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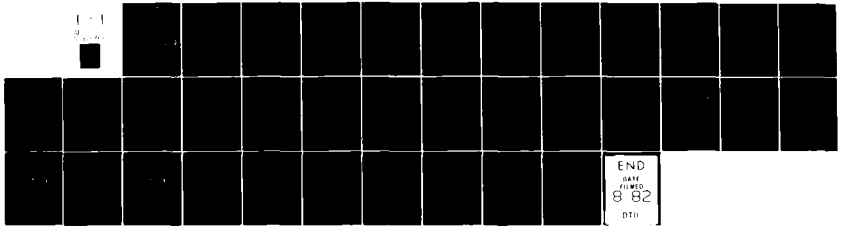

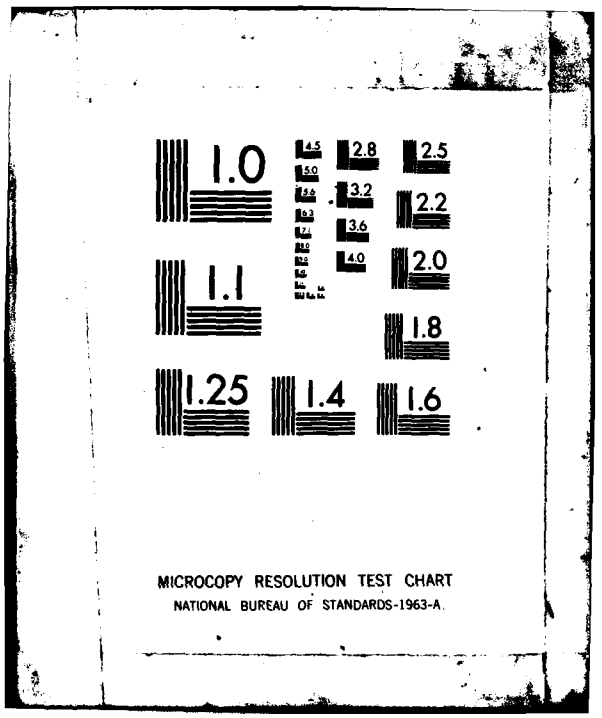
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In order to clarify the role of norepinephrine (NE) in visual cortical plasticity, we monocularly deprived kittens that had received systemic injections of the neurotoxin, 6-hydroxydopamine (6-OHDA), shortly after birth. We found, using high pressure liquid chromatography, that this means of drug treatment produces a permanent and substantial reduction in the level of cortical NE as compared with littermate controls. Nonetheless, single unit recording in area 17 of these kittens revealed no difference in the cortical response to monocular deprivation: both drug-treated and control kittens

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displayed large ocular dominance shifts to the open eye.

Because local depletion of NE by intracortical 6-OHDA in kittens can prevent the expected ocular dominance shift after short-term monocular deprivation, we conclude that neocortex has the capacity to compensate for chronic depletion of NE in a way which allows for the possibility of plastic changes.

THE PLASTIC RESPONSE TO MONOCULAR DEPRIVATION PERSISTS AFTER CHRONIC DEPLETION OF NOREPINEPHRINE IN KITTEN VISUAL CORTEX[1]

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ABSTRACT

In order to clarify the role of norepinephrine (NE) in visual cortical plasticity, we monocularly deprived kittens that had received systemic injections of the neurotoxin, 6-hydroxydopamine (6-OHDA), shortly after birth. We found, using high pressure liquid chromatography, that this means of drug treatment produces a permanent and substantial reduction in the level of cortical NE as compared with littermate controls. Nonetheless, single unit recording in area 17 of these kittens revealed no difference in the cortical response to monocular deprivation: both drug-treated and control kittens displayed large ocular dominance shifts to the open eye.

Because local depletion of NE by intracortical 6-OHDA in kittens can prevent the expected ocular dominance shift after short-term monocular deprivation, we conclude that neocortex has the capacity to compensate for chronic depletion of NE in a way which allows for the possibility of plastic changes.

INTRODUCTION

Several features of the noradrenergic innervation of the cerebral neocortex have focused interest on it's role in cortical development and plasticity. First, the noradrencergic axons from the locus coeruleus (LC) are likely to be the first extrinsic input to the cortical mantle, arriving well before birth (Levitt and Moore, 1979). Second, the tangential organization of this projection and the widespread collateral distributions of single LC axons allow the simultaneous release of norepinephrine (NE) in vast cortical fields (Morrison et al., 1981). Third, converging anatomical (Decarries et al., 1977) and biochemical (Reader et al., 1976) evidence suggest that NE can evoke a physiological response at sites distant from the point of release. Finally, the physiological action of NE in the neocortex is largely mediated by beta receptors (Minneman et al., 1979) and ultimately leads to an increase in the level of cyclic adenosine monophosphate (cAMP) in the target neurons. The exact consequences of increasing intracellular levels of this cyclic nucleotide in cortical neurons are not well understood, but cAMP could play a major role in cytodifferentiation, both in developing and mature cells (McMahon,1974).

Striate cortex, area 17, of the cat has proven to be a valuable system for the study of postnatal cortical development. This system offers several important advantages. First, the normal organization of adult striate cortex is relatively well understood and a strong data base exists on the postnatal development of the physiological properties of visual cortical neurons. Second, highly reproducible physiological and anatomical changes may be induced by simple environmental deprivation paradigms, such as, monocular lid closure, during a critical period that extends from approximately 3 weeks to 3 months of age (Hubel and Wiesel, 1970). Finally, the functional connectivity of striate cortex may be conveniently measured with the physiological assay of ocular dominance introduced by Hubel and Wiesel (1962). Using this system Kasamatsu, Pettigrew, and co-workers have investigated the contribution of the locus coeruleus to visual cortical plasticity. They

have employed the pharmacological agent, 6-hydroxydopamine (6-OHDA), a neurotoxin relatively specific for catecholamine-containing nerve terminals (Ungerstedt, 1968; Bloom et al., 1969; Uretsky and Iverson, 1970). These authors report that the depletion of cortical NE in kittens by either intraventricular (Kasamatsu and Pettigrew, 1979) or intra-cortical (Kasamatsu et al., 1979) administration of 6-OHDA prevents the ocular dominance shift that normally results from monocular deprivation during the critical period. Moreover, when NE is replaced by continous microperfusion, the cortex will again respond normally to environmental modification (Kasamatsu et al., 1979). These results led Kasamatsu and Pettigrew to hypothesize that the normal catecholaminergic innervation of cerebral cortex is required for developmental plasticity.

