to grow and extended larger number of filopodia and varicosities in E_2-treated group than in control group. After 48hr of culture, one process became longer than the others to form axon and the growth cone disappeared in E_2-treated group.

These results suggest that E_2 may promote the morphological and functional differentiation of the hypothalamic neuron by the establishment of the neuronal polarity and the formation of the varicosities in early stage of the culture.

70.43 DISUSE-DEPENDENT REORGANIZATION IN AGED RATS: CORRELATION OF CHANGES OF THALAMIC SOMATOSENSORY PAW REPRESENTATIONS WITH SENSORIMOTOR DEFICITS

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In a previous work [1], we have reported age-related modifications in the hindpaw representation in the primary somatosensory cortex (SI) of old rats with advanced degrees of locomotion deficits. The cutaneous paw's receptive fields (RFs) of these animals are several times enlarged and highly overlapping when compared with young rats. In the present study we extend the investigation of the organization of the paw somatosensory maps to the ventral posterior lateral (VPL) nucleus of the thalamus. RF sizes and neural responses to computer-controlled tactile stimulation (PSTHs) in the fore- and hindpaw were recorded in VPL in old Wistar rats (> 27 months) displaying severe locomotion impairments and in young animals (3 - 4 months) serving as controls. The results indicate a significant enlargement of RFs in the VPL hindpaw representation of aged rats but only non-signicant alterations in the RFs of the forepaw representation. However, the PSTHs recorded in the fore- and hindpaw of old rats revealed a significant lengthening of peak response latencies with approximately the same lengthening in the forepaw and in the hindpaw RFs. The represented skin areas also differ significantly between young and old rats. While in young rats RFs most frequently represent the digits and distal pads, in old rats there is an additional representation of the base of the paw at the expense of the digit representations. The results obtained indicate an age-related reorganization of the somatosensory map that are well correlated with the declined sensorimotor performance of the hindpaw and provide further evidence that experience and use are crucial factors influencing the layout of the skin representations not only at cortical levels, but also in subcortical structures.

[1] Spengler F, Godde B, Dinse HR, Neuroreport 6: 469-473, 1995. Supported by Coordenadoria de Aperfeicoamento de Pessoal (CAPES - Brazil) and Institut für Neuroinformatik, RUB.We acknowledge the supply of the old rats by Tropon Werke, Köln.

70.44 EARLY NEUROMERIC DISTRIBUTION OF TYROSINE-HYDROXYLASE AND DOPAMINE-ß-HYDROXYLASE IMMUNOREACTIVE NEURONS IN HUMAN EMBRYOS.

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This is the first and earliest description of the dopamine and noradrenaline cell groups in the human embyos CNS of 4.5 to 6 post-ovulatory weeks. Antibodies raised against tyrosine-hydroxylase (TH) and dopamine-ß-hydroxylase (DBH) allowed to visualize the different catecholaminergic (CA) neurons just after their genesis, as they migrated towards their final positions. A precise neuromeric description of TH-immunoreactive groups is made along the caudorostral extention of the brain: rhombencephalic groups, noradrenergic locus coeruleus (DBH positive) and dopaminergic prosencephalic (hypothalamic) groups are present a week earlier (at 4.5 post-ovulatory weeks) than the so-called dopaminergic mesencephalic cell groups. Also, transient immunoreactivity is observed in discrete brain areas as the inferior colliculus (TH) or some motor nuclei and roots (TH or/and DBH). A neuromeric and longitudinal model of organization of the embryonic brain has been proposed in lower mammals. This study is the first attempt in favor of this model in the human embryonic brain.

71. Poster Session: Motor systems, sensorimotor integration III

71.01 RELATIVE CONTRIBUTIONS OF THALAMIC INTERNEURONS AND RETICULAR NUCLEUS TO INHIBITION OF THALAMOCORTICAL NEURONS IN THE CEREBELLO-THALAMO-CORTICAL SYSTEM.

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Thalamic interneurons (TINs) and reticular nucleus neurons (RNNs) contain GABAergic neurons and are considered to control activities of thalamocortical neurons (TCNs) in various subnuclei in the thalamus. However, no detailed electrophysiological analysis has been performed regarding the contributions of RNNs and TINs to inhibition of TCNs produced by the cerebral cortex and the cerebellum, since both RNNs and TINs converge on TCNs. The present study was undertaken to determine the input-output organization of TCNs and morphologically-identified RNNs, and to analyze the relative contributions of RNNs and TINs to cerebellar and cerebral inhibition of TCNs in the VL by recording intracellular potentials in anesthetized cats. In intracellularly-HRP stained RNNs, stimulation of the contralateral brachium conjunctivum (BC) evoked disynaptic EPSPs, and stimulation of the motor cortex (Mx) evoked monosynaptic EPSPs at two different latencies. Collision experiments revealed that the Mx-induced first EPSPs were generated by axon collaterals of TCNs and the second EPSPs by corticothalamic neurons (CTNs). Intracellular staining showed wide axonal projection of RNNs in the VL. BC stimulation evoked di- and trisynaptic IPSPs in TCNs, whereas Mx stimulation evoked disynaptic IPSPs in TCNs at two different latencies. Mx-induced early IPSPs were induced via RNNs activated by axon collaterals of TCNs and late IPSPs via RNNs or TINs activated by CTNs. Spatial facilitation experiments confirmed that Mx-induced and BC-induced IPSPs were conveyed to TCNs via RNNs and TINs. The results suggest that corticothalamic excitation and inhibition may achieve shifting or shaping active areas in the VL for spatial output formation of the Mx.

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71.02 THE SUBJECTIVE STRAIGHT AHEAD IS DISPLACED BY ARM MUSCLE VIBRATION.

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We receive information about the position of our limbs from various sensory systems. Usually, visual and proprioceptive information on the position of, say, our right hand, are integrated to yield an unambiguous position percept. This integration can be studied by introducing a mismatch between the two kinds of information by means of muscle tendon vibration, which excites muscle spindles and thus induces an illusion of muscle stretch. When a weak light is attached to the index finger of a restrained and vibrated arm, the subject may see the light move as he feels an illusory arm movement. This has been taken to show that proprioception influences the visually perceived position because they are associated with the same body part. We now ask if such an identification is crucial to the combining of visual and proprioceptive information. An apparent displacement of the light would also result from a shift of the visual frame of reference.

We investigated if the visual straight ahead would be influenced by arm muscle vibration. Subjects sat in a dark room with their head aligned with the trunk and supported by a chin rest. Their arms were fixed symmetrically in arm rests. The subjects instructed the experimenter to position a light, which was not related to their hand, until they were satisfied it was straight ahead. The subjects experienced undue extension of the (unseen) vibrated arm and reported a movement of the (actually stationary) light. In spite of this illusory movement the subjects indicated the straight-ahead consistently. Arm muscle vibration caused a displacement of the subjective straight ahead: subjects put the light 2 to 4 deg more to their left during vibration of the right biceps muscle.

We conclude that the vibration-induced visual illusion does not require identification of the light with the vibrated arm. Apparently, vibration of an arm muscle causes a shift (or rotation) of visual space or of the visual frame of reference.

71.03 THE RELATION BETWEEN VOR-SUPPRESSION AND EYE-HEAD CO-ORDINATION DURING SACCADES.

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It is generally accepted that the movements of the eye during saccades with a contribution of the head are not simply a linear combination of a saccade and VOR. To investigate the relation between eye- and head-movements during saccades, we compared two types of perturbations of the head. Subjects made horizontal saccades between two continuously visible LEDs (40° apart), without moving their head. A motor attached to a helmet on their head could move their head: either by a torque-pulse, or by small amplitude, high-frequency oscillations (0.5°, 15 Hz).

The amplitude of the movement of the head induced by the torque-pulses depended on the direction: 5.6° if the pulse was in the same direction as the saccade, 4.5° otherwise. These head-movements changed the eye-in-head velocity relative to unperturbed trials. This change depended on the direction of the torque-pulse. If the pulse was directed opposite to the saccade, the increase in eye-in-head velocity amounted on average to 75% of the head velocity. If the pulse was in the same direction as the saccade, the decrease in eye-in-head velocity amounted on average to not more than 20% of the head velocity.

A direct measurement of the VOR using oscillations of the head showed that the VOR-gain decreased during the saccade to about 80% of its pre-saccadic value. This corresponds to the eye-in-head response to head movements opposite to the saccade. However, if the head moves in the same direction as the saccade, eye and head are better co-ordinated than one would expect from the suppression of the VOR.

71.04 **Zinc-containing telencephalic connections to the rat striatum: a combined Fluoro-Gold tracing and histochemical study. Jens Christian Sørensen[1], Lutz Slomianka[2], Jakob Christensen[3], Jens Zimmer[1]**

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The organization of telencephalic zinc-containing neurons projecting to the rat striatum was investigated by combining intrastriatal injections of the retrograde fluorescent tracer Fluoro-Gold with histochemistry revealing zinc-containing neurons and terminals.

Throughout the ipsilateral and contralateral neocortex, corticostriatal zinc-containing neurons with striatal projections were located predominantly at the border between deep layer V and superficial layer VI. Additional, but fewer zinc-containing neurons were located in layers II, III and deep layer VI of the ipsilateral neocortex. The main neocortical source of zinc-containing afferents to the striatum were the frontal motor cortices. Smaller contingents of zinc-containing projections arose from the motocortical forelimb and hindlimb areas and the parietal cortical areas. In the cingulate cortex zinc-containing neurons with striatal projections were found predominantly in the ipsilateral layers II and III with only few neurons in the ipsilateral layer VI and in the contralateral layers II and III and VI. Subcortically zinc-containing neurons belonging to the amygdalostriatal projection were found bilaterally in the basolateral and basomedial nuclei of the amygdala.

Zinc has been found to modulate the response of many ligand and voltage-gated ion channels including both GABA receptors and NMDA-, AMPA- and kainate-type glutamate receptors. The present findings raise the possibility that zinc in the corticostriatal projections might play a role in the selective, possibly excitotoxic, cell death of GABA-ergic projections seen in Huntingtons disease.

71.05 NEUROPEPTIDE Y (NPY) mRNA EXPRESSION IN VENTRAL AND DORSAL STRIATUM AND CORTEX: A COMPARISON USING A NON-RADIOACTIVE *IN SITU* HYBRIDIZATION TECHNIQUE

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Neuropeptide Y (NPY) is characterized by a widespread distribution in basal forebrain regions and cortex and is among others located in neurons of the ventral and dorsal striatum. The role of NPY in striatal function is unknown but its expression (on peptide level) is regulated by dopamine. Since the ventral and dorsal striatum have distinct roles in behaviour and are innervated by different dopaminergic cell groups (A10 and A9, respectively) we decided to compare NPY-mRNA expression in neurons of the striatal subregions, using a non-radioactive in situ hybridization technique in combination with automated image analysis. A positive hybridization signal was found in numerous neurons and several brain regions. Many NPY-mRNA positive neurons occur in the ventral and dorsal striatum and are evenly distributed over the striatum. Quantitation of the hybridization signal reveals that NPY-mRNA expression in the ventral striatum is 14% higher ($P<0.018$) than in the dorsal striatum. Moreover, NPY-mRNA levels of the striatum are much lower than those measured in cortical neurons (+ 59%). These findings clearly show that NPY is differentially expressed in neurons of the ventral and dorsal striatum. Since NPY expression is under the control of dopamine, this difference is at least partly due to differences in dopaminergic transmission in the ventral and dorsal striatum.

71.06 PRENATAL AND POSTNATAL DEVELOPMENT OF CALRETININ IMMUNOREACTIVITY IN THE DORSAL THALAMUS OF THE RAT.

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The Calcium Binding Proteins, Calretinin (CR) has restricted distribution in the rat brain. In a recent study, CR immunoreactive neurons were found in some dorsal thalamic nuclei and in selected regions of the Reticular nucleus (Rt). Recent data indicate that CR is early expressed during the corticogenesis of the rat, suggesting a possible role of this protein in some critical developmental events. Aim of the present work is to analyze the distribution of CR in the dorsal thalamus of rat during development, using immunocytochemical techniques. Preliminary data indicate that CR immunoreactivity (ir) is expressed at early stage of development. At E17 Cr ir is visible in Rt migrating neurons, and in few neurons of the Intermediate thalamus. At E19 CR ir is present on the medial border of Rt and an increase of Cr ir neurons was observed in the Intermediate thalamus. Labelled neurons in Lateral Geniculate (LG), in LP nuclei and bundles of ir positive fibers appear at this age. In neonatal and young rats the distribution pattern of ir was generally similar to that observed in adult animals, but the intensity of labelling was higher in immature rats, where a diffuse neuropil immunostaining was evident. In Rt of developing rats, CR-ir neurons were less visible and masked by bundles of fibers present along the medial border and through the nucleus. The mature pattern, characterized by clear immunolabelling, but present only in restricted areas, was achieved at the end of the third postnatal week. Our findings suggest that CR may be involved in morphological and functional maturations of some thalamic areas.

71.07 INHIBITION OF VESTIBULAR NEURONS BY IPSILATERAL GLYCINERGIC NEURONS IN THE FROG.

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Second order vestibular neurons receive a monosynaptic glutamatergic input from afferent vestibular fibers. This excitatory input expresses itself in a negative postsynaptic field potential of short duration. The amplitude of this negative field potential increased and its duration decreased with increasingly higher stimulus intensities. Conditioning afferent or commissural stimuli curtailed the afferent-evoked test response even more strongly. The activation of inhibitory neurons, suggested by these observations, was studied in the in-vitro brainstem. In the presence of the glycine antagonist strychnine (1-50μM), but not in the presence of the GABA antagonists picrotoxin (50μM) or CGP 35348 (100μM) in the bath, the duration of the afferent-evoked negative field potential was prolonged. The strychnine-sensitive part of this field potential had a latency of 5.6ms ($\pm$ 0.2; N=6), was still present after a midline section of the brainstem but disappeared after a section at the border between the vestibular nuclei and the reticular formation.

In a few vestibular neurons (12 out of 96 neurons) mixed EIPSPs (N=7) or pure IPSPs (N=5) were detected. The inhibitory response component had a latency of 5.9ms ($\pm$ 1.2) and could be reversibly blocked by strychnine (10μM). This glycinergic inhibition is disynaptic in nature, given that the first evoked spike in second order vestibular neurons has a latency of about 4ms and the synaptic delay is about 1.7ms. In conclusion, glycinergic neurons, located presumably in the reticular formation, receive a monosynaptic input from vestibular afferents and inhibit monosynaptically second and higher order vestibular neurons on the same side of the brainstem.

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71.08 **A NEW MODEL TO EXPLAIN THE GENERATION OF RHYTHMIC ACTIVITY IN LOCAL SPINAL NETWORKS**

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Central pattern generators of the spinal cord are believed to be composed of coupled local oscillating networks. Oscillations within these networks are proposed to be based on pacemaker activity in individual spinal neurons. Here an alternative model is presented to explain the generation of rhythmic activity in local networks of the mammalian spinal cord. The model is a random synchronous parallel update point model with the following key features for oscillatory activity: the degree of net excitatory coupling between the cells, the frequency response of individual synaptic connections, the use-dependent plasticity of this frequency response and the low rate spontaneous activity of few distributed neurons in the network. Adjusting these key parameters according to experimental findings in cultures of spinal cord slices of the embryonic rat, the typical patterns of rhythmic activity observed in these cultures were reproduced by the model. Furthermore the transition from random to rhythmic activity induced in the cultures by disinhibition were reproduced in the model by an increase in the excitatory coupling between the cells. It is suggested from these findings that mammalian central pattern generators may emerge from initially random networks. *Supported by SNF*

71.09 CHOLINE ACETYLTRANSFERASE IMMUNOREACTIVE TERMINALS IN RAT LUMBAR MOTONEURONAL CELLGROUPS: ULTRASTRUCTURAL EVIDENCE FOR THE CHOLINERGIC NATURE OF C-TYPE TERMINALS.

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The terminals in rat spinal motoneuronal cellgroups, can be classified on the basis of their morphological characteristics. Terminals with a subsynaptic cistern in the post-synaptic structure are designated as C-type terminals. There is some evidence that these terminals are cholinergic. In this study we used a monoclonal antibody against choline acetyltransferase (ChAT) to address the following questions: 1) are C-type terminals in rat lumbar motoneuronal cellgroups ChAT immunoreactive (IR), 2) are all C-types ChAT-IR and 3) which proportion of ChAT-IR terminals are C-type.

