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*Final Report on*

16th INTERNATIONAL NARCOTICS RESEARCH CONFERENCE

FINAL REPORT

E. LEONG WAY

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| <p>This conference was held from 23-28 June 1985 in North Falmouth, Massachusetts. The program consisted of three symposia, 56 orally presented papers, 198 poster presentations and one guest lecture. Representatives of the US Army Medical Research and Development Command were active participants.</p> |                                              |                                                                                                 |                                   |
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SIXTEENTH ANNUAL MEETING OF THE  
INTERNATIONAL NARCOTIC RESEARCH CONFERENCE

The meeting was held at the Seacrest Hotel, North Falmouth, Massachusetts, June 23-28, 1985. The registered attendance was 389. There were 278 presentations including four plenary lectures, five symposia with 15 speakers, 56 oral presentations and 198 poster presentations by participants from more than 20 countries. The plenary lecturers (Eric Barnard, Walle Nauta, Michael Raftery and Charles Stevens) covered general topics in depth to point future pathways for opiopeptin research. Symposia topics and chairpersons included: opioid receptors, A. Blume; molecular biologic approaches, J. Schwartz; peptide biosynthesis, B. Cox; opioid physiology, R. Dingledine; retrospective and perspective of opiopeptins, E. Simon.

Several presentations on the isolation of the opiopeptin receptors revealed varying states of purity and indicated that the isolation of a purified receptor should be accomplished within the next year. Genomic and cDNA probes for the opiopeptin precursors were utilized to provide answers concerning the regulation of expression of the genes and their mRNAs, which cells express specific genes, and the pharmacologic treatments that act through gene expression. Additional cleavage loci of precursor proteins for yielding bioactive site and cleavage enzymes were identified. Although enkephalinase may lack specificity, it may be conveyed by selective distribution of the enzyme at sites where the peptides are located such as in the ventrolateral striatum. Carboxypeptidase involved in the conversion of proenkephalin to smaller active peptides may also convert other neuropeptide precursors in some regions of the nervous system to more active forms. Tissue levels of the enkephalins and other opiopeptin can also fluctuate in response to changes in neuronal activity, stress, gonadal functional activity, etc. The release of met-enkephalin in mouse pituitary cells can also be stimulated by CRF or 8 bromo-cAMP.

New subtypes of multi-receptors were reported. Opioid receptors were identified at sites outside the brain including human red blood cells, rat heart and mesenteric artery. The red blood cell was suggested as a model system for assessing  $\kappa$  activity and hamster vas deferens for  $\delta$  activity. Evidence was presented to indicate that the  $\mu$ ,  $\delta$  and  $\kappa$  receptors were distinct and used to argue against intraconvertability or allosteric interaction. On the other hand, another paper provided evidence to argue for a mobile receptor system in membrane capable of allosteric interaction. Opioid ligands acting at  $\delta$  and  $\kappa$  sites were noted to interact with brain receptors for TRH. Proenkephalin mRNA was found in rat heart. Morphine-like compounds were reported to be native to bovine brain and adrenals.



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Several papers provided a better understanding of the neural circuits responsible for transmission or modulation of sensory signals for pain perception. Considerable progress has been made in identifying the neurons and synapses involved. Opiopeptins have a widespread distribution in laminae I, II and V of nociceptive efferents. They appear to have a selective influence on sensory input to brain but a non-selective inhibitory influence on motor systems. Three classes of cells in the medulla spinal system responsible for descending opioid inhibition of the tail flick were identified. Selective agonist and antagonist studies in sensory neurons (dorsal root ganglion cells in culture) substantiate that opioids may decrease  $Ca^{++}$  entry as evidenced by the decreased duration of the  $Ca^{++}$  dependent action potential.

The spinal dynorphinergic system may be involved in responses to aversive stimuli. Pro-opiomelanocortin in the germinal zone may play a role in neurogenesis or guidance of neuronal migration. The role of opiopeptins in anorexia and diuresis were further investigated. Diuresis by  $\kappa$  agonists were demonstrated to be central in origin and suggested a role for the  $\kappa$  system in controlling water and electrolytic balance. Pro-enkephalin A derived peptide production in association adrenaline synthesis were noted to increase in human pheochromocytomas. Involvement of opiopeptins in gastro intestinal function was suggested by the clinical finding that naloxone can be used for treating constipation.

Some novel compounds with interesting properties were reported: a somostatin analog, CTP, to be a  $\mu$  selective antagonist; a congener in the oripavine series, M 320 to be a powerful  $\kappa$  agonist; a quarternary levallorphan derivative, SR 58002, to be a pure antagonist for peripheral agonist effects; a NN diallyl derivative of delta kephalin, a potent delta agonist; a triazolo pyridine derivative SCH 30497, to be analgetic; a selective P antagonist substantiated the involvement of substance P in the naloxone contractural response of the guinea pig ileum; substitution of d-amino acid in  $\alpha$ -casein exorphins yielded opioid antagonists; reduction of the keto group of a aminotetralin derivative to a hydroxy group converted an agonist compound to an antagonist which blocked  $\mu$  but not  $\kappa$  agonist effects.

There seem to be agreement that although native ligands need not necessarily be specific for the receptors with which they interact, the need for selective agonists and antagonists is essential not only for therapeutic application but also for understanding of the mechanism of drug action and elucidating the functional roles of endogenous ligands.

E. Leong Way, Ph.D.