It is now clear that several mechanisms, acting independently or in concert, can account for a shifted ocular dominance histogram after monocular deprivation (see Movshon and Van Sluyters, 1981, for review). These include competition for synaptic territory by geniculate fibers (Guillery, 1972; Hubel et al., 1977) and intracortical suppression of the deprived eye responses (Kratz et al., 1976). Which mechanism predominates depends critically on the length of deprivation and the age at which deprivation is initiated (LeVay et al., 1980). An important step in defining the role of the noradrenergic innervation in visual cortical plasticity is to identify which of these mechanisms require NE. Unfortunately, this inquiry has been confounded by limitations in the techniques employed to deplete catecholamines. For example, the intraventricular dose of 6-OHDA required to deplete cortical NE adequately causes severe behavioral side-effects such as: sham rage, compulsive turning, and even grand mal seizures (Kasamatsu and Pettigrew, 1979). Although these problems are avoided when 6-OHDA is applied intracortically by a minipump - cannula system (Kasamatsu, et al., 1979), the NE depletion produced by this technique is local and not uniform (Kasamatsu et al., 1981). This restricts neurophysiological analysis to a limited sphere of depleted tissue surrounding

the cannula site and also complicates the biochemical confirmation of catecholamine depletion. Furthermore, both techniques limit the onset of monocular deprivation to ages when the surgical implantation of cannulae in cortex is feasible.

An alternative means to uniformly deplete cortical norepinephrine from birth has been well documented in rodents; namely, the systemic injection of neonates with 6-OHDA (Clark et al., 1972; Sachs and Jonsson, 1975). During the first postnatal week, the drug has access to the entire nervous system since the blood-brain barrier is incompletely formed at this age (Sachs, 1973). This treatment in rats lead to a pronounced and irreversible depletion of cortical NE In contrast, the noradrenergic innervation of subcortical structures rapidly regenerates (Sachs and Jonsson, 1975). We elected to try this paradigm for catecholamine depletion in kittens in an attempt to further test the idea that NE is required for visual cortical palsticity.

In this paper, we provide biochemical evidence that the cerebral cortex of kittens can be drastically depleted of norepinephrine with neonatal injections of 6-OHDA. In addition, we present physiological results indicating that visual cortex depleted of NE by this technique will nonetheless respond normally to monocular deprivation during the critical period. These results considered with those of Kasamatsu and Pettigrew, suggest that compensation for the lost NE may occur in kittens chronically depleted from birth.

METHODS

Drug Treatment and Lid Closure

A total of six litters of kittens (21 animals) from our quarantined colony of wild-type queens was used in this study (Table I). Approximately half the animals in each litter received intraperitoneal injections of 6-OHDA-Hcl (Sigma) dissolved in saline with 0.1% ascorbate. The remaining animals received vehicle injections and served as controls. All injections were performed blind, such that at the time of physiological recording, the investigators had no knowledge of the animal's drug history. It was found after several pilot animals, that the most effective dose was 200 milligrams 6-OHDA per kilogram of body weight, injected twice with a 24-hour interval on postnatal days one and two (Table I). After each injection, the kittens were returned to their mothers for normal rearing.

All kittens but four received monocular lid sutures under anesthesia (ketamine-acepromazine) ten days before the neurophysiological recording session. Ages at the time of lid closure ranged from 26-39 days (Table I). The remaining four animals were monocularly deprived from shortly after birth. Sutured lids were inspected daily and any windows promptly repaired.

Physiological Preparation

Animals were prepared for extracellular recording by standard techniques (Daniels, et al., 1978). Ketamine-acepromazine (25 mg/kg and 3 mg/kg respectively) anesthetized kittens received tracheal intubation, venous cannulation, scalp incision and craniotomy. The animals were secured in a mocified stereotoxic fram, 114 cm from a tangent screen. Paralysis was maintained by a continuous infusion of 12 mg/kg/hr of gallamine triethiodide (Flaxedil) and artifical respiration of 70% nitrous oxide, 28% oxygen, and 2% CO_2 maintained anesthesia throughout the experiment. EEG, body temperature, heart rate and expired CO_2 levels were continuously monitored.

Pupils were dilated with atropine and contact lenses were fitted to provide a slight positive correction and to prevent corneal drying. Optic discs were viewed with an opthalmascope and two observers marked the approximate projection of these landmarks onto the tangent screen. For the age of the kittens we worked with, a 20° inward and 10° downward standard, was employed to mark the respective area centralae (Olson and Freeman, 1980).

Single Unit Recording

Tungsten in glass microelectrodes (Levick, 1972) were fitted into our dual microdrive advance which allows stimultaneous recording from both hemispheres. Each electrode was positioned over the area centralis representation in area 17 and was passed anteriorly and ventrally down the crown and medial wall of the postlateral gyrus. Extracellular action currents were monitored through a variable filter system producing optimal signal-to-noise ratios for audio detection of cell discharges. Single unit data were collected from each hemisphere approximately every 100 microns.

Slit and spot visual stimuli, projected by independent systems onto the tangent screen were manipulated by two joystick controllers. The length, width and orientation of the slit stimulus, and the diameter of the spot, were variable. A footswitch controlled a shutter in each projector. With these stimuli, receptive fields of visually responsive cells were plotted and ocular dominance discriminations were made according to the criteria introduced by Hubel and Wiesel (1962). In addition, disparity of binocular cells, ON-OFF properties, and speed preferences were noted.

Neuronal selectivity for the direction of an oriented bar moved across the receptive field was classified as either aspecific, immature or specific (modified from Fregnac and Imbert, 1978). By our criteria aspecific cells respond within a factor of two to all directions of movement; immature cells respond to movement in all directions, but respond to a preferred direction two-times greater than

the minimum response; and specific cells, besides having a clearly preferred direction, will not respond to all directions (i.e. they have a null direction). We feel that this scheme allows the rapid and reliable classification of neurons without requiring the time-consuming generation of tuning curves.

Following the 36-hour recording session, the animals were sacrificed by a lethal intravenous dose of potassium tartrate followed by perfusion through the ascending aorta with saline. The brains were rapidly dissected and samples taken for biochemical analysis were frozen on powdered dry ice. Tissue samples always included the cerebellum and the visual cortex from one hemisphere. The cortical sample included areas 17, 18 and 19, and had a mean wet weight of 1.46 grams ($\pm$0.05 g, standard error). These tissues were stored overnight in a freezer at -30°C until the catecholamine purification procedure could be performed. The remaining hemisphere was preserved in 10% formaldehyde containing 30% sucrose for histological analysis.

Biochemistry and histology

Tissue catecholamines were measured by high pressure liquid chromatography (HPLC) with electrochemical detection. Samples were weighed, homogenized in 0.1M percholoric acid containing 0.1mM EDTA, and centrifuged to remove denatured protein. Dihydroxybenzlamine, a catecholamine with a different retention time in the HPLC system than any of the naturally occurring catechols was added to the perchloric acid supernatant as a standard to monitor recovery. Catechol compounds in the supernatant were then purified by a batch aluminum oxide chromatography technique, based on a column procedure described by Anton and Sayre (1962). An aliquot of the alumina-purified sample was applied to a high pressure liquid chromatography column (Biophase ODS, 5 um-Bioanalytical Systems, Inc.), which separates, in order of increasing retention time, norepinephrine, dihydroxybenzlamine, and dopamine from each other. The catechols were eluted off the column

with a 0.1 M monobasic sodium phosphate buffer containing 0.13 mM sodium octyl sulfate, 0.1 mM EDTA and 4% methanol. Buffer pH was adjusted to 2.6 with phosphoric acid. The electrochemical detector oxidized the catechol compounds and the subsequent currents were measured (Keller et al., 1976). Tissue concentrations of norepinephrine and dopamine were calculated and expressed as nanograms compound per gram tissue, wet weight. For each HPLC run, a "least detectable" NE amount was computed from the recovery values.