The L5 lumbar segments of 4 rats were routinely immunoprocessed for ChAT and embedded in Araldite. Eight ultrathin sections, containing the ventro-lateral motoneuronal cellgroups, were analyzed in the electron microscope.

A total of 500 terminal profiles were found to be ChAT-IR and 44 of these ChAT-IR terminals (9%) were of the C-type. C-type terminals that were not ChAT-IR were not found, in spite of detailed analysis of the entire section. The immunostained C-types were apposed to cell somata (64%) or proximal dendrites (36%). The other 456 ChAT-IR terminals were often difficult to classify, due to strong immunoprecipitation. In some cases these non C-type terminals could be classified as S-type terminals, characterized by spherical vesicles and asymmetrical synaptic contacts or as T-type terminals with post synaptic dense (Taxi) bodies. With respect to the postsynaptic structures of the immuno-labeled non-C-type terminals establishing a synaptic contact (n=265) it was found that 14 % contacted cell somata (n=36), 28% contacted proximal dendrites (n=75) and 58% contacted distal dendrites (n=154). Postsynaptic structures were also ChAT-IR, indicating they were moto-neurons. It is concluded that all C-type terminals in the motoneuronal cellgroups are cholinergic and the results further suggest that the C-type terminals constitute about 9% of all the cholinergic terminals in the motoneuronal cellgroups of rat lumbar cord.

71.10 PARIETAL INPUTS TO PHYSIOLOGICALLY DEFINED REGIONS OF DORSAL PREMOTOR CORTEX IN MACAQUE MONKEY. J. Tanné* (1), D. Boussaoud (1), N. Boyer-Zeller (1), V. Moret (2) and E.M. Rouiller (2). (1) INSERM U94, 69500 Bron (France); (2) Univ. Fribourg, CH-1700 Fribourg (Suisse).

Recent studies showed that the dorsal premotor cortex (PMd) plays an important role in visually guided movements. Yet, neither the intrinsic fonctional organization of this area, nor its cortical visual inputs, are exhaustively known. This study was aimed at describing the relationship between the distribution of neuronal properties in PMd and the cortico-cortical connections of this area by means of multiple tracers injections. For two among three animals, the injection sites have been determined using single unit recordings and/or intracortical microstimulation. One of them has been trained to perform a visuomotor task. The neuronal recordings revealed the existence of a visuomotor gradient in PMd: in the anterior part (PMda), neuronal activity was related to the visual stimulus onset ("sensory" zone); in the posterior part (PMdp), near the border with M1, neurons discharged predominantly in relation to movement execution ("motor" zone); in between, these two types of activity coexist with preparatory activity ("visuomotor" zone). Different retrograde tracers have been injected in PMda and PMdp.

The results confirm that both PMda and PMdp receive projections from prefrontal (8A, 46, orbitofrontal cortex), premotor (PMv and pre-SMA), cingulate (23 and 24), and parietal areas (MIP, MDP, 7b and 7m). PMdp, however, receives stronger projections from motor (M1 and SMA) and somatosensory cortex (3a, 3b, 5 and S2), whereas some prefrontal areas (46, A8) project mostly to PMda. In addition, we found connections of both PMd regions with visual areas of the parietal lobe (VIP, LIP, PO, 7a, 7m). The data suggest that to the distribution of neuronal properties within PMd corresponds a differential cortical connectivity. The "motor" zone is more heavily connected with somatosensory and motor areas, whereas the "sensory" zone is more connected with the prefrontal and posterior parietal cortex. Moreover, PMd may receive direct visual inputs from parietal visual areas.

71.11 CEREBELLAR SLICE CULTURES: A MODEL FOR STUDYING PURKINJE CELL AXONOPATHIES IN VITRO?

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Phenytoin (DPH) is a commonly used antiepileptic drug. The mechanism of both its action and its side effects are not jet fully clarified. We were able to show in vivo, that DPH can induce distal axonopathies in cerebellar Purkinje cells. In the present in vitro study, we investigate the effect of DPH in cerebellar slice cultures where tissue was allowed to develop in an "organotypic" manner. Slice cultures of early postnatal rodent cerebella are able to achieve relative mature status, although the extrinsic afferents are absent and the tissue was immature at the time point of explantation.

Cerebella from neonate to 10 day-old mice or rats were dissected parasagitally into 400µm slices and cultivated applying an interphase culture technique. The tissue was incubated with a culture medium containing 0 to 100 µM DPH up to 30 days. Purkinje cells were immunolabelled with either monoclonal antibody UCHT1 or anti-calbindin and analysed by light and electron microscopy.

In control cultures, the maintenance and development of the typical cerebellar lobulation and lamination was in relation to the time point of explantation, i.e. the tissue derived from 9 day-old rodents showed better preservation of the cerebellar cytoarchitecture than that of neonatal rodents. The shape of the denritic tree of the examined Purkinje cells was changed compared to in situ. In contrast, all immunostained axonal profiles seemed to be unaltered. The axons fasciculate in the white matter of each folium and project to the putative cerebellar nuclei. The staining pattern of cultured Purkinje cells axons was similar for both antibodies and comparable to that in situ.

Since slice cultures can be kept several weeks in vitro they can be used as a model for studying morphological alterations, neurotoxicity and selective vulnerability of cerebellar neurons. (Supported by SFB 364)

71.12 A CROSSED PROJECTION FROM THE OPTIC TECTUM TO CRANIOCERVICAL PREMOTOR NEURONS IN THE MALLARD (*ANAS PLATYRHYNCHOS* L.).

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Visual information plays an important role in positioning the head. In birds, cells in superficial layers of the optic tectum receive visual information from the retina and in turn project upon deep tectal layers. The orientation of the head is controlled by neck muscles, innervated by motoneurons in the caudal brainstem and upper spinal cord. In birds a direct tectospinal projection is absent. The present study was undertaken to describe the pathway by which visual information influences the activity of craniocervical muscles, which position the head with respect to the upper part of the neck. Craniocervical premotor neurons are located in the medial part of the brainstem reticular formation. Injections with the tracer WGA-HRP at different levels in the gigantocellular reticular formation close to the midline labeled cells in the contralateral deep layers of the optic tectum, as well as terminals in the ipsilateral craniocervical motor nucleus, the supraspinal nucleus. Fink-Heimer stained sections after a unilateral tectum lesion revealed a fibre bundle that crossed the midline at the level of the nucleus ruber and subsequently ran caudally in the ventral part of the gigantocellular reticular formation. Labeled terminals were present along the tract. These experiments show that craniocervical motoneurons receive visual information through an indirect pathway via premotor areas. These findings are in accordance with previous studies in pigeon and barnowl.

71.13 CLASSICAL CONDITIONING OF THE HUMAN FLEXION REFLEX: A PET-STUDY.

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Classical conditioning of the eyeblink or nictitating membrane reflex has frequently been used to study the role of the cerebellum for associative learning in humans and animals. However, the involvement of the cerebellum in the classical conditioning of limb withdrawal reflexes has never been examined in human subjects.

The first aim of the present study was to establish a method of classical conditioning of the cutaneo-muscular flexion reflex in humans. Secondly, the involvement of the cerebellum was demonstrated by an increase in regional cerebellar blood flow (rCBF) using positron emission tomography (PET).

The flexion reflex was elicited by a train of electrical pulses (100ms, 100Hz, 0.65ms) applied to the medial plantar nerve (unconditioned stimulus, US). A tone (1000Hz, 550ms) was presented via headphones as the conditioning stimulus (CS), which coterminated with the US. The muscle response (UR, CR) was recorded from the anterior tibial muscle. Normal subjects (n=10) were conditioned within one session of 50-100 trials.

An increase of rCBF in the cerebellum during the process of conditioning could be correlated with parameters of the CR in five additional normal subjects. These data suggest a possible role of the cerebellum in the acquisition phase of classical conditioning.

71.14 STRUCTURAL EVIDENCE FOR INTERRELATIONS BETWEEN THE THALAMIC PARAFASCICULAR NUCLEUS AND MOTOR AREAS OF THE CEREBRAL CORTEX IN RATS.

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The aim of this study was to examine the possible interrelations between the "non-specific" intralaminar parafascicular nucleus of the thalamus (PF) and the motor areas of the cerebral cortex and the details of terminations using the anterograde tracer biocytin for PF injections and different retrograde fluorescent dyes for cortical areas injections in rats.

After biocytin (1.0-1.5µl of 5% in 0.05 M Tris-HCL buffer at ph=7.6) was stereotaxically injected by pressure into PF, labeled ascending axons were seen to course laterally to the striatum, or to pass through it, to travel in the callosal radiation, and to terminate in the motor frontal areas (Fr1 and more heavily Fr2, as defined by Zilles). Some terminal fields were also found in the cingulate cortex. Labeled terminals were sparse. Terminal boutons and *en-passage* varicosities were found in layer V in close apposition to the somata and proximal dendrites of pyramidal cells. Few pyramidal cells were retrogradely labeled. The cortical projections originating from the PF were strictly ipsilateral.

Fitc and Tritc conjugated latex microspheres (0.1µm) were used as retrograde tracers in order to localize and map the thalamocortical neurons. In the same animal microiontophoretic injections of the two markers were made in the cortical areas where labeled terminals and cells had been found, and resulted in labeled neurons in PF nucleus. No double labeled cells had been observed so far.

The present observations, together with those of Deschenes et al. (1994), indicate that the PF and the pyramidal cells of restricted areas of the rat motor cortex are reciprocally and directly linked. These data confirm an involvement of the PF in the central organization of motor programs not only through the descending projections, as previously shown from this laboratory, but also via a direct linkage with the motor cortex in rodents.

71.15 THE EFFECT OF REPETITIVE APPLICATION OF FACILITATORY PHYSIOTHERAPEUTIC INTERVENTIONS ON ARM- AND HAND FUNCTION IN STROKE PATIENTS

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In the course of our studies concerning the neurophysiological basis of physiotherapy we investigated the prospective value of the repetitive application of five different physiotherapeutic approaches for the centrally paretic arm and hand.
In a multiple baseline study that started with a two or three week baseline phase followed by a four or six week therapy phase the patients received for fifteen minutes twice daily two of the following facilitatory interventions: cutaneous / proprioceptive stimuli, a weight bearing task, contraction of the affected and non-affected hand and finger extensors and proximal preinnervation. The respective facilitatory approaches were chosen according to the characteristics of motor evoked potentials in distal arm muscles obtained at the beginning of the baseline phase.
Grip strength, maximum force and maximum acceleration during isometric and isotonic extension at the wrist were investigated. Furthermore motor functions were assessed by means of the Fugl-Meyer-Scale for severely affected patients and by means of the Rivermead Motor Assessment Scale for moderately affected patients. Additionally psychometric scores (EWL, locus of control) were applied. Among the various facilitation techniques the direct voluntary activation of the paretic muscle exerted the highest impact on motor parameters. Further results and the implications for motor learning and the appropriate selection of physiotherapeutic approaches will be discussed.

71.16 Abstract withdrawn

71.17 INFLUENCE OF A REPETITIVE MOTOR TRAINING IN PROXIMAL ARM MUSCLES ON MOVEMENT PARAMETERS OF HAND AND FINGERS IN PATIENTS WITH UPPER MOTOR NEURON LESION

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In a multiple baseline study design we examined the effect of a repetitive training of proximal arm muscles in patients with central hemiparesis. Grip strenght, maximum force and maximum acceleration during isometric and isotonic extension at the wrist as well as range of motion and maximum acceleration of outward rotation at the shoulder joint in the hemiparetic arm were investigated. The patients were also rated by the Ashworth Scale and the Fugl-Meyer Scale. Our question was whether proximal arm training has a facilitatory effect on distal hand muscles since it is known that repetitive hand training improves not only distal but also proximal motor function. Our patients underwent a 1-3 week-baseline phase in which they received conventional physiotherapy followed by a 2-week phase of unspecific physiotherapy for the leg. Then our patients were submitted to a repetitive training of outward rotation of the paretic arm for 2x15 minutes on a specially constructed training device for two weeks.
No significant improvement of the distal parameters could be seen while the Fugl-Meyer Score showed a slight improvement of the overall arm function. As has been pointed out in previous studies (Bütefisch et al; 1995, Hummelsheim et al; 1995) physiotherapeutic strategies have to adress the centrally paretic distal muscles directly. Proximal manipulations alone do not contribute to improvement in relevant arm function, i.e.grasping and manipulating objects.

71.18 CENTRAL RHYTHM GENERATOR INVOLVED IN LICKING IS LOCALISED IN BRAIN STEM RETICULAR FORMATION OF RATS.

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Adult Long Evans rats were implanted with cannulae, aimed at the oral part of nucleus reticularis gigantocellularis (AP 9, L 0, V 9). The cannulae were used for introduction of the needle for tetrodotoxin (TTX) microinjection, as well as for insertion of the concentric stimulating electrode. Rostrocaudal gradient of the TTX (1ng/µl) effect on spontaneous water consumption, demonstrated by significantly weaker disruption caused by more caudal and more rostral TTX injections, deliminated the location of the generator. Two days later, spontaneously drinking thirsty rats were intracranially stimulated via the concentric electrode introduced through the same chronically implanted cannula that was used for the TTX experiment. Short-lasting (100ms) stimulation by the train of rectangular pulses of adequate intensity applied during a period of continuous licking caused a phase shift of licks following stimulus delivery, but did not change the licking frequency. The induced phase shift of licking suggests that stimulation have reset this generator. (Supported by grant GA ČR 309/93/0568.)

71.19 MOVEMENT RELATED CORTICAL POTENTIALS ASSOCIATED WITH SELF-INITIATED, VISUALLY GUIDED SACADDIC EYE MOVEMENTS AND SELF-PACED FINGER EXTENSION.

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We studied the cortical activity which precedes, is concomitant with and follows self-initiated vertical and horizontal saccadic eye movements. We also studied the pre-movement and motor potentials associated with self-paced finger elevation. The variables of interest included 1) the time course(s) of cortical motor related activity and 2) hemispheric response localization and lateralization. Eye movements from adult controls were monitored by electro-oculography (EOG) methodology; eye position in both the vertical and horizontal planes was measured. EOG electrodes were placed at the inner and outer canthi and directly above and below the eye. Finger movement was recorded by measuring the electromyographic activity (EMG) with skin electrodes overlying the forearm extensor muscle (extensor digitorum communis) of the middle finger. Cortical activity was recorded with scalp electrodes positioned at 12 loci including left, middle and right frontal, parietal and occipital cortex. The results demonstrate that for either eye or finger movements, the onset of motor activity was preceded by a slow cortical scalp negativity (Bereitschaft-like potential, BP) starting at about 1000 to 1500ms and 1500ms, respectively. In general, the pre-motor responses consisted of a BP, an increasing negativity (NS') and a primary negative peak. For finger extension, pre-motor positivity and a secondary negative peak also were recorded. For saccades, the primary negative peak was accompanied by a spike potential. In addition, regardless of ocular or finger movement, the primary motor response was localized at the vertex. Further, finger extension and self-initiated saccadic eye movements in the horizontal plane revealed contralateral cortical representation; saccades in the vertical plane appeared to show an amplitude asymmetry with greater peak activity for upward saccades. Application of these findings to study normal and abnormal development of movement related cortical potentials in infants and young children is now in progress.

71.20 THE EFFECTIVENESS OF THE INTEGRATION OF VISUAL AND PROPRIOCEPTIVE INFORMATION IN MAN.

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In planning and executing goal-directed arm movements, the central nervous system uses both visual and proprioceptive position information. The process of integration of the two types of information is not well understood. We studied this integration process by comparing performance variances between conditions where the subject had only one, or both, types of information.

In the experiment subjects were seated at a table. They were asked to match the felt position of the index finger of the unseen left hand under the table with an indicator (the index finger of the right hand or a pointer) on the table top. Three conditions were employed: the subject could have only proprioceptive, only visual, or both proprioceptive and visual, information about the position of the indicator. We measured the positions of the indicator and calculated the variances of the matching performance.

This variance was largest in the condition with only proprioceptive information, slightly smaller in the condition with visual, but no proprioceptive, information, and smallest when the subject had both visual and proprioceptive information about indicator position. The results show that neither type of information is fully dominant. Furthermore, it was not possible to fit the measurements to a straightforward model that combines the information in an intuitively correct way. This model combines the two information streams by weighting them according to their variances. The integration process appears to be more efficient than the model describes.