Formalin fixed hemispheres were cut on a freezing microtome in the coronal plane at 50 microns. Sections were mounted on glass slides, hydrated, stained with cresyl violet acetate, dehydrated, cleaned in xylene and coverslipped. Electrode tracts and marker lesions were reconstructed. Any units obtained from adjacent area 18 were discarded from ocular dominance histograms.

RESULTS

Biochemistry

The biochemical results shown in Figure 1 clearly confirm that neonatal administration of 6-OHDA is effective in depleting the cortical catecholamines in kittens. On the left side of Fig. 1, the tissue concentrations of catecholamines, expressed in nanograms per gram tissue wet weight, are plotted against the age of the animal at the time of sacrifice for both treated and control animals. No clear age-dependant changes in cortical dopamine (DA), cortical norepinephrine, or cerebellar norepinephrine are seen in either group of kittens in the age window we have examined. These data are recast in the histograms on the right side of Fig. 1 and also appear in Table II.

Visual cortex: norepinephrine (Fig. 1 middle panel). Drug-treated animals with detectable levels of NE had less than 5% of control cortical norepinephrine. In several kittens, NE was not detected in cortex at all, but least detectable amounts were relatively high (Fig. 1, asterisks). These points raise the calculated mean level of cortical NE in drug-treated animals to less than or equal to 11% of control. The control mean of cortical NE (105 + 17 ng/g) agrees well with that reported in the literature (Kasamatsu, Itakura and Jonsson, 1981) for kitten visual cortex.

Visual cortex: dopamine (Fig. 1, upper panel). While the cortical NE was at least 89% depleted in 6-OHDA treated kittens, cortical DA levels were as high as 51% of control. This is biochemical support for the existence of a separate dopaminergic projection onto feline visual cortex (Tork and Turner, 1981). As reported previously in the cat (Kasamatsu, et al., 1981), dopaminergic terminals are notably less susceptible to 6-OHDA than are noradrenergic terminals. In fact, two 36-day old, drug-treated kittens (K119 and K131) had cortical DA in the normal range despite the over 95% depletion of NE.

Cerebellum: norepinephrine (Fig. 1, lower panel). NE levels in the cerebellum were measured as an index of the extracortical effects of the 6-OHDA treatment. In rats, Kostrzewa and Garey (1975) found that after an initial depletion of less than 50% at two weeks postnatal the cerebellar NE content in 6-OHDopa treated animals increased to over 150% of control levels by eight weeks of age. There is no evidence for such a recovery in the cerebellum of the drug-treated kittens. In the age window we have studied, from five to eight weeks of age, the cerebellar NE in 6-OHDA treated kittens is only 40% of control.

Behavioral observations

Kittens treated with 6-OHDA by intraventricular injections suffer from severe behavioral side-effects such as sham rage, seizures and incontinence as well as aphagia and loss of body weight (Kasamatsu and Pettigrew, 1979). Although many of these side-effects are eliminated when 6-OHDA is delivered intracortically by a minipump-cannula system, drug-treated animals are nevertheless noticably listless and exhibit substantial weight loss (personal observation). In figure 2, body weight is plotted against age for kittens recorded in the present study. It appears that the rate of weight gain in kittens treated with 6-OHDA at birth falls within the normal range. Moreover, simple tests for visuo-motor reflexes and casual behavioral observations revealed no difference between experimental and control kittens.

Despite the lack of behavioral manifestations of neonatal 6-OHDA treatment, drugged animals did show an unusually high mortality rate (over 35%). Although two animals died within two days of the injection, one died unexpectedly after one month and another was over three months of age at the time of death. Postmortem examination of these animals uncovered no obvious pathology.

Single unit recording after monocular deprivation.

Monocular deprivation from the time of eye opening. Figure 3 illustrates ocular dominance and selectivity data from a pair of littermates, monocularly deprived from just after birth. K127 received i.p. injections of 6-OHDA (200 mg/kg) on postnatal days one and two. K129 served as the vehicle-injected control. We recorded from these kittens within three days of each other, on postnatal days 54 and 57 respectively. Reconstructed electrode tracts are shown in Fig. 4. The histograms in Fig. 3 are composities of data recorded from both hemispheres. The upper panel illustrates the ocular dominance histograms from these two kittens. Both histograms display a large ocular dominance shift to the open eye and no significant difference with regard to binocularity is observed between the two. The bottom of Fig. 3 illustrates the relative numbers of direction selective cells. Although both kittens have similar numbers of aspecific cells, the drugged kitten, K127, has many fewer specific and more immature cells. Biochemical analysis of K127 confirmed the depletion of cortical NE by the 6-OHDA treatment (Table II).

Monocular deprivation for 10 days prior to recording. Results from a representative pair of littermates with ten days of monocular deprivation appear in Fig. 5. Electrode tracts are reconstructed in Fig. 6. Again both animals display a shifted ocular dominance profile. These histograms fall within the range of normal variability found after a ten day monocular deprivation during the critical period (Olson and Freeman, 1975). The distribution of direction selective neurons in the two kittens is illustrated in the lower panel of Fig. 5. In this case, both animals have similar numbers of specific cells in area 17, but the drug-treated kitten has many more aspecific and relatively fewer immature cells than the control. HPLC analysis confirmed the effectiveness of the 6-OHDA treatment (Table II).

Neurophysiology: summary. The results from ten successfully recorded kittens were consistent with these representative littermate pairs (Table III). The data from all the animals in this study are compiled and normalized in Figure 7. Both 6-OHDA and control groups display ocular dominance histograms strongly shifted in favor of the open eye. Although there is some difference in the direction selectivity histograms of the two groups, the inter-individual variation weakens the significance of this trend (Table III).

DISCUSSION

Neonatal 6-OHDA treatment in kittens

It is well documented that i.p. injections of 6-OHDA (100 mg/kg) in newborn rats will result in a permanent 90% loss of NE in the cerebral cortex (cf. Sachs and Jonsson, 1975). This procedure usually spares the subcortical projections of the locus coeruleus and in the cerebellum NE levels may actually be elevated. These regional differences probably result from the selective destruction of the cells that project to cortex (Clark et al., 1979). In this study, we provide biochemical evidence that neonatal 6-OHDA treatment is also effective in depleting kittens of cortical NE. We note, however, two differences in the way these species respond to drug treatment. First, kittens require a larger dose (2X200 mg 6-OHDA per kg of body weight) to achieve the same degree of catecholamine depletion obtained with 100 mg/kg in rats. Second, the cerebellum of kittens is also depleted of NE by this procedure. These differences may relate to the anatomical organization of the feline locus coeruleus (Chu and Bloom, 1974). The monoaminergic neurons in the cat brainstem are widely distributed, while those in rat are clustered in discrete nuclei. Thus it is possible that blood-borne 6-OHDA penetrates to different populations of catecholamine-containing neurons in these two species.

While neonatal 6-OHDA treatment results in a virtually complete destruction of the noradrenergic innervation of kitten cerebral cortex, cortical dopamine levels remain remarkably high. This suggests that dopamine plays a role in visual cortex other than simply as a percursor to norepinephrine. Reader, et al., (1979) have argued for the existence of a separate dopaminiergic projection onto visual cortex and recently Tork and Turner (1981) have demonstrated a projection to visual cortex in the cat from dopaminergic cells in the ventromedial teqmentum. Our results indicate that this system is less sensitive to neonatally administered 6-OHDA than is the noraderenergic projection.

There were no obvious differences in the behavior of 6-OHDA treated and

control kittens. We were, therefore, surprised by the high mortality of NE-depleted animals. Since both peripheral and central adrenergic mechanisms play a role in cardiovascular regulation (Doba and Reis, 1974), it is possible that the neonatal 6-OHDA treatment interferes with this vital function. We can only speculate at this point because biochemical measurements of peripheral and brainstem tissues were not made in these kittens.

Effects of monocular deprivation on kitten visual cortex depeleted of NE from birth.

In our paradigm, we found no evidence that NE-depletion alters the cortical response to monocualr deprivation. The 6-OHDA treated kitten monocularly deprived from shortly after birth (K127) displayed a virtually complete ocular dominance shift toward the open eye, as did the littermate control. To investigate shorter periods of deprivation, we monocularly deprived kittens for ten days during the critical period. We were guided by Olson and Freeman's report (1974) that this relatively brief period of deprivation will produce a reliable and significant ocular dominance shift in kittens at the height of the critical period. Again, we found that 6-OHDA treated kittens responded to monocular deprivation as vigorously as did controls: both groups displayed ocular dominance histograms strongly shifted in favor of the open eye.

Although the response properties of cortical neurons were similar in drug-treated and control kittens, we did note that NE-depleted animals sometimes had fewer direction selective neurons than control kittens of the same age. However, the wide interindividual variability obscures any clear trend. More work is still required to establish that neonatal 6-OHDA treatment has an effect on the development of direction selective neurons in kitten's visual cortex.

Relation to other studies of cortical development and plasticity after NE removal.

Several aspects of cortical development have been studied after neonatal or prenatal destruction of the ascending noradrenergic afferents. In all cases,

the anatomical changes in cortex have ranged from subtle to nonexistent. For example, Wendlandt et al., (1977) found that neonatal lesions of the locus coeruleus had no effect on the dendritic morphology of cortical neurons. Parnavelas and Blue (1981) report a small difference in the rate of synapse formation in rat visual cortex after neonatal 6-OHDA, but only during the first postnatal week. It could be argued that because the NE fibers invade the cortical mantle as early as the sixteenth embryonic day in rats, NE may only be required for aspects of the prenatal differentiation of cortex (Schlumpf et al., 1980). However, the careful study by Lidov and Molliver (1982), in which rat fetuses were systemically administered 6-OHDA, demonstrated no changes in the development of cortical cytoarchitecture, dendritic morphology or afferent innervation.

Is there a special role for NE that cannot be clearly discerned in such anatomical studies? The provocative results from Kasamatsu's laboratory would suggest that this may be the case. Kasamatsu and colleagues found that while acute 6-OHDA treatment leaves the receptive field properties of visual cortical neurons largely unaffected, the response of kitten visual cortex to monocular deprivation is altered drastically (Kasamatsu and Pettigrew, 1979; Kasamatsu et al., 1979). These authors conclude that NE acts "not by altering patterns of connections directly, but rather by altering the ease with which changes in patterns of connections can be brought about" (Kasamatsu et al., 1981, p.265).

The results form the present study appear to contradict Kasamatsu's catecholamine hypothesis of visual cortical plasticity and instead to generally support the conclusion that NE is not required for normal cortical developmental plasticity. Nevertheless, the phenomenon of decreased sensitivity of visual cortex to sensory deprivation after intracortical delivery of 6-OHDA has been reproduced by Daw and Rader (1981) and recently in our own laboratory. This apparent discrepancy probably stems from the different methods employed to deplete cortical norepinephrine.[1] Kasamatsu administered the drug intracortically,

at least one month postnatally, and depleted the cortex acutely (ten days or less before recording). On the other hand, we have administered the 6-OHDA systemically, neonatally and have chronically depleted the visual cortex of NE (over one month before recording). At the moment, more experiments are still required to pinpoint the critical difference between these two paradigms. However, if a cirtical level of NE is normally required for the appropriate cortical response to deprivation, as Kasamatsu had proposed, then some mechanism must exist to compensate for the chronic loss of cortical NE in kittens treated with 6-OHDA at birth.

Compensation for chronic NE depletion

One compensatory mechanism for chronic denervation is receptor supersensitivity (Cannon and Rosenblueth, 1949). It is well documented in rodents that destruction of the cortical NE fibers will result in an increase in beta adrenergic receptors postsynaptically (Sporn et al., 1977). Will this increase in beta receptor number compensate for the almost 90% loss of NE after neonatal 6-OHDA treatment? One in situ index of NE action on beta receptors in cortex is the measurable blood volume shifts that are provoked by direct cortical stimulation (LaManna et al., 1981). Acute locus coeruleus lesions in rats partially abolish this response. Even when beta receptor binding is maximal, two weeks after unilateral destruction of the locus coeruleus, severe abnormalities in this functional index persist (Harik et al., 1981). These data suggest that receptor proliferation and supersensitivity alone may not be capable of compensating for the loss of cortical NE.

However, Harik et al., (1981) did document a compensatory mechanism independent of receptor supersensitivity. They observed that a normal response of blood volume to cortical stimulation returned four weeks after the locus coeruleus lesion. At four weeks, NE levels were still only 10% of control and the specific beta receptor binding had returned to normal levels. The mechanism

for this recovery of function is unknown. These authors speculate that other catecholaminergic systems could sprout to occupy territory vacated by locus coeruleus terminals.

Another possible compensatory mechanism involves interactions with other known transmitter systems in cortex. For example, one input to all of the cerebral cortex releases acetylcholine (Johnson et la., 1981) which at many sites, acts in physiological opposition to NE (Krnjevic and Phillis, 1963). Thus, it is conceivable that the functional compensation for the chronic loss of cortical NE could involve a down-regulation of the cortical cholinergic system.

Regardless of the mechanism, the idea of compensation for chronic NE depletion of cortex offers an explanation that is consistent with all the available data. We propose that a critical amount of norepinephrine is necessary for the normal developmental plasticity of cerebral cortex. At the same time, we speculate that early in development, remarkably adaptive mechanisms exist which can compensate rapidly for the depletion of NE. This idea predicts that many deficits stemming from early NE depletion would only be transient. Indeed, Parnavelas and Blue (1982) have found that the difference in synapse formation in 6-OHDA-treated neonates lasts only during the first postnatal week.

FOOTNOTES

1. Because 6-OHDA depletes cortical DA as well as NE, it could be argued that dopamine, not NE, is the critical factor for plasticity, and that it responds differently in the two depletion paradigms. However, the minipump delivery of 6-OHDA and the neonatal 6-OHDA injection are both relatively less effective for destroying DA terminals than NE terminals. Kasamatsu et al., (1981) report a loss of plasticity with dopamine levels as high as 75% of control. In our animals, dopamine was only 40% of control. Furthermore, replacement experiments (Kasamatsu et al., 1979) suggest that norepinephrine is the catecholamine required for plasticity.