We conclude that the integration of visual and proprioceptive position information is a relatively complex process, which is more efficient than one would expect.

71.21 REVERSAL OF MOTOR-UNIT RECRUITMENT ORDER IN HUMAN ARM MUSCLES.

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We have studied the activity of motor units in the elbow flexor muscles m. brachialis, m. brachioradialis and m. biceps in man during isometric contractions and during sinusoidal movements in the elbow against a constant preload. The range of frequencies was between 0.3 and 1.4 Hz.

Since the arm behaves as a second order system, the force exerted by elbow flexor muscles is more or less in phase with elbow flexion for low frequencies and shows a progressive phase lead up to 180 degrees for sinusoidal movement at high frequencies. Therefore, one would expect a progressive phase-lead of motor-unit firing for higher frequencies. This was observed, but in a different way for motor units with a different isometric recruitment threshold.

Simultaneous recording of the activity of several motor units during sinusoidal movements revealed that motor units with a higher isometric recruitment threshold were recruited well before motor units with a lower recruitment threshold. The reversal of recruitment order showed up in a systematic way: high threshold motor units were active during the lengthening phase of the muscle in the sinusoidal movement, whereas the motor-units with the lower recruitment thresholds tended to be active in the shortening phase. As a result, the firing rate of high-threshold motor-units had a phase lead relative to that of the low-threshold motor units. We never observed that the firing rate of low-threshold motor units was reduced for higher movement frequencies.

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71.22 OBJECTIVE ASSESSMENT OF SPINAL CORD FUNCTION AFTER CONTUSIVE SPINAL CORD INJURY IN THE RAT.

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The Weight drop technique was used in this study to produce a contusive injury of the spinal cord in the rat. Spinal cord trauma induced by this technique are reproducible, suitable for the investigation of the so called secondary injury and for the evaluation of pharmacological intervention. It is of fundamental importance in experimental spinal cord trauma to be able to evaluate or accurately compare subtile differences in spinal cord function. In this study we present newly developped and modified existing techniques for the assessment of three functional modalities of the spinal cord. After an "incomplete" thoracic spinal cord injury in adult rats, spinal cord function was evaluated during eight weeks. To assess hind limb deficit during locomotion, a modified version of the Tarlov scale was used. This scale distinguishes 6 degrees of hindlimb paresis. Although this is the scale most frequently used by other authors it depends wholly on subjective observer evaluation. Therefore we developped a second behavioural test wherein the mean height of the thoracolumbal kyfosis (TLH) was measured by computer added video images. The results indicated significant correlations between TLH and modified Tarlov scores. For the electrophysiological examination we recorded motor evoked potentials from the rubrospinal tract. Amplitudes of the evoked responses appeared to correlate well with behavioural outcome. Histomorphological analysis was carried out using the total amount of preserved white matter area on cross-section samples, (1 per mm) of a 10 mm spinal cord injury segment, as parameter. In contrast to the results of other authors, the in this manner calculated white matter quantities did not correlate to behavioural and electrophysiological parameters.

We conclude that the behavioural tests described in this study and electrophysiological investigation of the rubrospinal pathway are objective and accurate assessment techniques for the evaluation of rat spinal cord function.

71.23 DEVELOPMENT OF POSTURAL ADJUSTMENTS DURING REACHING IN INFANCY: AN EMG STUDY.

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Movements are accompanied by a complex of fine-tuned postural adjustments. Postural adjustments of standing adults performing fast, voluntary movements have an anticipatory nature, but similar movements performed in a sitting position do not evoke anticipatory postural control. No data exist on the development of postural adjustments during voluntary arm movements in infancy. Therefore, we carried out a longitudinal study on the development of postural control during reaching in healthy, fullterm infants. Special attention was paid to the development of anticipatory postural control.

We studied ten infants at 3, 4, 5, 6, 8, 10, 12, 15, and 18 months. During the recordings right-handed reaching was elicited with attractive toys while the infants were sitting in an infant chair. Each session consisted of simultaneous video-recordings and surface EMG recordings of arm muscles, and neck, trunk, and leg muscles ('postural muscles') on the right side of the body.

Consistent reaching in sitting position appeared at 5 months, but without reaching-related activation of the 'postural muscles'. From 6 months onwards reaching elicited activation of the neck flexor and trunk extensor muscle. Neck extensor muscle activation was added to this 'postural pattern' at 8 months. This pattern was also found at 10 and 12 months. A transition occurred at 15 months: the trunk extensor muscle showed high background activity, while reaching related activation disappeared. Reaching movements at this age were associated with neck flexor, neck extensor, and abdominal muscle activation, a 'postural pattern' reminding of the adult configuration. Indications for the development of consistently present anticipatory postural control were absent.

71.24 ULTRASTRUCTURAL DISTRIBUTION OF CGRP IN THE RAT OLIVOCEREBELLAR SYSTEM DURING POSTNATAL DEVELOPMENT.

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CGRP-immunoreactivity (CGRP-IR) was analyzed at the EM level in the rat inferior olive, deep nuclei and cerebellar cortex. Previous studies provided evidence for a neonatal expression of CGRP-IR in the inferior olive (IO) and in the cerebellar cortex (Morara et al., 1989; Chedotal and Sotelo, 1992). The topographical correspondence between IO labeling and terminal-like structures over the cerebellar cortex, indicated that CGRP-IR is related to climbing fibers (Morara et al., 1989). CGRP-IR was analyzed by utilizing a polyclonal rabbit CGRP antiserum (gift of C. Sternini) and by applying the GSSP method to rats aged 0 to 14 days. In the inferior olive, CGRP was found apposed to clear vesicles that aggregate in large Golgi complexes. CGRP labeled vesicles could also be found in the axoplasm and in terminals, most likely of recurrent fibers, that could represent olivocerebellar collaterals. In the cerebellar cortex, CGRP-IR was mostly found in the perisomatic phase of the climbing fiber synaptogenesis on Purkinje cell (Pc) somata and proximal dendrites. The expression of CGRP over the two first postnatal weeks, when reshaping and stabilization of synaptic contacts takes place in CFs, suggests a role for the peptide as a key signal in the transition from the perisomatic transient stage, to the mature phase of the CF-Pc synapse.

71.25 DISTRIBUTION OF DOPAMINE AND DOPAMINE-β-HYDROXYLASE CONTAINING FIBERS AND PRESUMPTIVE TERMINALS IN RAT AND MONKEY BRAIN STEM.

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The distribution of catecholamine containing neurons in the brain stem is well documented. However, much less is known about the distribution of catecholaminergic, and in particular dopaminergic, fibers and terminals in the brain stem. In the present study the distribution of fibers and terminals immunoreactive for dopamine or the (nor)adrenaline synthesizing enzyme dopamine-β-hydroxylase was investigated light microscopically in rat and monkey brain stem using specific antibodies to dopamine (kindly provided by Dr. R.M. Buijs, Netherlands Institute for Brain Research) and dopamine-β-hydroxylase (Eugene Tech).

In the mesencephalon, at levels caudal from the substantia nigra, dopamine-immunoreactive fibers and terminals were present in the periaquaductal gray, the colliculi, and deep mesencephalic nuclei. In the pons the most prominent labeling was found in the locus coeruleus, parabrachial nuclei, pontine reticular nuclei, and the trigeminal nuclei. In the medulla oblongata, dopamine-immunoreactive fibers and terminals were present in the inferior olive, prepositus hypoglossal nucleus, nucleus of the solitary tract, dorsal motor nucleus of the vagus, cochlear nuclei, cuneate and gracile nuclei, and the spinal trigeminal complex. Furthermore, all raphe nuclei contained labeled fibers and terminals. Dopamine-β-hydroxylase containing fibers and terminals were distributed more ubiquitous throughout the brain stem. In most areas there was much overlap with the dopaminergic innervation, but the regional innervation pattern differed. In other areas like area postrema, cerebellum and external cuneate nucleus, which were sparsely innervated by dopaminergic fibers, the (nor)adrenaline synthesizing enzyme was abundantly present.

These results indicate that dopaminergic fibers and terminals are distributed throughout the rat and monkey brainstem as a separate neurotransmitter system.

71.26 EXPERIMENTAL STUDY OF LOCAL FEEDBACK IN SACCADES.

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Several lines of evidence suggest that the saccadic system contains an internal feedback loop which guides the instantaneous trajectory of the eye. For example, stopping a saccade in mid-flight by briefly stimulating the omnipause region, yields a subsequent movement bringing the eye on target in complete darkness. Furthermore, a large drug-induced kinematic variability does not affect the accuracy of saccades. However, these results may also be explained by a system ignorant of current eye position. This paper therefore investigates whether the saccadic system fully compensates for a naturally-imposed disturbance of the eye-movement trajectory. In our study, subjects made large eye movements towards suddenly appearing targets in two dimensions, which disappeared at saccade onset. Movements of the right eye and upper eyelid were measured with the search coil technique. In 50% of the trials, a brief air-puff was applied to the left eye, which was usually followed by a short-latency (±50 ms) blink response of both upper eyelids. When the blink occurred in saccade mid-flight, the eye deviated from its approximately straight trajectory by several degrees. In all cases, the saccadic system fully corrected for this deviation within one continuous movement. These experiments therefore provide valuable additional support for the local feedback hypothesis.

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71.27 LAMINAR AND AREAL DISTRIBUTION OF THE CONTRALATERAL CORTICOTHALAMIC PROJECTIONS.

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We have studied the laminar distribution and topography of the contralateral cortical afferent projections of the medial, intralaminar, anterior and ventral nuclei of the thalamus, and of the habenular complex.

For this study, we have analyzed the case material from 97 HRP and fast blue tracing experiments in adult cats.

In all cases the contralateral retrograde labeling of the cerebral cortex was less abundant than in the ipsilateral side. And there was a dorsocaudal displacemente of the labeling following a medial to lateral displacement of the tracer injections in the nuclei here considered.

Following stereotaxic injections in the medial and intralaminar nuclei, labeling in the contralateral cerebral cortex was most abundant after injections in the mediodorsal, medial central, reuniens and rhomboidal thalamic nuclei. The labeling was consistently present in the prefrontal and cingular cortices. Some cortical areas that contained labeled cells in the ipsilateral cortex were not labeled in the contralateral hemisphere. The ratio between labeling in layer V/ layer VI in the contralateral cortex was slightly greater than in the ipsilateral side.

After injections both in the anterior and the ventral nuclear group of the thalamus, the laminar and areal distribution of the labeling in the contralateral cerebral cortex was similar to the ipsilateral side.

The contralateral cortical labeling after injections in the habenular complex was restricted to the dorsolateral and dorsomedial portions of the prefrontal cortex. As in the ipsilateral side, cells were labeled exclusively in layer V of the cerebral cortex.

Projections from layers V and VI are known to have a different distribution in particular thalamic subnuclei. However, our study shows that there are no consistent differences in the laminar origin of the crossed corticothalamic projections compared to those directed to the ipsilateral side.

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71.28 INVESTIGATION OF THE VESTIBULO-OCULOMOTOR PATHWAYS IN THE IN VITRO, ISOLATED AND PERFUSED, WHOLE BRAIN OF GUINEA-PIG.

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Following our description of the physiological and pharmacological properties of medial vestibular nucleus (MVN) neurones, we have now begun to study the vestibulo-oculomotor pathways on a new, in vitro preparation of isolated and perfused, whole brain of guinea-pig (150 to 230 g). This technique allows stable extracellular and intracellular recordings, while the observed cells can be functionally identified as in acute in vivo preparations. We have first recorded the extracellular field potentials induced in the vestibular complex by orthodromic stimulations of the ipsilateral and contralateral vestibular nerves. Both fields were very similar to what had been observed in vivo. Their latencies, however, were markedly increased (by 30 to 40%), due to lower recording temperature (29°C). Oculomotor and abducens motor nuclei were then localized by the observation of the antidromic field potentials elicited by stimulations of the corresponding nerve stumps, using suction electrodes. In each nucleus, disynaptic field potentials could be extracellularly recorded, together with superimposed spikes, following stimulations of both vestibular nerves. We could furthermore record the corresponding, vestibular-induced spike discharges at compatible latencies in the abducens and oculomotor nerves. In order to further describe the properties of this network, we obtained stable intracellular recordings both in the MVN and in the abducens nucleus. Synaptic potentials evoked by stimulation of both vestibular nerves were recorded in MVN neurones of the three main cell types that we have defined in slices (A, B and B+LTS neurones). Antidromically-identified abducens motoneurones were characterized by their disynaptic responses (EPSPs and IPSPs) to stimulation of the vestibular nerves. These results demonstrate that the isolated whole brain can be readily used for detailed, functional studies of the vestibulo-oculomotor pathways.

71.29 **HETEROGENEOUS DISTRIBUTION OF KAPPA OPIOID RECEPTORS IN THE HUMAN STRIATUM.**

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Selective kappa opioid receptor autoradiography with [^{3}H]bremazocine (BRM) was used to examine regional and subregional kappa receptor distribution patterns at five rostrocaudal levels through the human striatum. [^{3}H]BRM binding densities were measured in the individual striatal nuclei and in subregions therein. The distribution of [^{3}H]BRM binding sites has a strongly heterogeneous character. At the regional level a rostral to caudal decrease in [^{3}H]BRM binding densities was observed. Also, a dorsal to ventral differentiation was seen, with high values in the ventral striatum, especially in the nucleus accumbens, and lower values in the dorsal parts of the caudate nucleus and putamen. These findings suggest an association of kappa receptor function with limbic-related processes in the ventral striatum. Along the ventral edge of the nucleus accumbens, neurochemically unique domains (NUDAPs) with extremely high [^{3}H]BRM binding values were identified. The function of the NUDAPs is at present unknown.

71.30 **THE DISTRIBUTION OF MU OPIOID RECEPTORS DEFINES THE CORE AND SHELL OF THE HUMAN NUCLEUS ACCUMBENS.**

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Selective mu opioid receptor autoradiography with [^{3}H]DAMGE was used to examine regional and subregional mu receptor distribution patterns at five rostrocaudal levels through the human striatum. [^{3}H]DAMGE binding densities were measured in the individual striatal nuclei and in subregions. The distribution of [^{3}H]DAMGE binding sites has a strongly heterogeneous character. At the regional level a U-shaped distribution of density values was observed along the rostrocaudal axis, with highest values in the rostral- and caudalmost levels. Furthermore, a dorsal-to-ventral high-to-low gradient was found, with lowest binding densities in the ventral one-third of the Putamen (Put) and in nucleus accumbens (Acb). Binding in Caudate (Cd) and Put did not show a patch-matrix-like pattern as in the rodent. In the Acb, areas of low, intermediate and extremely high binding density were present. Comparison with ligand binding patterns of other receptors indicated that the low-density area represents the "core" region of the Acb, whereas the "shell" is characterized by intermediate density. Along the ventral periphery of the Acb and Put, several regions were found that displayed the highest binding values of the entire striatum. These regions could also be recognized in the distribution of other receptors and in the cyto- and myeloarchitecture of the Acb. They are referred to by the acronym NUDAP: Neurochemically Unique Domains of the Accumbens and Putamen.

71.31 ENDOCYTOSIS AND EXOCYTOSIS IN DENERVATED SKELETAL MUSCLE.

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Previous studies have shown that skeletal muscle exhibits an increase in endocytotic and lysosomal activities after denervation. This is most prominent in the denervated endplate region which is also the preferred site for reinnervation of muscle fibres. Our working hypothesis has been that the increased endocytotc activity is coupled to increased exocytosis of substances which stimulate reinnervation of the denervated muscle fibres. We have obtained experimental support for such a coupling mechanism in experiments with brefeldin A, a drug which inhibits forward membrane transport from the endoplasmic reticulum. In denervated muscle this substance inhibits both exocytosis of proteins labelled with 3H-leucine and endocytosis of FITC-labelled dextran. After denervation we have observed that the pattern of 35S- labelled proteins secreted from muscle is altered but we have not detected any new proteins present in the material secreted from denervated muscle. In studies of hydrolytic enzymes such as the acid hydrolase ß-glucuronidase and plasminogen activators in skeletal muscle we have shown that secretion of these enzymes is markedly increased after denervation. Plasminogen activators are known to be of importance in the regulation of neurite outgrowth, degradation of the basement membrane in skeletal muscle and in tissue remodelling in several other cell systems. We believe that secretion of hydrolytic enzymes from denervated muscle may play a role in neuromuscular interrelations by interfering with the extracellular matrix, altering its composition and possibly also by cleaving off membrane bound proteins that promote neurite outgrowth. The results presented here suggest that denervated skeletal muscle secretes regulatory factors in order to establish optimal conditions for reinnervation.