FIGURE LEGENDS

Figure 1: Catecholamine levels in cortex and cerebellum after neonatal 6-OHDA. On the left side, the tissue content of catecholamines is plotted against the age of each kitten at the time of sacrifice. Open circles are control kittens, closed circles are 6-OHDA-treated. Catecholamines were not detected in some tissues of drugged kittens and in these cases asterisks indicate the least detectable amount. The dotted lines show the control means, the solid lines illustrate the drug means. These data are recast in the histograms on the right side. Particularly note the degree to which visual cortical norepinephrine is depleted after neonatal 6-OHDA.

Figure 2: A plot of body weight against age for both groups of kittens. Drug treated animals (closed circles) show a normal rate of weight gain as do control kittens (open circles). This observation is consistent with the virtual absence of behavioral side-effects in the drug treated animals.

Figure 3: Ocular dominance and selectivity histograms from a pair of littermates monocularly deprived from just after birth. K127 received neonatal injections of 6-OHDA, K129 was injected with vehicle. In the upper panel, the number of cells in each of the seven ocular dominance groups are illustrated. The open circle is under the open eye group, the closed circle is under the closed eye group and the B labels the strictly binocular group (group 4). A strong shift toward the open eye is observed in both kittens. In the lower panel, the number of cells in each selectivity class are illustrated. A is aspecific, I is immature and S is specific. See Materials and Methods for the criteria for classifying neurons.

Figure 5: Ocular dominance and selectivity histograms from a pair of littermates monocularly deprived for the ten days prior to recording. K131 received neonatal injections of 6-OHDA, K132 was injected with vehicle. All conventions are as in Figure 3. A substantial ocular dominance shift is evident in both animals.

Figure 6: Drawings of a series of coronal sections to illustrate the electrode tracts for K131 and 132. The dotted line marks the 17-18 border. In K131, the electrode passed down the medial wall of the postlateral gyrus, well within the confines of area 17. The final placement of the electrode was approximately 6MM deep and 1-2MM anterior to the site of entry. In K132, the electrode passed down the crown of the postlateral gyrus for several millimeters before entering area 18. The ocular dominance histograms for these two kittens were illustrated in Fig. 5. No data from area 18 was included.

Figure 7: Summary of ocular dominance and selectivity data obtained from the kittens in this study. Of 157 cells recorded in 6-OHDA treated kittens, almost 60% were driven exclusively by the open eye. Conventions are as in Fig. 3.

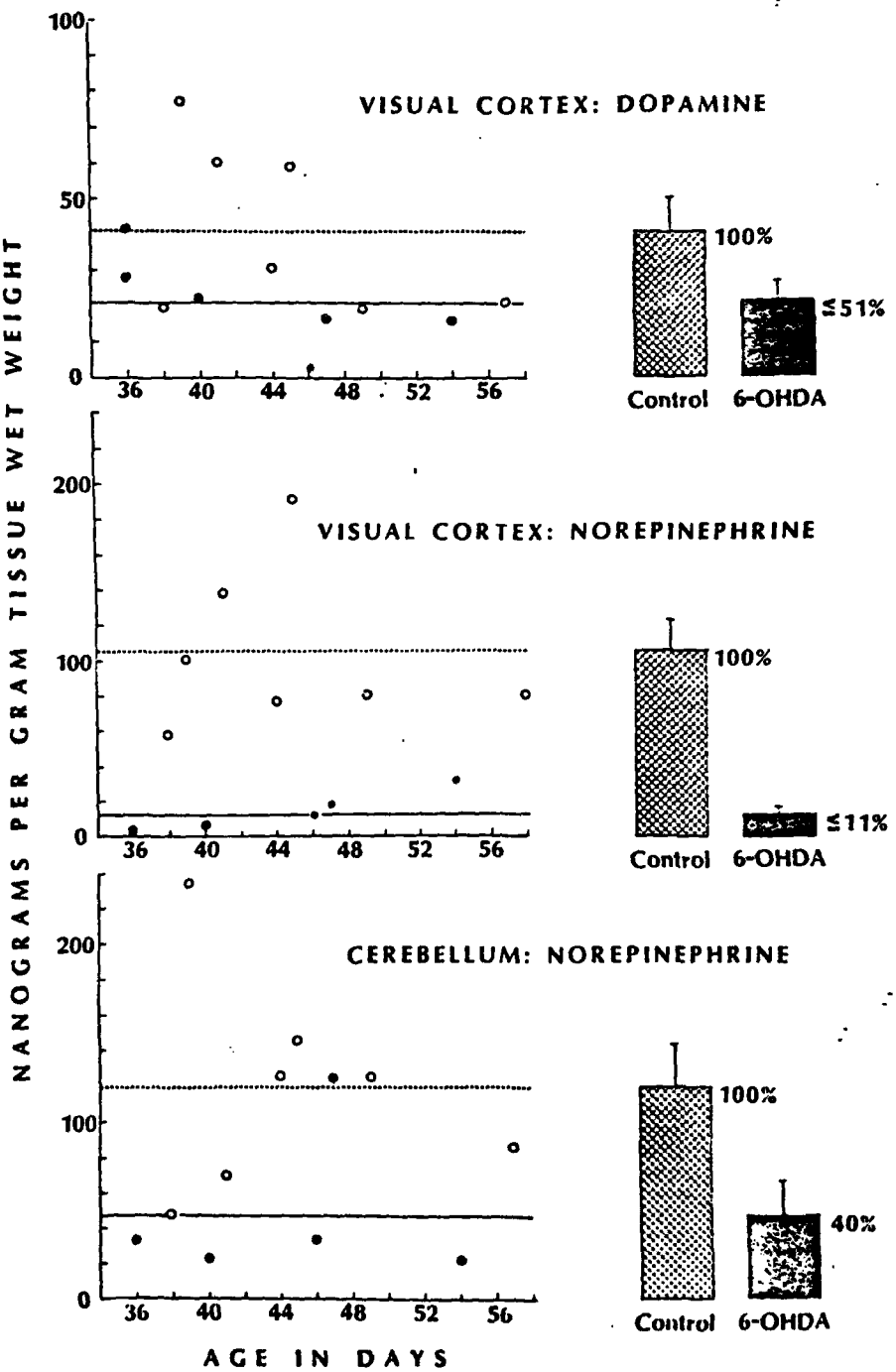
VISUAL CORTEX: DOPAMINE
100
50
0
36
40
44
48
52
56
100%
≤51%
Control
6-OHDA
VISUAL CORTEX: NOREPINEPHRINE
200
100
0
100%
≤11%
Control
6-OHDA
CEREBELLUM: NOREPINEPHRINE
200
100
0
100%
40%
Control
6-OHDA
NANOGRAMS PER GRAM TISSUE WET WEIGHT
AGE IN DAYS

FIGURE 1

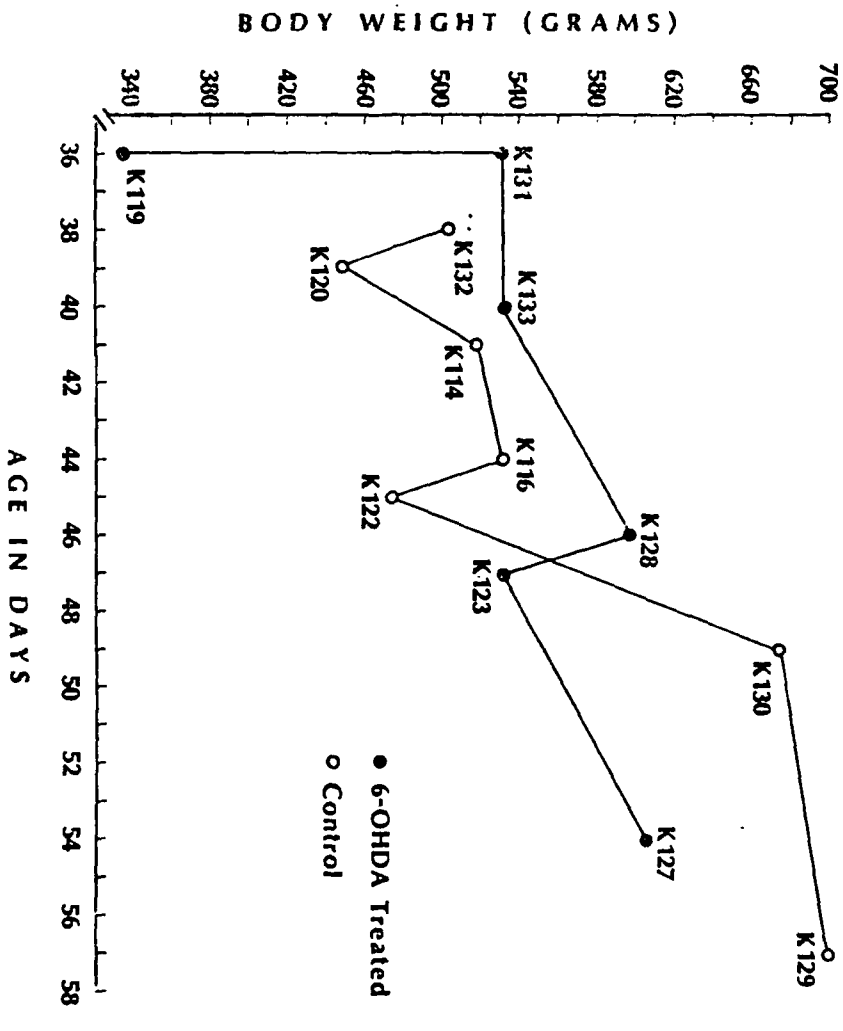
BODY WEIGHT (GRAMS)
340
380
420
460
500
540
580
620
660
700
36
38
40
42
44
46
48
50
52
54
56
58
AGE IN DAYS
K119
K131
K132
K120
K133
K114
K116
K122
K128
K123
K130
K127
K129
● 6-OHDA Treated
o Control

FIGURE 2

K 127
AGE: 54 days
MD: from birth
DRUG: 6-OHDA

K 129
AGE: 57 days
MD: from birth
DRUG: none

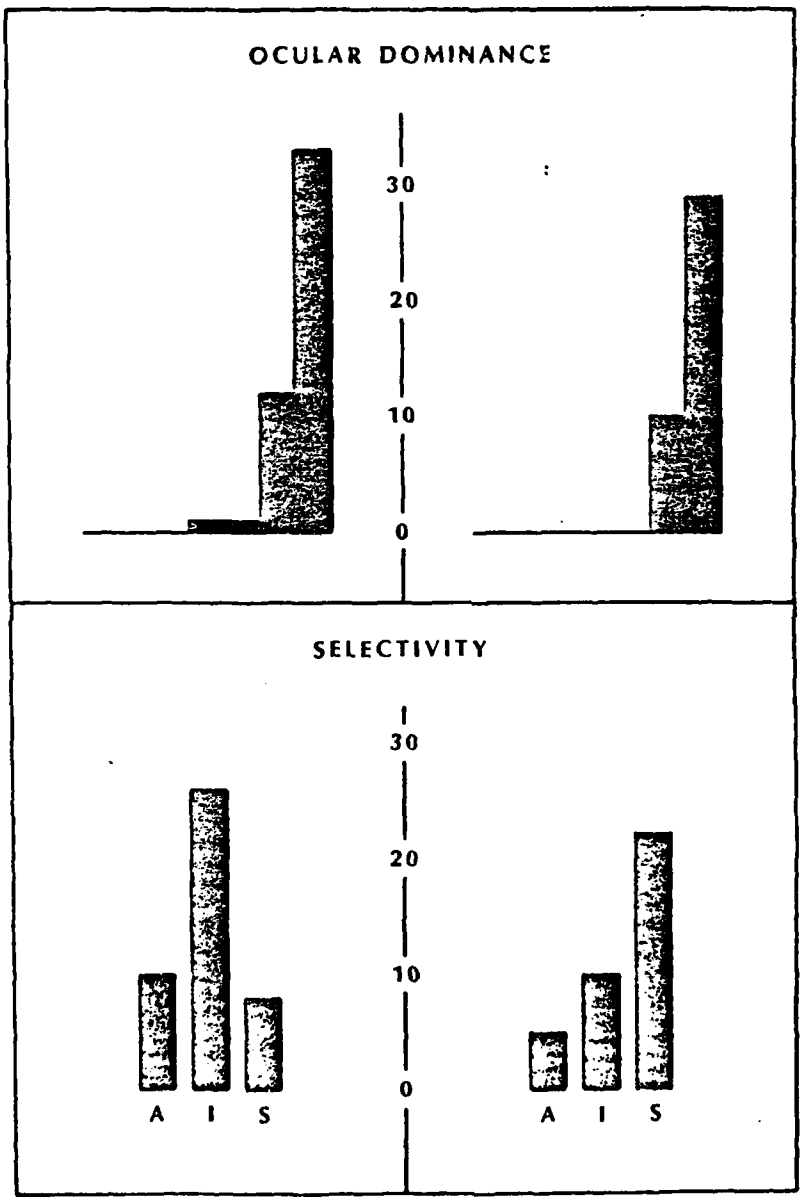

FIGURE 3

K 131

AGE: 36 days

REARING: 10 day M.D.

DRUG: 6-OHDA

K 132

AGE: 38 days

REARING: 10 day M.D.