71.32 CEREBELLAR CONTROL OF THE HORIZONTAL VOR GAIN IN FROGS.

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Available evidence suggests that the inhibitory vestibulo-cerebello-vestibular feedback loop is relatively weak in frogs. To estimate its relative strength for the horizontal VOR we used stable, long-term recordings of the abducens nerve from decerebrated, ipsilaterally hemilabyrinthectomized frogs. In this preparation abducens output reflects the excitation of contralateral type I vestibular neurons (VN) which in turn are controlled by type I Purkinje cells (PC). Responses to sinusoidal horizontal oscillations (0.2 Hz 5 - 30°/s) or to velocity steps (2 - 10°/s) were recorded before and acutely after a complete cerebellectomy by aspiration.

The resting rate in the abducens nerve increased after cerebellectomy. In response to velocity steps the peak discharge rate was enhanced and the time constant of decay was prolonged, each by a factor of about 1.2. The sensitivity of the responses to sinusoidal oscillations increased by a factor of about 1.6. The phases of the responses remained unchanged.

To estimate the synaptic weighting factors of afferent and of PC inputs onto VN we related our data to known single unit data from afferents, PC and VN in intact frogs. Calculations showed that PC sensitivity is relatively low (0.10 [imp/s]/[deg/s^2]) in comparison with the sensitivity of afferents (1.6 [imp/s]/[deg/s^2]) but PC synaptic strength is relatively high (3.3) in comparison with that of afferents (0.68).

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71.33 AN ANATOMICAL STUDY OF NIGRAL AND CEREBELLAR OUTPUTS CONTROLLING MOVEMENT OF THE HEAD AND MOUTH.
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The dorsolateral substantia nigra reticulata (DL- SNR) projects directly to the parvicellular medullary reticular formation (PCRt), an oral premotor region, and to the lateral intermediate layers of the superior colliculus (L-SC), which participate in head control. Both the L-SC and the PCRt also receive direct projections from the lateral deep cerebellar nucleus (L-DCN). The purpose of the present study was to determine the extent of correspondence between nigral and deep cerebellar terminal zones in the L-SC and PCRt. Retrograde and anterograde tracing techniques were used to identify neural connectivity at the light microscopic level.

Injections of retrogradely transported fluorescent tracers were made into the PCRt (True Blue) and L-SC (Diamidino Yellow). The main findings were: (i) In rostral DL-SNR (where transport from L-SC predominated) most (70-100%) of the label from PCRt was present in double labelled cells. In caudal DL-SNR (where PCRt label dominated) only 30-50% of the label from L-SC was in double labelled cells. (ii) Retrograde transport from PCRt was also observed in the contralateral L-SC; i.e. a principal target zone of the ipsilateral DL-SNR. This suggests that DL-SNR can influence PCRt on both sides of the brain through direct ipsilateral projections and indirect contralateral contacts via L-SC. (iii) Retrograde labelling of L-DCN was seen following fluorescent tracer injections into PCRt (bilateral) and L-SC (contralateral); within the L-DCN the two tracers were regionally segregated.

Simultaneous injections of PHA-L into DL-SNR and biotinylated dextran into L-DCN produced intermingling patterns of anterograde terminal label in L-SC which surrounded cells retrogradely labelled with cholera toxin B injected into PCRt.

These data suggest (i) that premotor circuits controlling the head and mouth are highly interconnected; and (ii) that such circuits are heavily influenced by complementary input from both the basal ganglia and cerebellum.

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71.34 INDEPENDENCE OF COGNITIVE AND VOLUNTARY MOTOR DEFICITS IN WILSON'S DISEASE.
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In Wilson's disease (WD) the brain copper content is elevated not only in the basal ganglia but also in the cortex. Thus it can be hypothesized that there is a cognitive deficit independent of the motor slowing.

To test this hypothesis, 18 patients with Wilson's disease (WD) underwent psychometric and electrophysiological motor testing. The psychometric test-battery included the multiple-choice-vocabulary-test (MWT-B), the syndrome-short-test (SKT), digit span, trail-making-test A and B and a rhythm discrimination test, while the motor analysis contained reaction time (RT) and contraction time (CT) of fastest voluntary single contractions as well as the highest possible frequency of rapid voluntary alternating finger movements (VAM). Spearman rank correlation was used for statistical analysis.

Compared to normal controls, the group of WD patients exhibited pathological performance in most of the psychometric and electrophysiological motor tests. Since the SKT, Trail A and Trail B tests were motor dependent, correlations were observed with VAM. Furthermore, there was a significant correlation ($p<0.1$) between motor reaction time and Trail B test. No significant correlation was observed between the motor parameters and the MWT-B (premorbid intelligence), digit span (working memory), and rhythm test (auditory discrimination) as well as the ratio between the times for Trail B and A testing cognitive flexibility without motor component.

In summary, comparison between electrophysiological motor and psychometric testing reveals a cognitive deficit in Wilson's disease independent of motor impairment. (Acknowledgement: The study was supported by the German Ministry for Research and Technology BMFT 01 KL 9408 and the DFG SFB 194, A5)

71.35 INTRAOPERATIVE SUBDURAL PERFUSION AFTER SPINAL CORD INJURIES: A REPORT ON 4 CASES
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In experimental investigations on primates it has been shown that after a standardized transverse lesion of the spinal cord subdural perfusion with an artificial liquor solution (Elliot`s B solution) of the region of the injury improved the eventual motoric function achieved. The mechanism by which perfusion exerts its beneficial effect is unknown, but it is suggested that dialysis of noxious substances from the injured cord may play a role. For example norepinephrine has been shown to accumulate at the site of cord injury and it has been postulated that the presence of an abnormal amount of this substance within the cord has a harmful effect because of a local vasoconstrictive mechanism. We tried to reproduce these experimental results in the management of four patients with acute spinal cord injury after trauma of the vertebral column. Due to the difficulty of an exact evaluation in this initial study an objective positive effect of this normothermic perfusion could not be confirmed in these patients. Nevertheless the possibility of a positive influence of this adjuvant operative treatment on spinal cord injuries should be studied in a greater collective of patients.

71.36 OCULOMOTOR RESPONSES TO DICHOTIC AUDITORY STIMULATION IN ECCENTRIC GAZE FIXATION
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When a subject attempts to maintain a given eccentric gaze direction in the dark without visual input, the eyes drift backwards to the primary position, with a definite time constant. Target fixation seems to stabilize eccentric gaze by a continuous feedback mechanism. Robinson's neural integrator in a hypothetical eye stabilization system is described as a "leaky" integrator with the transfer function Tn/(sTn+1) with Tn about 25 seconds. Becker (1973) investigated gaze stabilization in darkness in humans and the results demonstrate drift towards the primary position far from random and corrective saccades. In the present experiments we investigated the effects of eccentric auditory target fixation in the dark on the gaze holding function.

Six healthy subjects were instructed to maintain eccentric gaze fixation in a completely dark room after disappearance of a visual target. Eye movements were recorded by means of the IRIS-infra-red eye movement recording technique (optimal resolution: 2 min. of arc; bandwith DC to 100 Hz). In all subjects drift towards the primary position and infrequent corrective saccades ocurred. The auditory tasks were performed under binaural dichotic stimulus conditions (headphones/AKG - simulating different sound source locations) providing virtual azimuth angles from -40° to +40°.When the disappearing visual target was replaced by an auditory target of the same azimuth angle the number of corrective saccades increased significantly. The position information of the auditory target is thus fed into the system of gaze holding function but does not prevent the nonrandom eye drift in darkness.

71.37 INTRA-AND INTERAREAL MODULATION OF INHIBITORY INTERNEURONAL ACTIVITY AS EVIDENCED BY TRANSCRANIAL MAGNETIC STIMULATION.
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Using transcranial magnetic stimulation (TMS) corticocortical (1) as well as transcallosal inhibitory effects have been demonstrated to be effective on cortical motor output neurones. After TMS a period of electrical silence (SP) can be observed in voluntary tonic EMG activity starting directly after the early response. Converging evidence exists that SP reflects the activity of local cortical GABAergic inhibitory interneurones. In a recent paper from our group (2) it was demostrated that SP-duration is influenced by transcallosal pathways. In the present paper we have dealt with corticocortical effects on the SP.

SP measured in the tonically innervated first dorsal interosseus was reduced by up to 50 per cent when electrical conditioning stimuli (CS) were applied over the leg area and magnetic test stimuli (TS) were released over the hand area. Effectiveness of SP shortening was maximal when delivering the CS 1-4ms before the TS. The latency of maximal SP shortening was similar when TS were applied over the hand area indicating that stimulus spread from the site over the leg area towards neuronal elements within the hand area played a major role in this effect. The intensity of both CS and TS influenced the shortening of SP. With smaller TS the effects on SP was more pronounced than with larger TS. Larger effects on SP-duration were seen with larger CS. Electrical and magnetic CS were equally effective.

A second period of shortened SP was present when the CS preceded the TS by 25 up to 50 ms. With the TS applied over the hand (leg) area this modification was only present when CS were applied over the leg (hand) associated cortex but not observed when CS were released over the target cortex of the TS.

Intra-and intercortical pathways modulate cortical inhibitory interneurones within the primary motor cortex. While the short latency effect might result from intraareal modulation of inhibitory interneurone activity, the long latency effect is specific for an interareal test setting. Latency and extension of the second period are compatible with presynaptic rather than with postsynaptic inhibition of GABAergic inhibitory interneurones. In humans interareal motor control might be effected predominantly presynaptically.

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72.01 EFFECT OF DEXAMETHASONE ON HIPPOCAMPAL NEURONAL ACTIVITY AND EXTRACELLULAR LEVEL OF AMINO ACIDS. I. Ábrahám*, K.J. Kovács, K.A. Kékesi and G. Juhász. Institute of Experimental Medicine, Budapest, 0Hungary; Eötvös Loránd University, Dept. of Animal Physiology, Budapest, Hungary

Effect of type II receptor agonist dexamethasone on extracellular amino acid levels and neuronal excitability in the hippocampus were studied by combination of in vivo microdialysis and eletrophysiology in freely moving animals.

Microdialysis probe was implanted to the CA1-CA3 regions of dorsal hippocampus. Local dexamethasone infusion resulted in a transient peak of glutamate levels at 30 min, while glutamine concentration decreased by 30-40% throughout the 180 min sampling period. Taurine level increased by 50 % and remained elevated up to 180 min. No significant changes of other amino acid transmitters were detected. Effect of intrahippocampal dexamethasone on the neuronal activity elicited by perforant path stimulation was studied using a bipolar recording electrode attached parallel to microdialysis probe. Dexamethasone infusion resulted in a decrease of population spikes from 60 min to end of the sampling period. The effects on population spikes disappear one day after washing out the dexamethasone. The paired pulse facilitation was not changed.

Adaptation of the brain microdialysis technique with extracellular recording of neuronal excitability is a useful method to follow the dynamics of the effect of the glucocorticoids on hippocampal amino acid metabolism and neuronal activity in freely moving rat. These data indicate that dexamethasone affects neuronal excitability and extracellular concentration of amino acid neurotransmitters.

72.02 BODY TEMPERATURE THROUGHOUT THE DAY ASSESSED BY A TWO-TERM FUNCTION.

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The pattern of a biological circadian rhythm is rarely symmetrical. As an example, in human body temperature the time between the minimum and the maximum thermal values is approximately of 16 hours, and the time between the maximum and the minimum of 8 hours. The present study proposes a two-term function to modellize circadian temperature rhythms. The first, a potential function, reflects that the heat gain process is predominant, the second term is a negative exponential function and reflects the predominance of heat dissipation.The parameters of the model summarizes the rate of these opposite and simultaneous processes. This two-term function has been fitted to 300 circadian temperature series published in the literature. Data were obtained by scanning the figures and obtaining the hourly values by a graph program. Results show that the percentage of variance accounted for this function is in general higher than the percentage of variance accounted for the cosine approximation. Experimental and/or pathological conditions can affect the asymmetry of heat gain and loss processes.

72.03 ABSENCE OF BRAIN CAPILLARY RESERVE IN THE AWAKE SPONTANEOUSLY HYPERTENSIVE RAT (SHR). E. Andreoli,[1]* G. Zoccoli,[1] M.L. Lucchi,[2] T. Cianci,[1] P. Lenzi[1] and C. Franzini[1]. Institutes of [1]Human Physiology and [2]Veterinary Anatomy, University of Bologna, Italy.

Brain microcirculation in the spontaneously hypertensive rat (SHR) is characterised by increased arteriolar resistance with respect to normotensive controls. The increased arteriolar resistance might underlie a functional rarefaction of the capillary bed (reduced percentage of perfused capillaries), thus augmenting the diffusion distances for O_2 and other substances; this unperfused capillary reserve could be recruited in pathophysiological conditions to reduce hypoxic damage. The present study aims therefore to assess the existence of a brain capillary reserve in the hypertensive state. The experiments were carried out on SHR rats (n=3), in an apparatus where the animal could be decapitated while unrestrained. Brain capillary perfusion was evaluated with a fluorescent marker (Evans Blue, 2% solution in saline, 0.2 ml/100g body wt) injected into the femoral vein over 40s during a quiet, unstressed waking condition assessed by polygraphic recordings (EEG; EMG; blood pressure and heart rate); arterial gas pressures were also monitored. At the end of the injection the rats were decapitated and the head frozen in liquid nitrogen. Sections cut on a microtome-cryostat (5 µm) were photographed twice, under fluorescent light and after staining for alkaline phosphatase (identifying the anatomical capillary bed); the two series of pictures were then compared with an image analyser. Percentages of perfused capillaries in different brain regions were:

Hemisphere	*Diencephalon*	*Pons*	*Medulla*	*Cerebellum*
94.9 %	96.1 %	96.1 %	95.1 %	95.8 %

The high relatively uniform perfusion percentages indicate that in basal conditions during wakefulness the quota of unperfused brain capillaries is functionally negligible in the spontaneously hypertensive rat.

72.04 PROPERTIES OF POSTGANGLIONIC SYMPATHETIC FIBERS ISOLATED FROM THE RIGHT RECURRENT LARYNGEAL NERVE.

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The pattern of response of 41 single postganglionic sympathetic axons dissected from the right recurrent laryngeal nerve was examined in chloralose-anesthetized cats. Each neuron, based on the presence of cardiac and respiratory rhythmicities in its resting activity, and reaction to systemic hypoxia (10% O_2 in N_2 for 2 min.), was classified into one of two classes. Class I neurons (n=29, 71%) were activated during systemic hypoxia and had a pronounced cardiac and inspiration-related rhythmicity in their resting activity. Class II neurons (n=12, 29%) were inhibited during systemic hypoxia and their cardiac and respiratory rhythmicities were either negligible or totally absent. We conclude that class I and class II neurons innervate the arteries and the smooth muscles of upper airways, respectively.

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72.05 SUPPRESSION OF VIP-BINDING SITES IN BLOOD VESSELS OF THE HAMSTER SEMINAL VESICLE FOLLOWING CASTRATION

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The presence and distribution of vasoactive intestinal polypeptide (VIP) binding sites in blood vessels supplying the hamster seminal vesicle was studied before and following castration.

Adult male hamsters were castrated by scrotal route and sacrificed 15 days later. For receptor autoradiography, unfixed cryostat sections (12 µm) of seminal vesicles from intact and castrated animals, were incubated with 0.125 nM ^{125}I-VIP either in the absence or in the presence of 1.250 µM unlabeled VIP to assess specific or non-specific binding, respectively. Autoradiograms obtained by dipping were exposed for 24 hours at 4°C, and analyzed by a computerized image analysis system. The results were compared by one way analysis of variance (ANOVA).

Our results show that VIP-binding sites are localized in the gland muscle coat and arterial smooth muscle. A 15 days castration period has no effect on the binding of ^{125}I-VIP to the gland muscle coat, however, it abolishes the binding to vascular smooth muscle.

Our results indicate that VIP-binding sites in arteries supplying the hamster seminal vesicle are under androgenic control and are more sensitive to androgen deprivation than VIP-binding sites associated to the gland muscle coat.