DRUG: none

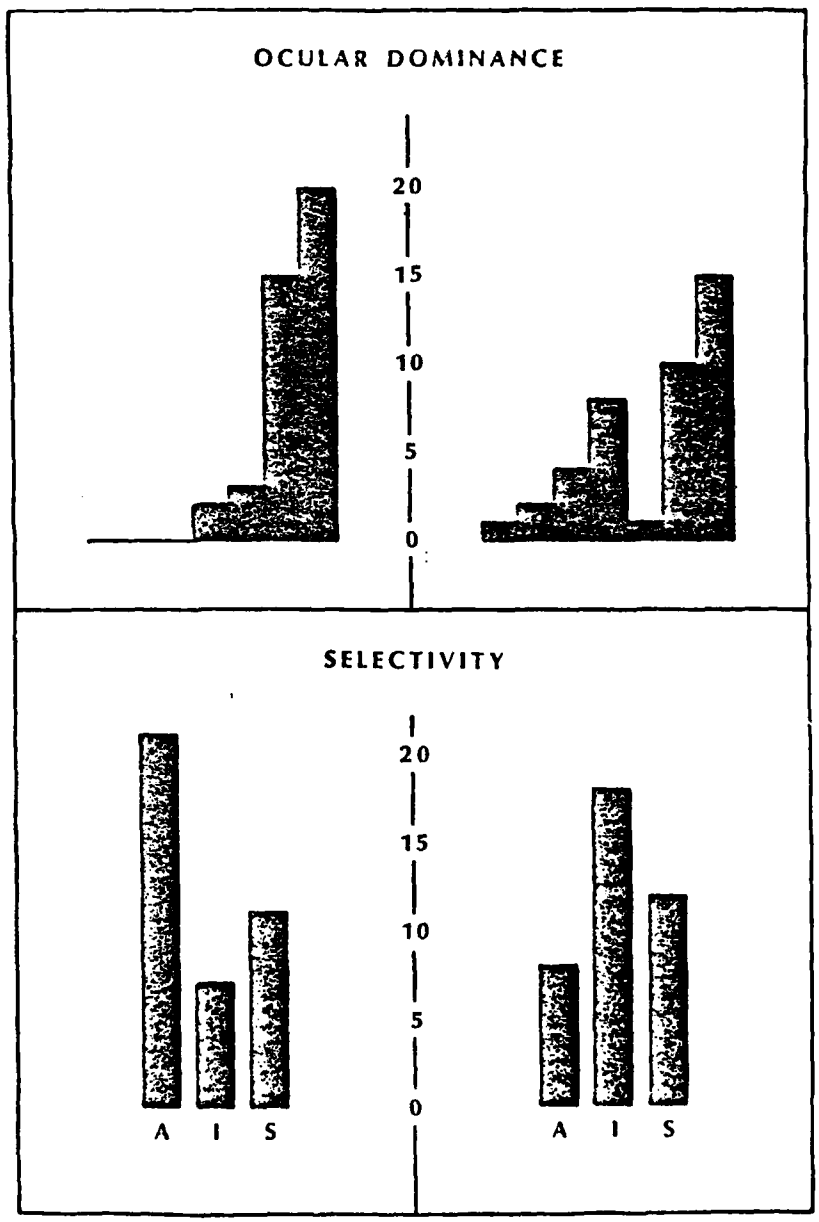

FIGURE 5

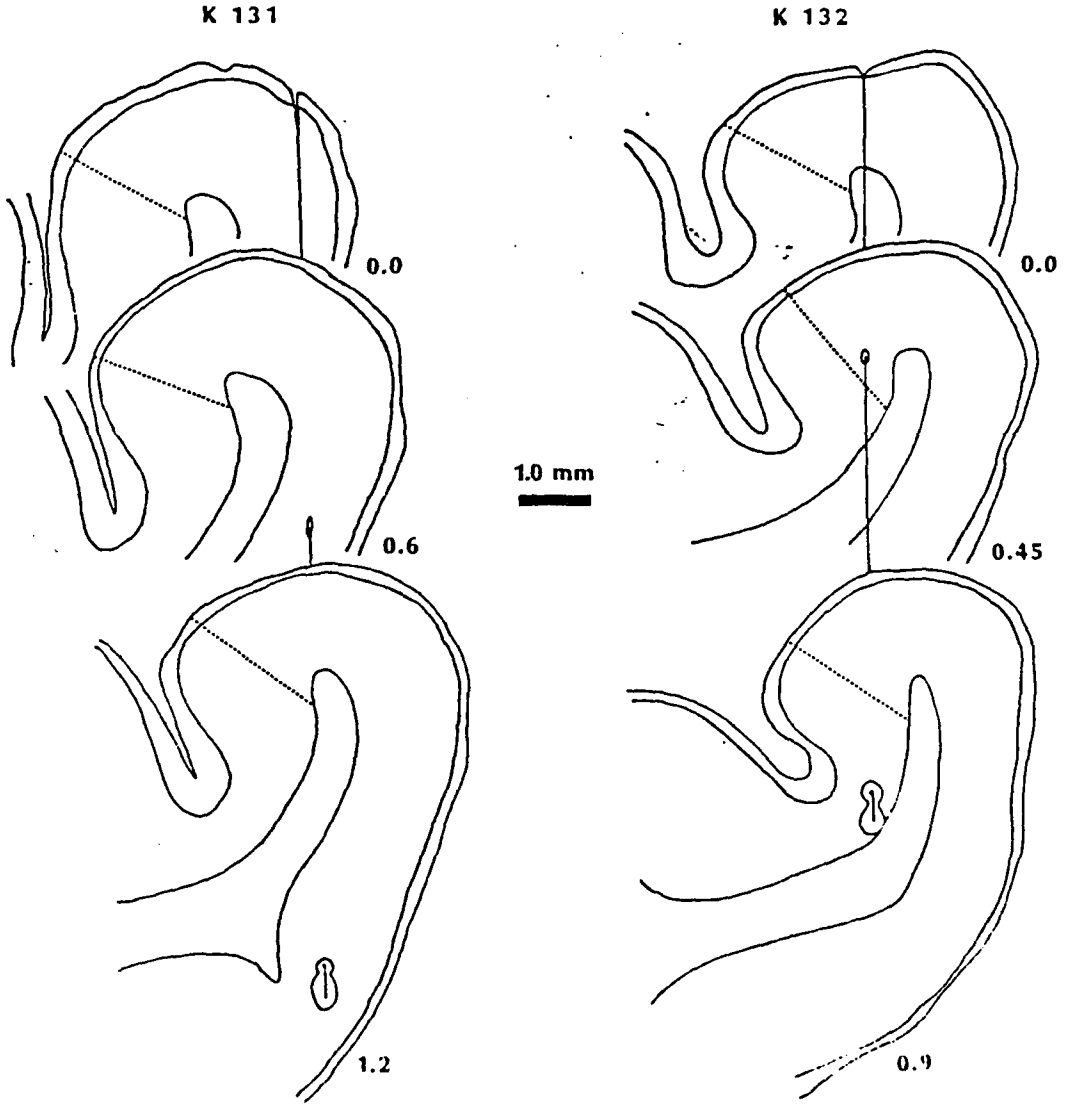

FIGURE 6

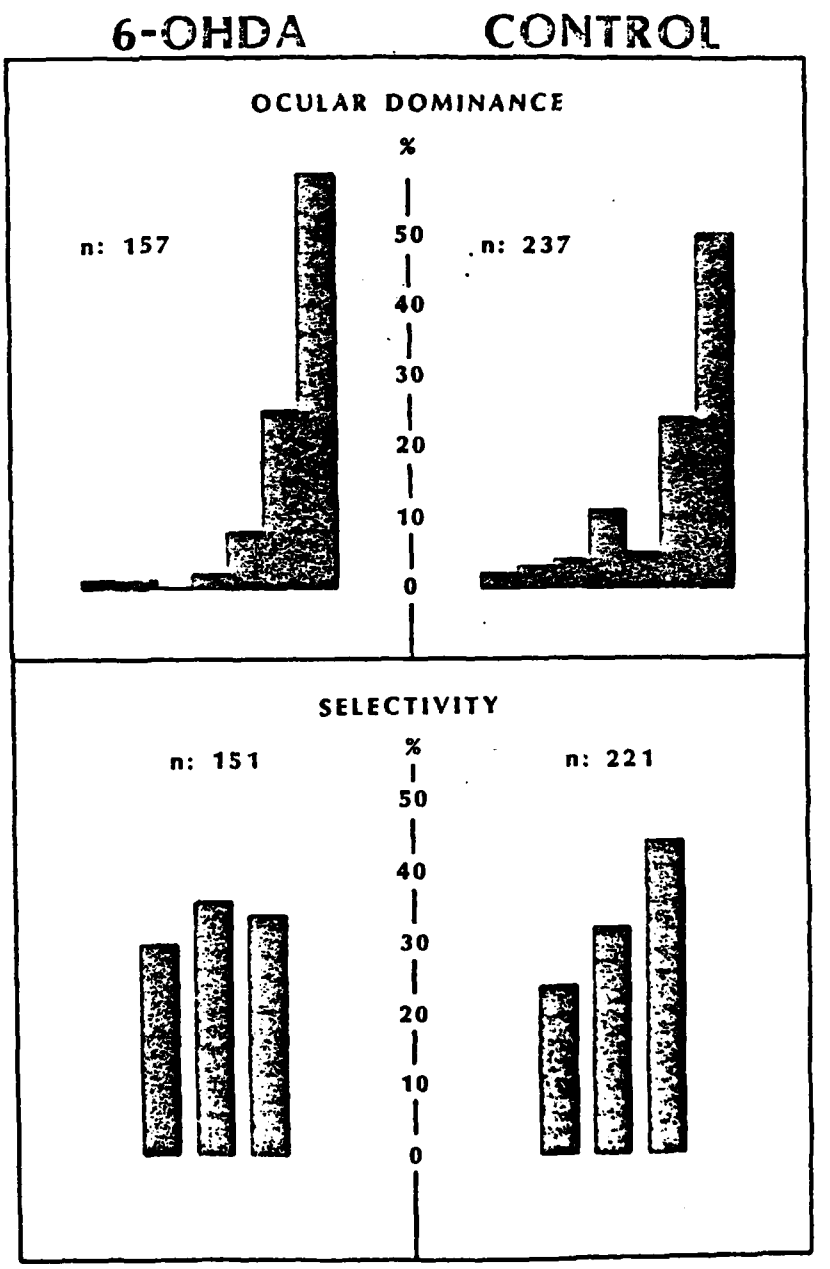
6-OHDA
CONTROL
OCULAR DOMINANCE
%
n: 157
n: 237
50
40
30
20
10
0
SELECTIVITY
n: 151
n: 221
%
50
40
30
20
10
0

FIGURE 7

TABLE I

ANIMAL HISTORY

LITTER	ANIMAL	DRUG TREATMENT	VISUAL DEPRIVATION	AGE AT RECORDING	COMMENT
#1	K 113	1 X 100	M.D. 7 days	39	pilot
	K 114	——	M.D. 7 days	41	pilot
#2	K 115	1 X 100	M.D. 10 days	42	—
	K 116	——	M.D. 10 days	44	—
	K 117	2 X 150		—	died, PND 2
	K 118	2 X 300		—	died, PND 2
#3	K 119	2 X 200	M.D. 10 days	36	——
	K 120	——	M.D. 10 days	39	——
	K 121	2 X 100		—	died, PND 2
	K 122	——	M.D. 10 days	45	——
	K 123	2 X 300	M.D. 10 days	47	——
#4	K 124	2 X 200	M.D. from birth	—	died, PND 1
	K 125	2 X 200	M.D. from birth	—	died, PND 9
	K 126	——		—	——
#5	K 127	2 X 200	M.D. from birth	54	—
	K 128	2 X 200	M.D. 10 days	46	—
	K 129	——	M.D. from birth	57	—
	K 130	——	M.D. 10 days	49	—
#6	K 131	2 X 200	M.D. 10 days	36	—
	K 132	——	M.D. 10 days	38	—
	K 133	2 X 200	M.D. 10 days	40	—

TABLE II

BIOCHEMISTRY = SUMMARY

CONTROL

ANIMAL	CORTICAL NE (ng/g)	CORTICAL DA (ng/g)	CEREBELLAR NE (ng/g)
K 114	138	60	70
K 116	77	30	125
K 120	111	78	235
K 122	192	59	146
K 129	81	21	86
K 130	80	19	125
K 132	58	19	50
$\bar{X} \pm$ SEM	105 ± 17	41 ± 9	120 ± 23

6 - OHDA

K 119	≤ 1	28	NA +
K 123	≤ 17*	17	124
K 127	≤ 32*	16	23
K 128	≤ 11*	≤ 2 *	34
K 131	4	41	33
K 133	7	22	24
$\bar{X}$ ± SEM	≤ 12 ± 5	≤ 21 ± 5	48 ± 19

* least detectable amount

\+ NA = value not available

TABLE III

NEUROPHYSIOLOGY SUMMARY

	Animal	#Cells	Induction	Binocularity	Selectivity
6-OHDA	K 115	37	0.81	0.46	0.38
	K 119	22	1.0	0.27	0.68
	K 127	47	0.98	0.20	0.20
	K 131	40	0.95	0.50	0.27
	K 133	12	1.0	0.0	0.33
	$\bar{X}$	32	0.95	0.30	0.37
CONTROL	K 116	40	1.0	0.27	0.59
	K 122	45	0.87	0.51	0.46
	K 129	39	1.0	0.26	0.59
	K 130	38	0.66	0.39	0.34
	K 132	41	0.63	0.63	0.32
	$\bar{X}$	41	0.83	0.41	0.46

Tables

Table III: Summary of the neurophysiological results. Induction is an index of the degree to which an ocular dominance histogram shifts after monocular deprivation, and is defined as the number of cells dominated by the open eye divided by the total number of neurons recorded (after Blakemore, 1976). Binocularity is defined as the number of cells in ocular dominance groups 2-6 over the total (after Kasamatsu and Pettigrew, 1979). Selectivity is defined as the number of "specific" cells over the total number of classifiable neurons. See Materials and Methods for criteria for the classification of neurons.

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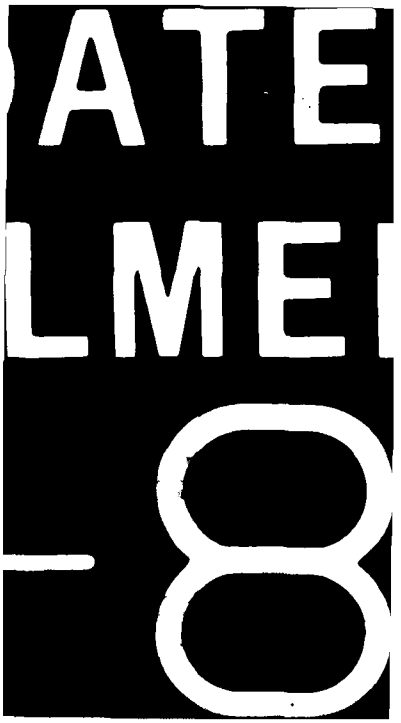
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