72.06 NERVE DENSITIES IN THE HUMAN BASAL CEREBRAL ARTERIES.

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In order to quantify the intrinsic nerves of the major cerebral arteries in humans, both topographically and with respect to age, segments of the circles of Willis, including afferent and efferent arteries, from 3 groups of patients (middle aged: 32-52 years, n=6; aged: 62-85 years, n=7; Alzheimer's disease: 62-85 years, n=7) were processed as whole-mount preparations and immunohistochemically stained for the general neural marker PGP 9.5. The intrinsic nerve plexuses, located at the adventitial-medial border were quantified by image analysis and expressed as area% of the vessel wall. The results demonstrated that for the middle aged group nerve density was generally high in vessels of the circle of Willis proper (highest in the posterior communicating artery and intracircular part (P1) of the posterior cerebral artery) and in two efferent arteries: the posterior cerebral artery (P2) and the anterior choroidal artery (ChA). Comparison of groups showed that area% decreased significantly with age for the internal carotid artery, P1 and the ChA. In Alzheimer's patients nerve density was significantly lower in the intracircular part of the anterior cerebral artery compared to the aged group. There appeared to be no clear relation between vessel diameter and nerve density. These results suggest a stronger neuronal influence on this part of the cerebral circulation than hitherto reported. It is hypothesized that locally appropriate innervation is determined by nerve-target interactions in relation to changes in flow fluctuations.

Supported by the Netherlands Organization for Scientific Research (NWO), by the Foundation "De Drie Lichten" in the Netherlands and by the British Heart Foundation. The cerebral arteries were partly obtained from the Netherlands Brain Bank, Amsterdam (Coordinator Dr. R. Ravid).

72.07 MAPPING MICTURITION CONTROL AREAS IN THE CENTRAL NERVOUS SYSTEM WITH POSITRON EMISSION TOMOGRAPHY

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Little is known about the brain structures controlling micturition or voiding. Indirect evidence from patients with cerebrovascular lesions, large brain tumors or lobotomies suggest that voluntary control of micturition in humans depends on the integrity of the medial surface of the frontal lobe (the superior frontal gyrus and anterior cingulate gyrus) and the septal and preoptic regions of the hypothalamus. In this study an attempt was made to identify cortical and subcortical areas involved in micturition in healthy human volunteers.

Cerebral activation was monitored in seven healthy right-handed male subjects, 23-46 years old) using a Siemens ECAT 951/31 whole body positron emission tomograph. Changes in regional cerebral blood flow (rCBF) were measured using the intravenous radioactively labeled water ($H_2{}^{15}O$) bolus technique. A bolus injection of 50 mCi $H_2{}^{15}O$ was given for each run. Scanning was made during three successive conditions: with a filled bladder, during micturition, and with an empty bladder. Shifting from the condition with a filled bladder to the condition in which the micturition took place greatly altered the pattern of brain activation. During micturition, activation was found in the periaqueductal gray, the hypothalamus, parts of the striatum and the anterior cingulate gyrus. These data support previous animal research which indicated that the periaqueductal gray and the preoptic area of the hypothalamus play a central role in the control of micturition (Holstege, 1987; Blok and Holstege, 1994). The results give better insight in the human control of micturition, which might help to understand the pathophysiology of urge incontinence, one of the major problems in the elderly.

72.08 LIGHT-INDUCED FOS EXPRESSION IN THE SUPRACHIASMATIC NUCLEUS OF THE SABRA MOUSE.

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Photic input, the prime entrainer of the suprachiasmatic nucleus (SCN) is expected to impinge on the intrinsic oscillatory mechanism, which has not yet been defined. c-Fos-immunoreactivity (-ir), induced in SCN cell nuclei by a phase-shifting light pulse, may help trace the oscillator(s) input pathway. A 15-minute light pulse induced c-Fos-ir in approximately 2,000 cell nuclei within the bilateral mouse SCN, regardless of the light intensity (50-2,300 lux). Ultrastructural dual-labeling revealed that a considerable number of Fos-positive cells were VIP-containing or vasopressinergic or glial (GFAP-containing). Within the framework of the present experiments, it cannot yet be deduced whether a temporal order in Fos-induction occurs, or whether retinal input impinges directly on all Fos-positive cells in the SCN.

72.09 VIRAL LABELING OF NEURONAL NETWORKS PARTICIPATING IN AUTONOMIC CONTROL OF THE RAT HEART.

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The anatomy of neuronal networks and location of neurons participating in cardiovascular regulation is obscure. Using retrograde transneuronal viral labeling methods we have now characterized the locations in the brain and spinal cord of neurons that may modulate functioning of the various parts of the rat heart. *Methods*: After deposition of *pseudorabies virions* (PRV) in the myocardium of male Wistar rats (n=65), employing the Sauerbruch technique for approaching of the heart, virus infected cells and cell groups could be revealed immunocytochemically at different levels of the spinal cord and brain. Thoracotomy at Th1 (n=45) was employed for determining of the effector pathway(s) used by the higher order neurons. *Results*: After inoculations of the left and right ventricular myocardium the preganglionic orthosympathetic neuron groups were found bilateral in the intermediolateral area (IML) of the upper thoracic spinal cord, predominantly levels Th1-Th7. Surprisingly, additional single virus infected neurons were found in the IML of Th8 - Th11 of these cases. Moreover, the various parts of the heart had different thoracic levels of innervation dominance; for example the sinus node region was innervated predominantly by neurons that were located in the left IML at level Th4 and Th5. Similar observations were done with the preganglionic parasympathetic innervation of the heart. Preganglionic neurons were found in the dorsal motor vagus nucleus (5-10%) and the peri-ambiguus area (90-95%), and locations of the infected neurons in these brainstem nuclei again were related to the injection-site in the heart. Such "myocardiotopy" was found in higher order cardiovascular control areas in the ventral medulla oblongata such as the rostral and caudal ventrolateral cell groups but not at the suprabulbar levels, where labeled cells were revealed for example in the parabrachial area, peri-aqueductal gray, hypothalamus, central amygdala, insular and anterior cingulate cortex. The latter cortical area could be linked to sympathetic effector pathways in the thoracotomy experiments. Labeling in the insular cortex was not affected by such spinal cord transsections, which couples this cortical region to the parasympathetic heart innervation. The latter finding substantiates the suspected role of the insular cortex in vagally mediated sudden cardiac death. *Conclusion*: We demonstrate a "myocardiotopy" in cardiac neuronal networks of the spinal cord and brainstem.

72.10 DIURNAL VARIATION IN PLASMA CORT IS NOT ATTRIBUTABLE TO CHANGES IN ADRENAL SENSITIVITY TO ACTH BUT POSSIBLY TO ACTIVATION OF THE SPLANCHNIC NERVE

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In rats, diurnal variation in corticosterone secretion by the adrenal gland can be observed. The elevated evening levels of plasma corticosterone are believed to be due to a simultaneous rise in plasma ACTH and a concomitant increase in adrenal sensitivity to ACTH. Interestingly, during chronic stress and depression in man, the adrenal glands show an increased sensitivity to ACTH resulting as well in elevated plasma cortisol levels. In this study we focussed on the mechanisms that possibly regulate adrenal responsivity. First, we tested adrenal responsiveness to exogenous ACTH (7.5 ng/rat) in dexamethasone treated (0.5 mg/kg) rats both in the morning and in the evening. It appeared that plasma corticosterone responses did not show morning/evening differences, which is in contrast with earlier reports, unless ACTH was administered in an acid vehicle. These results demonstrate that adrenal sensitivity to ACTH per se does not change diurnally in the rat. Administration of ACTH in an acid vehicle, which can be considered a noxious stimulus, however, apparently triggers an additional mechanism controlling adrenal corticosterone secretion in the evening. This led us to hypothesize that this additional, rather than potentiating, mechanism may also play a role in the diurnal variation in corticosterone secretion. Stimulation of the splanchnic nerve, the primary source of sympathetic input to the adrenal gland, is known to increase cort secretion in the presence of constant plasma levels of ACTH whereas sectioning of this nerve results in a decrease of adrenal sensitivity to ACTH. We investigated whether splanchnic innervation of the adrenal gland is involved in the regulation of diurnal variation in corticosterone secretion under stress free conditions. Indeed, sectioning of the splanchnic nerve resulted in suppression of evening corticosterone secretion and had no effect on morning plasma corticosterone levels. Splanchnic innervation of the adrenal gland, therefore, appears to be an important mechanism that regulates corticosterone secretion, at least diurnally, and this innervation may also play a role in the regulation of corticosterone secretion under stress conditions.

72.11 IMMUNOCYTOCHEMICAL DETECTION OF FOS-PROTEIN IN BRAIN AREAS INVOLVED IN THE CONTROL OF THE CARDIOVASCULAR SYSTEM FOLLOWING ELECTRICAL STIMULATION OF RAT SENSORIMOTOR CORTEX

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Neuroanatomical studies have shown direct projections from the sensorimotor cortex (SMC) to the dorsal nucleus of the vagus/nucleus of the solitary tract (NDV/NTS) and to the rostroventrolateral medulla (RVLM), bulbar nuclei known to be directly involved in the cardiovascular control. The aim of the present study was to establish a functional connectivity between the SMC and the subcortical areas involved in the control of the cardiovascular system. Electrical stimulation for 1 hour (500ms trains at 0.5Hz; pulses of 1ms at 200Hz, 300-400μA) of the right SMC of 8 rats induced the expression of c-*fos*-protein-like immunocytochemistry in nuclei of postsynatic neurons of the central nucleus of the amygdala, paraventricular nucleus of the hypothalamus, NDV/ NTS and RVLM. In control brains (n=6) into which electrodes were inserted but no current passed, cell nuclei were stained in a reproducible pattern in the same areas, but with a number of cells significantly less important. Finally, as the NTS and RVLM are known to contain catecholaminergic neurons (group A2-C2 and C1 respectively), we used an antibody raised against tyrosine hydroxylase (TH) to identify the chemical nature of Fos-positive cell nuclei in these areas. Double-labelled cells were found in the RVLM (C1 group) and in the NTS (A2-C2 groups).

These data support the view that SMC establishes a functional connectivity with neurons involved in the cardiovascular control. Furthermore, some of these neurons, probably implicated in the regulation of cardiovascular functions, are catecholaminergic.

72.12 A SECRETIVE ACTIVITY IN THE FRONTAL ORGAN OF THE FROG *Rana Esculenta*. AN ANNUAL HISTOLOGICAL AND ELECTROPHYSIOLOGICAL STUDY.

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The frog *Rana esculenta* has, in the skin between the lateral eyes, an extracranial photoreceptive structure, the frontal organ (FO), that belongs to the pineal complex. In the FO we have shown an annual cyclical presence of glia-type cells that contain a granular substance in a vacuolar formation. This formation appears in spring; during the summer, the number of cells with the vacuol is maximum and its size is greater, while such cells are almost absent in autumn and in winter. The above morphological features are related proportionally with the frequency of the spontaneous potentials that we have recorded in the FO in the same seasonal periods. The potentials were picked up extracellularly with NaCl-filled glass microelectrodes by standard electrophysiological technique, amplified and photographed on the oscilloscope screen. The histological control of each FO, from which the potentials were recorded, was carried out by anaesthetizing the animals in a tricaine methanesulfonate solution (MS222) and fixing them intracardially by perfusion with a glutaraldehyde-paraformaldehyde phosphate buffer solution at pH 7.4. The dissected FO was post-fixed in osmium tetroxide, treated with uranyle acetate maleate buffer, dehydrated and embedded in Spurr's resin. Serial semithin sections, 1 μm thick, were cut by an ultramicrotome and stained with toluidine blue.

The results of this study speak in favour of an involvement of the FO not only in the already known photoreceptive function, but also in a strong secretive activity, stimulated by the light during the warm season, which might play a significant role in the cyclic seasonal mechanism of the reproduction.

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72.13 MODULATION OF 5HT$_{1A}$ RESPONSIVENESS IN CA1 PYRAMIDAL NEURONS BY ACTIVATION OF CORTICOSTEROID RECEPTORS.

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The adrenal hormone corticosterone can bind to two different receptors in the CNS: the high affinity mineralocorticoid receptor (MR, $K_{d,cort}$~0.2 nM) and the lower affinity glucocorticoid receptor (GR, $K_{d,cort}$~2-3 nM). Upon ligand binding a transcriptionally active complex is formed which can induce long lasting changes of cellular characteristics. The hippocampus is one of few areas where MR and GR are colocalized. We investigated effects of differential activation of MR and GR in CA1 neurons on serotonergic (5HT) responsiveness, by means of intracellular recording techniques in hippocampal slices. We found that selective in vitro activation of MR in slices obtained from adrenalectomized rats (ADX) leads to a suppression of 5HT$_{1A}$-mediated hyperpolarizations. Simultaneous activation of MR and GR yielded large responses similar to those measured in untreated ADX-slices. We next investigated effects of single in vivo applications of corticosterone (1-1000 µg/100g body weight) to ADX-rats. When rats were injected with relatively low doses (10-30 µg/100g) 5HT-responses were significantly smaller than responses in CA1 neurons from rats that received either (almost) no (0-1 µg/100g) or a high dose of corticosterone (1000 µg/100g). This dose-dependency can be explained by differential occupation of MR and GR: at low plasma levels of corticosterone mainly MR will be activated whereas at higher concentrations also the lower affinity GR will become activated. The 5HT-induced hyperpolarization was also modulated in adrenally intact rats: high plasma levels of corticosterone induced by ether stress correlated with large 5HT-responses when compared to rats with low levels of corticosterone occurring early in the morning. Pretreatment with RU38486, a GR antagonist, prevented the stress-induced increased 5HT-responsiveness. This study shows that the sensitivity of CA1 neurons towards 5HT is modulated by physiologically relevant variation in the activation of MR and GR.

72.14 AN ATTEMPT TO USE POWER SPECTRAL ANALYSIS OF EEG TO DIAGNOSE LATERAL HYPOTHALAMIC INSOMNIA IN RATS.

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Bilateral lesions of the lateral hypothalamus (LH) produce disturbances in sleep-waking pattern consisting in an increase of waking time and a decrease of sleep (insomnia) as evidenced by visual inspection of EEG records and simultaneous observations of behavioural indices of a vigilance state. However, when lesions are large enough EEG waking pattern shows several abnormalities which are difficult to specify using standard analysing procedures. Therefore in the present study an attempt was undertaken to apply spectral analysis to diagnose EEG abnormalities after LH damage.

In male Wistar rats bilateral electrolytic LH lesions were performed and hippocampal and cortical EEG were recorded before and after the lesions. One-hour samples of EEG taken from the light part of the day were fed to a computer and power spectral density by Fast Fourier Transform routine was calculated off line at delta (0.5-5.5 Hz), theta (5.5-9.0 Hz), alpha (9.0-12 Hz) and beta (12.0-25 Hz) bands as well as at 1 Hz bands from 0.5 to 25 Hz (the whole registered spectrum).

After the lesion the following power density distribution was found: 66.3% of the whole power density for delta, 21.8% for theta, 6.1% for alpha and 4.7% for beta frequency. Preliminary analysis revealed that LH lesions resulted in an increase of a power density in 4.0-5.0 Hz and 5.0-6.0 Hz (theta frequency) and also in bands exceeding 12 Hz. The comparison of visual scoring of EEG records and power spectral analysis will be presented.

72.15 SEROTONIN RELEASE IN THE HYPOTHALAMUS IS INFLUENCED BY NEUROACTIVE DRUGS AND HAEMODYNAMIC CHANGES

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It has been shown that central serotonergic neurons are important in cardiovascular regulation, although their exact role is not well understood. Serotonin (5-HT) applied centrally influences blood pressure (BP) and heart rate but the cardiovascular effects seem to be dependent on animal species, concentration, as well as site of drug injection. In the present study, we investigated the influence of experimentally induced BP changes on the release of endogenous 5-HT and its metabolite 5-hydroxyindol acetic acid (5-HIAA) in the posterior hypothalamic area (PH) of conscious rats.

Push-pull superfusion coupled with HPLC and electrochemical detection was used to determine the in vivo release of 5-HT and 5-HIAA in time periods of 10 min. The PH was perfused with artificial cerebrospinal fluid (CSF) at a rate of 15 µl/min. After a stabilization period of 80 min, the release rates of 5-HT and 5-HIAA remained fairly constant for more than 6h. Superfusion of the PH with CSF which contained 80 mM KCl for 10 min increased greatly 5-HT release. Veratridine (1µM) also induced a pronounced increase in 5-HT release, whereas superfusion with tetrodotoxin (TTX, 5µM) for 20 min decreased 5-HT release to 40 % of control values, pointing to an action potential dependent release of 5-HT in the PH. TTX also diminished transiently 5-HIAA outflow. Intravenous infusions of phenylephrine or noradrenaline elevated BP by about 60 mm Hg and led to a concurrent increase (50%) in the release rate of 5-HT in the PH. Even a slight rise in BP elicited by hypervolaemia (injection of blood) enhanced drastically the hypothalamic 5-HT release. Hypovolaemia induced by controlled haemorrhage elicited a long-lasting fall of BP and diminished the release of 5-HT after a delay of 10 min. A short-lasting fall of BP by intravenous infusion of nitroprusside tended to decrease 5-HT outflow, but this effect was statistically not significant. 5-HIAA release was influenced only by TTX.

Our data demonstrate that, in the conscious rat, 5-HT is released in an action potential dependent manner from serotonergic neurons in the PH. Futhermore, 5-HT release in the PH is altered by cardiovascular stimuli thus pointing to an involvement of the amine in BP homeostasis.

72.16 CIRCADIAN CONTROL OF CORTICOSTERONE AND MELATONIN RELEASE

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Phaseolus tracing to label suprachiasmatic nucleus (SCN) efferents together with immunocytochemistry for SCN transmitters has revealed VP, VIP, GRP and GABA containing projections to the paraventricular and dorsomedial nuclei of the hypothalamus (PVN/DMH). This area not only harbours a major population of hypophysiotropic neurons but also provides an important hypothalamic output pathway to all autonomic preganglionic cellgroups. In order to test the involvement of SCN projections to this area in the control of hormonal rhythmicity we infused SCN-transmitters (or their antagonists) via permanent microdialysis probes.

Initial results showed that infusion of VP, but not VIP, in the PVN/DMH area of SCN-lesioned animals inhibited the release of corticosterone. The physiological significance of this inhibitory effect of VP was certified by infusion of a VP-antagonist or VP itself in intact animals at the appropriate through and peak times of the corticosterone rhythm. The immediate increase of plasma corticosterone (and ACTH) levels evoked by the infusion of VP-antagonist at CT6 confirmed the inhibitory effect of the elevated release of VP by SCN terminals during this time of the day. Furthermore, extending the period of increased VP release by infusion of VP during the last 4 hours of the lightperiod completely prevented the endogenous rise of corticosterone normally observed at this time of the day.

Comparable experiments showed that infusion of a GABA-agonist at the level of the PVN/DMH area decreased elevated melatonin levels in SCN-lesioned animals and prevented the nocturnal increase of plasma melatonin in control animals.

72.17 REORGANIZATION OF THE FUNCTIONAL CONNECTIONS WITHIN THE SYMPATHETIC NERVOUS SYSTEM DURING THE CEREBRAL ISCHEMIC REACTION.

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Partial coherence analysis of the simultaneous discharge in three sympathetic nerves (vertebral(VN), cardiac(CN), and renal(RN)) showed that, at rest, there are three preferred patterns of relationships between the generators of these nerve activities: 1. uniform coupling (VCR); 2. non-uniform coupling in which VN and CN but not RN are driven by a functionally common generator (VC-r); and 3. in which the major rhythmic component in CN is common and dominant in all three nerves (v-C-r).

The aim of the present study was to analyze the pattern of relationships between these same nerves during the massive activation of the sympathetic nervous system during cerebral ischemia (CI). We have previously shown that differential sympathetic control during CI involves uneven augmentation of the regional sympathetic outflow and also non-uniform changes in the discharge pattern in different sympathetic efferents. We found that the frequency characteristics of C discharge differed from those of vasomotor nerves i.e. the CN generator had a greater capacity to generate synchronized discharge in the 2-6 Hz range. Complementing these findings, partial coherence analysis revealed that during the CI reaction CN carried most of the common variance of the three nerve signals. When pattern v-C-r could be recorded at rest, the relationships between VN, CN, and RN did not changed In other experiments, with either VCR or VC-r there was a reorganization within the sympathetic generators changed and the pattern of relationships switched to v-C-r.

72.18 CYCLIC-AMP EFFLUX DURING INHIBITION OF α-MSH SECRETION BY THE *XENOPUS* NEUROINTERMEDIATE LOBE.

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Cyclic-AMP is known to be released from tissue and cells and the amounts released have been reported to reflect the intracellular levels. To measure cyclic-AMP egress the phosphodiesterase inhibitor IBMX is often used to increase the amount of cyclic-AMP to detectable levels. Using this method to follow cyclic-AMP dynamics for neurointermediate lobe melanotrope cells of the amphibian *Xenopus laevis* we have previously shown that the α-MSH secreto-inhibitors dopamine (working through the D_2 receptor) and baclofen ($GABA_B$ receptor agonist) inhibit egress of cyclic-AMP. These findings are consistent with the conclusion that the D_2 and $GABA_B$ receptor mechanisms inhibit secretion through inhibition of adenylyl cyclase. Using a highly sensitive cyclic-AMP radioimmunoassay we can now measure cyclic-AMP egress from *Xenopus* neurointermediate lobes without the use of IBMX. In such experiments both dopamine and baclofen inhibited α-MSH secretion but stimulated egress of cyclic-AMP. This suggests that cyclic-AMP egress is a physiologically regulated process which may be used to lower intracellular cyclic-AMP levels associated with the secretory compartment. No differences could be found in the tissue content of cyclic-AMP at the termination of secreto-inhibitor treatment, indicating that the intracellular cyclic-AMP compartment associated with secretion is small relative to the total amount of cyclic-AMP present in the tissue.

72.19 PATHWAYS VIA WHICH PERIPHERALLY ADMINISTRATED ENDOTOXIN ACTIVATES THE HPA AXIS.

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Several pathways by which peripherally administrated bacterial endotoxin activates the hypothalamus-pituitary-adrenal (HPA) axis have been proposed. One pathway involves the stimulation of cells of the immune system to produce and secrete cytokines (e.g. interleukin-1), which, subsequently, may act as humoral signals at the brain. A second proposed pathway is a neuronal route that involves the stimulation of primary afferents by endotoxin or by locally produced IL-1 in the periphery.
Recent results showed that repeated administration of endotoxin induces tolerance for the febrile response, which was dependent on the exact route of administration (iv or ip) of the endotoxin. To investigate whether the two proposed pathways are differentially activated by ip or iv administration of endotoxin to rats, in a first series of experiments we determined the pharmacokinetics of endotoxin after ip or iv injection.
IV injected endotoxin (E.Coli 055:B5 Westphal, Difco, 100 μg/kg) was distributed within 5 minutes over an imaginary volume of 18 ml/rat. Endotoxin levels remained high (1.2 μg/ml) for at least 90 minutes. IP injection of an equal dose of endotoxin resulted in a progressive increase of endotoxin levels in the plasma over 90 minutes. However, after 90 minutes, these levels were still 10-fold lower than those observed after iv injection. Both the plasma concentrations of ACTH and corticosterone showed a delayed increase after ip as compared to iv injection of endotoxin. Strikingly, some animals did not respond to ip injected endotoxin with an ACTH or corticosterone response, the appearance of which correlated with the appearance of endotoxin in peripheral plasma.
These results are the first to demonstrate that ip injected endotoxin can actually reach the peripheral circulation. They suggest that ip injected endotoxin is likely to act through a humoral pathway to activate the HPA axis.

72.20 EFFECTS OF METOPROLOL ON THE MIDBRAIN PERIAQUEDUCTAL GRAY IN REGULATING THE CARDIOVASCULAR SYSTEM IN THE CAT.

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ß-adrenergic receptors are found in high concentrations in selective areas of the brain, but little is known about their specific function. It has been hypothesized that the extra beneficial effects of ß-blockers with high lipophilicity, such as metoprolol, might be the result of the relatively high penetration rate of the agent through the blood-brain barrier. A very important center for autonomic regulation is the midbrain periaqueductal gray (PAG). The PAG can influence nociception, micturition, vocalization and reproduction. In respect to the cardiovascular system, stimulation of certain areas of the PAG induces changes in blood pressure, heart rate, peripheral blood flow and vascular conductance. The question arises, whether administration of metoprolol into the PAG influences its cardiovascular response.

Effects of local application of 100 nl S-metoprolol in the PAG was studied in the cat, and compared with the effect of its relatively inactive enantiomere R-metoprolol, to rule out any local anesthetic effects. Before and after administration of metoprolol the PAG was electrically stimulated (10s train, 0.5ms pulse, 80Hz, 100μA) at fixed time-intervals. Changes in blood pressure, heart rate, carotid and femoral flow and conductance were compared with those of the baseline value before administration of metoprolol.

The experiments show that administration of S-metoprolol into the PAG greatly reduced the cardiovascular response elicited by PAG stimulation. In contrast, its inactive enantiomere R-metoprolol had only a limited effect. The results suggest that lipophilic ß-blockers have an effect in the central nervous system, and that the PAG is an important target of lipophilic ß-blockers.

This study is supported by the Dutch Heart Foundation and ASTRA.

72.21 **DIFFERENTIAL DYNAMICS OF CARDIOVASCULAR AND BEHAVIORAL RESPONSES TO NOVELTY IN THE RAT DURING THE LIGHT AND DARK PHASE.**

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The effects of repeated exposure to a novel cage (one 15 min test per day on five consecutive days) on cardiovascular and behavioral activities were studied in groups of rats tested during the dark or light phase of the lighting cycle. A telemetry system with intraperitoneally implanted transmitters was used for continuous registration of ECGs during the first and fifth test. Behavior was videotaped simultaneously. In the light phase, first and fifth exposure to the novel test cage resulted in higher increases of active behavior and heart rate (HR) as compared to basal levels (homecage) than testing in the dark phase. Only in rats tested in the light phase, PQ interval was increased during first and fifth exposure to the experimental cage. In addition, only these rats showed less active behavior during the fifth than during the first exposure. From these data it can be concluded that exposure to novelty in the light phase induces active behavior associated with an increase in sympathetic (increased HR) and vagal (increased PQ interval) outflow. In the dark phase, however, novelty-induced behavioral and sympathetic activation were not associated with changes in vagal outflow. In addition, the present data show that the behavioral habituation to the test cage that occurs in the light phase is not paralleled by cardiovascular habituation.

Supported by a research grant from the Netherlands Heart Foundation.

72.22 ELECTROPHYSIOLOGY OF THE RAT SUPRACHIASMATIC NUCLEUS IN VITRO: DIVERSITY OF MEMBRANE PROPERTIES.

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Although the basic electrophysiological characteristics of neurons in the suprachiasmatic nucleus (SCN) have been previously described in a number of studies, little attention has so far been paid to the heterogeneity of their membrane properties as assessed by intracellular recordings in brain slices. The preliminary data presented here suggest a considerable diversity of electrophysiologically distinct cell types within the SCN *in vitro*.

Slices (400 mm) were prepared according to standard methods following chloral hydrate anaesthesia of the rat and transcardial perfusion with cold sucrose-containing saline. Intracellular recordings were made using sharp microelectrodes filled with 3 M KCl (60-120 MW). The mean (± s.e.m.) resting membrane potential, spike amplitude, spike duration, amplitude of afterhyperpolarization (AHP) and input resistance were -53 ± 2 mV, 60 ± 3 mV, 1.0 ± 0.1 ms, 16 ± 4 mV and 202 ± 64 MW, respectively (n=7). All but one neuron showed irregular spontaneous firing patterns or low-frequent firing (<1 Hz) in the absence of continuous current injection. All cells exhibited slow transient depolarizations interleaved with spike trains, and rebound spikes upon relaxation of hyperpolarizing current pulses. Two cells had multiple abnormal membrane characteristics. In one cell a very shallow AHP (1.6 mV) was found in conjunction with burst-like clusters of spikes, while we detected no signs of deterioration in this neuron. Another cell had an unusually broad spike (1.4 ms), a very deep AHP (30 mV), a high input resistance (583 MW) and exhibited clusters of spike trains. These findings, albeit limited in number, illustrate an electrophysiological heterogeneity of SCN neurons *in vitro*. It remains to be investigated what the interrelationship between these unusual characteristics is, and whether the observed cells represent distinct classes of neurons or are merely samples from a continuous distribution within a variable population of cells.

72.23 PYROGLUTAMYL PEPTIDASE I LEVELS AND THEIR LEFT-RIGHT DISTRIBUTION ARE INFLUENCED BY LIGHT-DARK CONDITIONS

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Previous work has shown a significant circadian rhythm of pyroglutamyl peptidase I activity (pGluPI) in the retina and hypothalamus, together with an asymmetrical distribution of this activity. To evaluate the effects of light and darkness on pGluPI levels and their left-right distribution, pGluPI was measured in the left and right sides of the retina and hypothalamus using arylamide derivatives as substrates, under selected light-dark schedules. Male rats were previously maintained for at least two weeks under 12 h light-12 h dark cycles. Four experimental groups were used. 1) Animals kept two additional hours in darkness at the end of the 12 h dark period; the experiment done under dark conditions, 2) Two hours in light after the end of the 12 h dark period, the experiment done under light conditions, 3) Two hours in darkness after the end of the 12 h light period; the experiment done under dark conditions, and 4) Two additional hours in light at the end of the 12 h light period; the experiment done under light conditions. In the retina, the previous 12 h light period (long period) (Groups 3 and 4) led to higher values of enzyme activity than dark periods (Groups 1 and 2) ($p<0.05$). Left-right predominance, however, depended on the previous short period (2h), light short period leading to left predominance(Groups 2 and 4) ($p<0.001$), whereas right predominance was found after the dark short period ($p<0.001$). In the hypothalamus, previous exposure to light or darkness did not influence the enzymatic activities, whereas left predominance was found only in group 3 ($p<0.001$) which was conditioned by the interaction between the previous long period of light and the subsequent short dark period. These results demonstrate that environmental light conditions influence pGluPI activity in retina and hypothalamus.

72.24 COLOCALIZATION OF PHI, GRP, VIP AND VP WITH FOS IN THE RAT SUPRACHIASMATIC NUCLEUS AFTER A 15-MIN LIGHT PULSE AT CT14 AND CT19.

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Light transmitted via the retinohypothalamic tract is known to induce a phase delay early in the (subjective) dark period and a phase advance late in the dark period. Light stimulation at these circadian times (CT) is also known to induce an immediate-early gene response (c-fos). In order to study whether the c-fos response occurs in the same population of neurons at these different CT times, two groups of 4 rats each, received a 15-min light pulse during the night at CT14 and CT19, respectively. After 45-60 min, the animals were sacrificed by formaldehyde perfusion fixation. Adjacent vibratome sections through the SCN were alternately double-immunostained for PHI, GRP, VIP or VP with Fos using fluorophore-conjugated secondary antibodies. Sections were analysed with a confocal laser scanning microscope. It turned out that at CT14 the Fos induction was low but, nevertheless, numerically and proportionally most prominent in the PHI-like immunoreactive neurons. At CT19, Fos induction was overall high, showing a substantially increased colocalization with PHI-, GRP- and VIP-like IR cells. This increase was numerically and proportionally most prominent in the GRP-like IR neurons (no difference was observed for the number of IR cell profiles per SCN section between both CT times).

This outcome suggests that PHI- and GRP-containing neurons play a role, respectively, in the phase delay and phase advance of the biological clock as induced by light at CT14 and CT19.

72.25 EFFECTS OF THE INTRACEREBROVENTRICULARLY ADMINISTERED SOMATOSTATIN ON THE ACTH PITUITARY CELLS

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The purpose of this study was to examine effects of the intracerebroventricularly adminstered somatostatin (S-14 and S-28) on the ACTH anterior pituitary cells of adult male Wistar rats. 1 μg of S-14 and S-28 per 5 μl of saline was administered 3 times every other day. Rats in the control group were subjected to the same procedure, except that they were administered the same volume of saline only. Samples of blood and pituitary tissue were collected 5 days after the last dose, and immunocytochemical technique and RIA were used for analyses. The volume of the ACTH cells and their nuclei increased by 5% in the S-14 treated rats, and by 6% in the S-28 treated rats. In comparison with the control group of rats, the ACTH plasma level was significantly increased by 27.5% in the S-14 treated rats, and by 17% in the S-28 treated rats. These results suggest that the somatostatin stimulates ACTH cells in contrast to its inhibitory effects on most other pituitary cells. This may be due to somatostatin's different mechanism of action via separate receptors in the plasma membrane.

72.26 **ACUTE MYOCARDIAL INFARCTION CAUSES BLOOD BRAIN BARRIER LEAKAGE VIA CYTOKINES.**

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Acute myocardial infarction (AMI) is accompanied by inflammation in the coronary vessels. This inflammatory process may become systemic and reach the brain where it then leads to adverse effects on the functioning of the central nervous system. *Method:* AMI was induced in male Wistar rats by ligation of the left ventricle wall. Between 2 and 4 days after AMI the rats were perfused. Regional blood brain barrier (BBB) damage was revealed immunocyto-chemically with antibodies directed against serum albumines and immunoglobulines (IgG). Evidence for cerebral inflammation after AMI derived from intercellular adhesion molecule-1 (ICAM-1) immuno-cytochemistry which stains positively immune activated endothelial cells. *Results*: ICAM-1 positive vessels were present locally in the prefrontal, entorhinal, somato-sensory and insular cortex, and the reticular formation. Many of these affected regions participate in cardiovascular regulation as could be demonstrated in parallel studies with transneuronal viral labeling of the heart innervating neuronal networks. Staining for serum albumin immunoreactivity showed that specifically round the ICAM-1 positive vessels there was extravasation of serum proteins. This indicates regional BBB leakage probably caused by reactive, cytokine producing cells adhering to the vessel wall. In order to assess whether or not systemic inflammation rather than the surgery was a cause of regional BBB leakage we injected Tumor Necrosis Factor alpha (1 μg/ml) in the tail artery of Male Wistar rats (n=10). Solvent injections were used in the control experiments. The same histological procedures as described above for the AMI experiments were employed. One and two days after the TNFα injections ICAM-1 positive vessels and patches of serum albumin extra-vasation were present in the areas showing BBB-leakage after AMI. *Conclusion:* AMI causes a systemic inflam-mation which stimulates leukocyte adherence to cerebral endothelial cells in certain well-defined areas, among those are cardiovascular control regions. This non-specific immune "over" reaction causes extravasation of blood constituents and may result in regional hypo-function of areas participating in cardiovascular regulation which consequently leads to disturbed autonomic nervous system activity in the heart. This may enhance the progression of cardiac disease.

72.27 CORRELATION OF SMALL FREQUENCY VARIATIONS OF RHYTHMIC SLOW ACTIVITY (RSA) IN WISTAR RAT THALAMIC AND HIPPOCAMPAL REGIONS.

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Our previously introduced mathematical description of spontaneous EEG oscillations as amplitude and frequency variable cosine function predicts that if small frequency variations of signals recorded from two brain structures (1) and (2) are correlated so should be time dependent amplitudes of k-th Fourier components: $a^1_k(t)$ and $a^2_k(t)$. Sets of such corr. coefficients $r^{1,2}(k)$ were computed (0.5-32 Hz) for adult male Wistar rat RSA recorded from left/right VPL thalamic nuclei and CA3 hippocampal regions. Left vs. right CA3 hippocampal structures showed increased $r^{1,2}(k)$ values in the whole frequency range, highest in theta, while for left vs. right VPL thalamic nuclei this was observed in some cases for the low half of the analyzed frequency band. Except in few cases no increased $r^{1,2}(k)$ values were found for thalamo-hippocampal combinations of each hemisphere.

72.28 **BENEFICIAL EFFECTS OF ORG 2766 ON THE ADRENERGIC RESPONSIVENESS OF THE BLOOD SUPPLY TO SCIATIC NERVE IN DIABETIC RATS.**

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Evidence is accumulating that direct vascular disturbances (microangiopathy) resulting in reduced nerve blood flow (NBF) play an important role in the pathogenesis of diabetic neuropathy. Moreover, direct damage to autonomic innervation of the vascular supply to neurons may add to the blood flow disturbances in diabetes. In order to differentiate between a direct vascular or an adrenergic autonomic underlying cause of disturbed flow we investigated the effects of the $ACTH_{4-9}$analogue Org 2766 on sciatic NBF under basal and adrenergic stimulated conditions. This peptide has been shown to be without direct effects on cardiovascular structures whereas Org 2766 has been shown to ameliorate a neuropathy in the sciatic nerve of the diabetic rat (DR). Treatment with Org 2766 was started 6 weeks after the induction of diabetes mellitus with streptozotocin and was continued for 6 weeks. At week 12 the sciatic NBF, measured by laser-Doppler flowmetry, was reduced to 64% of non-diabetic level and blood pressure was unchanged in DR compared to non-DR. Both haemodynamic values were not affected by Org 2766 treatment. Vasa nervorum adrenergic responsiveness was also investigated by responses to tyramine (TYR, presynaptic) and phenylephrine (PHE, mainly postsynaptic). DR showed a adrenergic hyporesponsiveness. Treatment with Org 2766 restored the reduced response to TYR without an effect on reduced PHE responsiveness. It is concluded that, Org 2766 exerts beneficial effects on reduced adrenergic responsiveness mainly at the presynaptic level, and that adrenergic autonomic disturbances in the vasa nervorum are of minor importance on reduced NBF.

74. Poster Session: Late posters

74.01 **INSENSITIVITY OF AGED WISTAR RATS TO CONTEXTUAL CUEING IN THE MORRIS MAZE SPATIAL MEMORY TASK.**

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It is now well documented that two of the major symptoms associated with senile dementia or neurodegenerative diseases are deficits in spatial memory and insensibility to contextual cueing. It was therefore of interest to develop an animal model associating these two kinds of cognitive deficits, to better understand these pathologies and to provide suitable models to search for therapeutic agents.

Young (6-7 weeks) and old (21 months) male wistar rats were given one daily learning session for 5 or 10 days in the Morris water maze. Four different experimental conditions were used : presence of extra-maze context (EC) associated with absence (1) or presence (2) of visual intra-maze cues (IC); and absence of extra-maze context associated with absence (3) or presence (4) of intra-maze cues.

In the first experimental condition (EC+/IC-), aged rats were able to learn the position of the hidden platform but their performance was far worse than that of young animals. The introduction of intra-maze cues (EC+/IC+) improved the performance of young rats, but had no effect in aged animals. Furthermore, an over-training procedure (5 additional learning sessions) failed to improve the performance of aged rats but was effective in young animals. When the external context was removed and no internal cues were present (EC-/IC-), both young and aged rats were unable to learn the task. In this condition, introduction of intra-maze cues (EC-/IC+) restored learning in the young but not the aged rats.

These results show that aged rats are unable to use intra-maze contextual cues, even though they see them, as was shown by the swimming trajectories. The deficit of aged rats in this task could be related to a decrease of spatial cognitive abilities or use of cues associated with the context rather than to alterations in visual capacities. This model may be of an interest in the search for therapeutic agents.

74.02 AUTOMETALLOGRAPHIC SILVER AMPLIFICATION OF ZINC SULPHIDE CRYSTALS CREATED IN FROZEN HUMAN BRAIN SECTIONS. A new approach that allows detection of zinc ions in zinc enriched (ZEN) vesicles in biopsy material

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A new effective technique for the demonstration of zinc ions in animal and human biopsies has been developed. The biopsies are frozen either in liquid nitrogen or by CO_2 gas immediately after removal. The tissue blocks are then cut on a cryostat and the sections are placed on glass slides. The slides are placed in a chamber kept at -25°C furnished with an inlet and outlet through which H_2S gas can be introduced.

After a period of time (from 5 min to 24 h) the sections are removed, fixed, and rehydrated. The sections are then exposed to an autometallographic (AMG) developer for 60 min at 26°C and the in situ created zinc sulphide crystal lattices in the tissue are silver amplified.

The method has been applied to rat brain and the human neocortex for the demonstration of ZEN neuronal terminals.

74.03 NICOTINE INJECTED INTO THE STRIATUM OR PONS POTENTIATES CATALEPSY INDUCED BY SYSTEMIC HALOPERIDOL. Z. Elazar* and M. Paz, Department of Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, Israel.

Systemic administration of nicotine potentiates the effect of haloperidol in rats and in patients with Tourette's syndrome (Sanberg et al., 1989). We have previously reported that carbachol injected into the pontine reticular formation (PRF) induced catalepsy which showed synergism with the effect of systemic haloperidol (Elazar et al. 1990). In the present study we microinjected nicotine directly into the striatum or PRF of rats. Unilateral injections did not induce circling. Bilateral injections (10, 20, 30, 40 $\mu g/1\mu l$ per each side) in both brain regions induced mild catalepsy (10-50 sec). At the higher doses, in some rats, catalepsy evolved into convulsions. Nicotine (20 μg) greatly potentiated the catalepsy effect of systemic haloperidol (1 mg/kg i.p.) when microinjected either into striatum or PRF. We suggest that both the striatum and the PRF are involved in the potentiating effect of systemic nicotine.

74.04 CLONING, DEVELOPMENTAL AND REGIONAL EXPRESSION OF ACIDIC CALPONIN IN RAT BRAIN; INTERACTIONS OF CALPONIN WITH ACTIN IN TRANSFECTED CELLS.
L. FERHAT, A. REPRESA, G. CHARTON, A. BERNARD, H. TRABELSI-TERZIDIS, L. FATTOUM, Y. BEN-ARI, E. DER TERROSIAN, and M. KHRESTCHATISKY. Université René Descartes Paris V, Unité INSERM 29, 123 Bd de Port Royal, 75014 Paris France.

Calponin is an actin-, tropomyosin- and Ca^{2+} calmodulin-binding protein that inhibits in vitro the actomyosin MgATPase and that has been isolated from several vertebrate smooth muscle tissues. Transcripts encoding acidic Calponin have been reported in the adult rat brain (Applegate et al., J. Biol. Chem. 269 pp 10683-10690, 1994) and the presence of an acidic isoform of Calponin in rat brain and in cultured cerebellar neurons was demonstrated (Trabelsi-Terzidis et al., Biochem. J. 306, 211-215, 1995). We report the isolation of cDNAs for the entire coding region of rat brain acidic Calponin. Sequence analysis reveals that brain acidic Calponin is identical to that previously described in rat aortic smooth muscle. RT-PCR shows that Calponin mRNA levels are highest in the early stages of development and that expression levels are low in many adult structures. In situ hybridization confirmed this trend and reveals in particular that Calponin is highly expressed during ontogenesis in cerebellar granule neurons of the external and internal layers. In the adult rat brain, Calponin expression in the cerebellar granule cells is low, but is maintained at high levels in layers of the olfactory bulb, and in the subventricular zone. It is suggested that during development, acidic Calponin is expressed in cells that terminate mitosis or that are in the process of migration. Transient transfections of acidic Calponin show that Calponin affects dramatically actin filament organization.

74.05 NEUROTROPHIN EXPRESSION AND REGULATION IN THE AVIAN VISUAL SYSTEM. F.Hallböök*(1) and N. G. Carri(1,2) (1)Dept. Developmental Neuroscience, Uppsala University, Sweden, (2) Dept. Molecular Biology, Imbice, La Plata, Argentina.

We have found that the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) mRNA are expressed in the avian retina during development. Using RPA it is shown that the expression peaks around embryonic day 12 to 15 with decreasing levels at later stages of development. NGF, BDNF and very low levels of NT-3 mRNA are found in the adult retina. The cellular localization of the mRNA for the neurotrophins and Trk receptors in retina shown by in situ hybridization suggest that specific cell populations express the neurotrophins and Trk receptors in the neural retina. NGF as well as TrkA are expressed in cells proposed to be horizontal cells. In agreement with previous data from other groups we found TrkB and BDNF in retinal ganglioncells. NT-3 labeling was found in cells in the internal nuclear layer whereas TrkC labeling was found over all cell layers in the retina. Using the RPA we analyzed retina from 5 day-old chickens which had been exposed to light or darkness and found that NGF and BDNF mRNA levels were reduced in the darkness exposed animal group.

In the optic tectum, distinct BDNF mRNA levels but only low levels of NGF or NT-3 mRNA were found. A peak in BDNF expression around E12 in optic tectum correlate in time with the periods of naturally occurring cell death in the ganglion cell population and axon terminal invasion of the tectum. In situ hybridization showed that BDNF mRNA is present over cells in the layers where ganglion cell axons terminate. Stimulation of electrical activity of ganglion cells after intra ocular injections of kainic acid was shown to increase the levels of BDNF mRNA in the contra-lateral E15 optic tectum, as shown by RPA and in situ hybridization. These data show all together that normal neuronal activity and kainic acid induced activity regulate neurotrophin expression in the visual system during development and the data also suggest that the neurotrophins play local roles in the retina.

74.06 PREFRONTAL NEURONS DETERMINE DIRECTION OF SACCADE DURING AN OCULOMOTOR DELAYED MATCHING-TO-SAMPLE TASK.
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To examine the role of the prefrontal cortex (PFC) in determing the direction and execution of directional saccades, we recorded neuronal activities from the dorsolateral PFC of two rhesus monkeys performing an oculomotor delayed matching-to-sample task. While the monkeys were fixating on a central spot, a sample cue was presented in the center of the visual field. After a delay of 1.5 s, two peripheral figures, one of which was identical to the sample, were presented (matching period; 0.5 s). After another 1.5 s delay (2nd delay), the monkeys made a saccade to the remembered location of the part of the matching cue which was identical to the sample cue (GO period). We analyzed a total of 262 neurons located in the periprincipal sulcal area (PS, Brodmann's area 46; N=136) and in the frontal eye field (FEF; N=126) that were found to respond during the matching, the 2nd delay, and/or the GO periods. Forty percent of the FEF neurons (N=50) and 21% of the PS neurons (N=29) showed presaccadic activity during the GO period. In contrast, 22% of the FEF neurons (N=28) and 76% of the PS neurons (N=104) showed activity during the matching period. Further, 62% of the PS neurons responding during the matching period (64/104) coded the direction of the forthcoming saccade rather than the physical property of the matching cue, and 39% of them(40/104) sustained their activity until the GO period. These results suggest that the PS are involved in determing the direction of the forthcoming saccade based on a combination of visual and mnemonic information and that they retain this information and transfer it to saccade-related neurons in the FEF.

74.07 CHL1, A NEW MEMBER OF THE L1CAM IMMUNOGLOBULIN SUPERFAMILY IN THE MOUSE.
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Cell surface molecules of the L1CAM gene family are involved in cell-cell recognition phenomena in development of the nervous system and in synaptic plasticity in adult animals. With the help of an immunoaffinity purified polyclonal antibody against L1, a partial clone closely related to L1 was isolated from a λgt11 library derived from day 8 mouse brain RNA. Using this cDNA as a probe clones with full length sequences were isolated from a plasmid library constructed from day 6-14 mouse brain RNA. The deduced primary structure contains six immunoglobulin-like domains, a transmembrane domain and a short cytoplasmic region as also found for the cell adhesion molecules mouse L1 and chicken Ng-CAM and Nr-CAM/BRAVO. In contrast to these molecules, only 4.5 instead of 5 fibronectin type III-like repeats have been detected in CHL1. Polyclonal antibodies raised against a bacterially expressed protein fragment detect CHL1 at the cell surface of CHL1 transfected COS-1 and L929 cells. As observed for L1, CHL1 appears to be susceptible to proteolytic cleavage, since in addition to a 185 kD band, bands of 165, 125 and 50 kD were observed by Western blot analysis. Northern blot analysis revealed a 8 kb message in early postnatal mouse brain. CHL1 from postnatal day 9 mouse brain was shown to carry the HNK-1 carbohydrate epitope which is also carried by NCAM, L1 and several L1-like molecules. Western blot analysis revealed expression of CHL1 protein in brain and heart. In liver a 50 kD immunoreactive band was observed. *In situ* hybridization revealed predominant expression by cerebellar neurons at postnatal day 14. Neuronal expression was also detected by immunostaining of primary cultures derived from early postnatal cerebellum, dorsal root ganglia and embryonal spinal cord.
Experiments are underway to investigate the functional role of this molecule in cell interactions during neural development.

74.08 A DECREASED CONDUCTION VELOCITY IN PERIPHERAL NERVE OF PATIENTS WITH CHRONIC UREMIA. A. KAMAL, Rudolf Magnus Institute for Neurosciences, P.O. Box 80040, 3508 TA Utrecht.

Although the neuropathy in peripheral nerves in patients with chronic uremia been known for many years, the data on specific disorders in peripheral nerves in these patients are still scares. In this study, the compound action potential (cAP) and conduction velocity (CV) sensory and motor nerves of the upper limb (median and ulnar nerves) and lower limb (peroneal and sural nerves) were measured in 116 uremic patients. The patients were asigned to 4 groups according to the treatment (conservative, haemodialysis, intermittent peritoneal dialysis and kidney transplantation). The results were compared with measurements obtained from a control group of 40 healthy volunteers. The amplitude of cAP and the CV of nerves in uremic patients were significantly smaller than those of controls. The sensory nerves were more severely affected than the motor nerves, and cAP and CV of the nerves of the lower limb were on average smaller than those of the upper limb. Although no significant differences was found in either cAP of CV between the groups with different treatment, the patients with kidney transplantation were on average slightly better that the remaining patients. The study shows that uremic patients develop a severe peripheral nerve neuropathy that is characterized by a decrease in the number of nerve fibers and their conduction velocity.

74.09 EXPRESSION OF NR1 SPLICE VARIANTS IN THE RAT BRAIN DURING ONTOGENESIS AND FOLLOWING EPILEPSY AND CELLULAR LOCALIZATION IN TRANSFECTED CELLS.
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Two families of NMDA receptor subunits have been cloned: the NR1 and NR2 types. Functional receptors result from the combination of NR1 with either one of the NR2 (A, B, C or D) subunits. Eight NR1 isoforms are generated by alternative splicing. Such isoforms are characterized by the presence or absence of one or two insertions in their N- and C- terminal regions, respectively. We are interested in the distribution of these isoforms in the developing and epileptic rat brain, as well as their cellular localization and specific electrophysiological features. We have studied by RT-PCR and in situ hybridization in the developing and adult rat brain the expression of the mRNA of the N- and C-terminal splice variants. Our results show specific spatial and temporal changes of both transcripts with different distribution patterns. Levels of the same transcripts seem to be slightly modified in the epileptic rat brain. We have also studied the cellular distribution of NR1.1a and NR1.4a, two C-terminal splice variants, in transfected HEK 293 cells. Using an anti-NR1 antibody directed against an epitope common to both subunits we show that NR1.1a and NR1.4a have different cellular distributions. The NR1.1a is diffusely detected throughout the cell in contrast with the punctuated aspect of the NR1.4a.

74.10 CEREBRAL BLOOD FLOW INCREASES IN THE LIMBIC SYSTEM OF CONSCIOUS HUMANS DURING CO_2-STIMULATED BREATHING.
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Carbon dioxide (CO_2) is a potent vasodilatator and is widely used for increasing cerebral blood flow (e.g. in patients with cerebrovascular disease). Additionally, CO_2 causes dyspnoea and stimulates breathing. The contribution of supra-brainstem structures in the ventilatory response to CO_2-induced dyspnoea is unknown and needs to be investigated.

Using positron emission tomography (PET) with $H_2{}^{15}O$ to assess changes in relative regional cerebral blood flow (rCBF) we identified areas of neuronal activation during CO_2-stimulated breathing in 5 naive male volunteers. Group data were analyzed using Statistical Parametric Mapping (SPM; Wellcome Department of Cognitive Neurology, London). Anatomical location of activation sites was obtained using the Talairach & Tournoux standard stereotactic space.

Group data analysis revealed significant ($P<0.05$, corrected for multiple comparisons) increases in relative rCBF during CO_2-stimulated breathing within the hippocampus and parahippocampus, cingulate area, upper brainstem, midbrain/hypothalamus, insula, frontal, temporo-occipital and parietal cortex, and the cerebellar vermis.

rCBF increases within the limbic system suggest, that this system is involved in the sensory/and or motor response to CO_2-induced dyspnoea in awake man.

We are grateful to Prof. Frackowiak and Dr. Friston (Wellcome Deptartment of Cognitive Neurology, London) for advice and SPM software.

74.11 LESION-INDUCED CHANGE IN CHONDROITIN SULFATE PROTEOGLYCAN EXPRESSION IN THE ADULT RAT CEREBELLUM.
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Proteoglycans (PGs) are a group of macromolecules formed by glycosaminoglycan (GAG) chains covalently attached to a core protein. Chondroitin sulfate proteoglycans (CSPGs) carry three types of GAG chains which are a sequence of unsulfate, 4-sulfate or 6-sulfate disaccharides. The degree and type of sulfation characterize three types of CSPGs: unsulfate proteoglycan (COSPG), 4-sulfate proteoglycan (C4SPG) and 6-sulfate proteoglycan (C6SPG). C4SPG was detected at both light and electron microscopy using the 2B6 monoclonal antibody in adult male Wistar rat brain. C4SPG was distributed in the hindbrain at neuronal perikarya of the lateral reticular, external cuneate, pontine and superior vestibular nuclei. In the cerebellum, C4SPG immunoreactivity (ir) was localized in Purkinje, Golgi and granular cells. Occasionally, C4SPG-ir was also associated with mossy fibers. Following a unilateral injection of kainic acid in the crus I ansioform lobule of the cerebellum, neurons near to the injection site did not show C4SPG-ir. Instead, a strong immunoreactivity to both COSPG and C6SPG was detected surrounding Purkinje and Golgi cells. At the electron microscopy, COSPG- and C6SPG-ir were associated to the plasma membrane of the cell soma and dendritic processes of neurons as well as in presynaptic terminals. In conclusion, a change in CSPG expression occurs in the adult rat cerebellum following chemical injury. While the expression of intracellular CSPG is dramatically reduced, Purkinje and Golgi cells near to the injection site recapitulate their expression of extracellular CSPGs.
(Supported by DGICYT PB92-0198 and FIS 92/0269)

74.12 THE RELEASE OF AMINO ACIDS FROM THE RAT STRIATUM (STR) AND SUBSTANTIA NIGRA (SN) *IN VIVO*
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Previous studies using dual probe microdialysis have demonstrated that it is possible to stimulate the release of GABA from the STR by local application of the excitatory amino acid receptor agonist, kainic acid (KA), and to detect at the same time the release of GABA from the ipsilateral SN (Bianchi et al 1994). The object of the present experiment was to examine the release of endogenous aspartate (ASP), glutamate (GLU) and taurine, as well as GABA, under similar conditions. Rats were implanted with microdialysis probes in the STR and in the SN pars reticulata. 24 hours later, the probes were perfused with artificial CSF (1.2 µl/min). The STR was perfused with 100 µM KA alone or in the presence of 10 µM DNQX or 3 µM tetrodotoxin (TTX). Fractions (20 min) were collected for 2 h before, and up to 3h after the KA perfusion. Following derivatisation and separation (hplc) the amino acids were detected fluorometrically. KA in the STR stimulated the release of the amino acids from both the STR and the distal probe in the SN. The local release of GLU, ASP and GABA was attenuated in the presence of DNQX or TTX suggesting that the release was, at least in part, receptor-mediated and dependent on action potentials. The release of taurine in the STR was greater but was *not* affected by the DNQX nor TTX. In contrast, the release of taurine from the distal probe in the SN followed a similar pattern to that of GABA and GLU (but not ASP), i.e. it was abolished by TTX and DNQX. This implies that the release of GABA, GLU and taurine in the SN following stimulation of the STR is dependent upon the activity of striatofugal neurons. The nature of the release of taurine in the STR is unknown but may be related to activity of glial cells and/or osmoregulation.
Supported by the EU (BIOMED grant BMH1-CT94-1402) & grants from CNR and MURST (IT)

74.13 FACTORS THAT INFLUENCE PROLIFERATION AND DIFFERENTIATION OF MUSCLE SATELLITE CELLS IN PRIMARY CULTURE
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Satellite cells, the immediate precursors of muscle fibers, play a key role in muscle regeneration after damage. Following injury they are activated to proliferate and subsequently differentiate to fusion-competent cells that form myotubes which develop into muscle fibers. We studied factors that may promote their proliferation and differentiation. We developed a primary culture system for satellite cells from young and adult rats, kept in culture up to 7 days. Several factors were added; basic fibroblast growth factor (bFGF, 5-10 ng/ml), retinoic acid (RA, 10^{-8}-10^{-4} M), and ciliary neurotrophic factor (CNTF, 3-100 ng/ml). Methylprednisolone (MP, 10^{-9}-10^{-5} M) was studied in view of its possible role in the treatment of Duchenne Muscular Dystrophy. Their effect on proliferation was measured with a bromodeoxyurine ELISA. Creatine kinase activity was used as marker for myogenic differentiation.

Proliferation and differentiation increased linearly over 4 days. RA (10^{-8}-10^{-4} M) inhibited proliferative activity of both young and adult satellite cells, max. 30% after 4 days, and promoted differentiation, as indicated by increased CK activity. bFGF (5-10 ng/ml) stimulated proliferation (25%) and did not affect differentiation. MP decreased the proliferative activity but had no effect on differentiation. CNTF had no effect at all. This model enables us to study satellite cell dynamics, influenced by factors that may play a role in therapy for neuromuscular disease.

75.01 HYPERBRAIN: MULTIMEDIA EDUCATIONAL SOFTWARE FOR NEUROSCIENCE USING CD-ROM AND VIDEODISC.

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Educational multimedia software is constantly evolving and improving. HyperBrain began in 1988 with the first release of HyperCard. It has continued to be Macintosh based, the newest version (6th) includes color digitized images, access to 20,000 still images, and 20 minutes of 3D animations and patient videos on the "Slice of Brain I" NTSC videodisc (Univ. of Utah). Most recently 540 MB of animations and still images from John Sundsten in the "Interactive Brain Atlas" CD-ROM (Univ. of Washington) have been linked to the program's text and glossary. While the software does not use all of the resources on these discs, the advantages of full screen real time video as well as a database of images presents the user with multiple resources for multimodal learning and browsing. In addition, the program has a syllabus that is also available in printed copy, animated quizzes, atlases in 3 planes, and an extensive glossary with links to both discs. Automatic menus are created to other neuroscience software programs such as Lazy Eye, Synapse the Movie, Animated Embryo, and Embryo Images. The software is left unlocked to permit translation, modification and an understanding of the scripting. Evaluation data from 100 students using the software at the University of Utah is also available over a 6 year period (n=600). All items demonstrated are commercially available from a variety of non-profit sources. The program is designed to be used in multimedia learning centers and not on an individual basis.

75.02 **VISUCARD, OTOCARD, EUROCARD** - A TUTORIAL PROJECT ON NEURO-PHYSIOLOGY FOR UNDERGRADUATE STUDENTS.

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The increasing numbers of medical students require increasing concentration on essentials when teaching Sensory and Neuro-Physiology. Providing a computer based tutorial is not only a supplement to other learning options but also allows to implement hypermedia elements to deepen the "learning experience". The present project is based on a growing set of Hypercard-Stacks related to introductory courses on Sensory and Neuro-Physiology. They can be accessed from an explanatory introduction leading to three main sections adressing topics on the Visual system, the Auditory/Vestibular System and the Neuronal System. The tutorials a) provide theoretical background on them topics, b) instructions required to perform the practical tests, and c) discuss some related clinical aspects.

Several of the stacks are designed by medical students who had first participated in introductory seminars on computer based tutorials, specifically on Hypercard. The environment also allows easy integration of stacks that become available commercially on specific topics.

This approach leads to the accumulation of teaching material in close contact to the presumptive user and connects theory to patient related observation. To provide a comprehensive teaching tool however will require professional expertise for improving interactivity and implementation of more sophisticated animations and simulations, and possibly by porting it to a multi-platform shell.

75.03 COMPUTERIZED 3-D RECONSTRUCTION OF THE RABBIT HIPPOCAMPAL REGION

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In the study of the rabbit hippocampal region we performed a computer assisted alignment procedure for alignment of images of standard histological sections. With the images aligned in a consistent matrix it is possible to simulate or "cut" artificial slices in the computer so that different planes from the same animal can be studied. This is not possible in the real histological world as the slice procedure there represents an irreversible and definite process.

The aim of the study was to map and separate histological artifacts as geometric distortion from artifacts introduced by the aligning procedure itself.

407 serial standard histological sections of the rabbit hippocampal region were digitized and computer assisted alignment was performed by an algorithm working in the PC windows environment without use of artificial landmarks.

In order to simulate the histological slicing and separation of the slices, 640 artificial frontal and sagittal slices were cut in the computer through the aligned and assembled object and the artificial frontal/sagittal slices were moved relative to each other by a random movement generator. Then the alignment procedure was repeated on the disordered artificial frontal/sagittal planes and a new set of horizontal slices were cut through this re-aligned object. Finally the new set of horizontal slices was compared with the original horizontal slices. Any difference between these two sets will be caused by the artificial slicing and aligning procedure alone because the matrix was consistent before the artificial slicing, and the errors introduced by the alignment itself can be estimated.

75.04 TWO COMPUTER PROGRAMS FOR FAST ANALYSIS OF MOTOR FUNCTION AFTER EXPERIMENTAL PERIPHERAL NERVE AND SPINAL CORD LESIONS

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In the investigation of therapies that might enhance peripheral nerve regeneration, the Sciatic Functional Index (SFI, de Medinacelli & al, Exp.Neurol.1982:77;634) is much used. This index is a measure for the degree of asymetry between experimental and normal hind paw function during walking. The SFI is computed from several parameters such as step length, print length, distance between toes I-V and II-IV from the free walking pattern as recorded on photographic paper. Measuring these parameters by hand is a tedious job and prone to errors. We have written a computer program for PC that uses a digitizer tablet to enter these parameters. Data are written to disk and can be imported by word processors and spreadsheet programs.

After (mild to moderate) experimental spinal cord injury (ESCI), motor function in the hind quarters of the rat disappears. After several weeks function returns and one measure for this is the height of the back. The highest point of the back is normaly the thoracolumbal region. We measure this height by automatic video analysis during the walk of an animal along a corridor. The thoracolumbal region of the animals back is marked with black ink. The walking rat is observed by a video camara connected to a PC equipped with a frame grabber. Fifty times a second, the thoracolumbal height is measured and the resulting trace is stored on disk. The maximal height reached is given directly but more extensive analysis can be performed offline.

These programs are a great help in the analysis of functional recovery from nervous system injury.

75.05 AN IMAGE-PROCESSING SYSTEM TO DISTINGUISH DIFFERENT RESIDENT-INTRUDER INTERACTIONS IN A COLONY OF RATS.

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An video tracking and motion analysis system was developed which is able to track 4 rats living in a colony situation. The system the individually identifies the rats by means of a colour mark applied to their dorsal fur. A female and a male intruder were introduced into the colony and observed by the automated system for a period of 45 minutes. The X,Y-coordinates corresponding to the spatial locations of the rats were stored on file and used to quantify the temporal and spatial characteristics of the interactions between the residents and female or male intruder. Human observations, conducted over a period of 10 minutes, were compared to parameters calculated from the X,Y-coordinates. These parameters are: travelled distance, average distance between rats, dyadic net movement-towards/movement-from and the frequency with which the distance between members of a dyad fell within a certain range. The relative hierarchical position of residents and behavioural differences as determined by the human observer, were replicated by the automated system.

75.06 EXPERIENCES IN EARLY LIFE: DETERMINANTS FOR ADULT SOCIAL BEHAVIOR

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The reaction of an organism to environmental challenges depends on the properties of the situation, genetic composition of the individual and experiences in "critical periods" during development. In this study we have altered the adult social behavior of male Wistar rats by interefering with their social experience in the first three weeks of during week 4 and 5 of age. Pups demonstrated preference for their "own" nest during the first three weeks of life. During week 4 and 5 young rats are motivated to frequently display play behavior. To study the long-term function of this preference and play behavior pups have been changed from one nest to another in order te prevent bonding to their "own" nest. In week 4 and 5 young rats have been isolated in order to prevent the display of play behavior. Pups who had been daily changed from one nest to another showed a delay in copulatory behavior, an alterd performance (gender dependent) in the elevated plus maze and increased alterness in a shock prod-burying task. Young animals deprived of the possibility to play had severe problems with coping with the offensive behavior of another dominant male. Both a decrease in freezing behavior and an increase in plasma corticosterone levels have been observed in these animals. Apparently, the nature of social experience of young rats has far reaching consequences for their social behavior in adulthood.

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