1

An Endogenous Peptide Ligand for the PCP/σ-Opiod Receptor

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1. INTRODUCTION

1.1. Classification of Opioid Receptors

Opioid receptors comprise a heterogeneous group that can be divided into at least four biochemically and topographically distinct subtypes, designated μ, κ, σ, and δ. Martin *et al.* (1976) proposed the existence of μ-, κ-, and σ-opioid receptors based on observed differences in pharmacological profiles of drugs seen with variably selective opioid agonists and antagonists. Other groups have provided evidence for the δ subtype (Hughes *et al.*, 1975).

The μ-opioid receptor has been extensively characterized (Lord *et al.*, 1977; Chang *et al.*, 1979; Chang and Cuatrecasas, 1981). Classical opioid effects, such as analgesia induced by morphine and its congeners, are thought to be mediated by the μ-opioid receptor, which preferentially binds the levorotatory isomer. δ-Opioid receptors, which have been well characterized (Simantov *et al.*, 1978), are believed to be involved in reward processes and seizure. From the evidence available on κ-opioid receptors (Kosterlitz and Paterson, 1980; Chang and Cuatrecasas, 1979), it appears that these sites are involved in mediating analgesia and sedation. Finally, it has been postulated that σ-opioid receptors are involved in mediating the psy-

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chotomimetic actions seen with some of the benzomorphans such as cyclazocine, N-allylnormetazocine (SKF 10,047), phencyclidine and phencyclidine analogues (Quirion *et al.*, 1981b).

1.2. Endogenous Opioid Ligands

The μ-, κ-, and δ-opioid receptors have been found to interact with endogenous peptide ligands that share certain pharmacological properties with opioid drugs. These peptide ligands are derived from at least three different prohormones located in both the central and peripheral nervous sytems and also in the endocrine system.

δ-Opioid receptors are relatively selective for two related pentapeptides, methionine enkephalin and leucine enkephalin (Met- and Leu-enkephalin), which were originally isolated from porcine brain (Hughes, 1975). Both Met- and Leu-enkephalin inhibit electrically induced contractions of guinea pig ileum, an effect that mimics that of opioid drugs and is naloxone reversible. The enkephalins are processed posttranslationally from proenkephalin and secreted from central and peripheral neurons and endocrine cells in the adrenal medulla.

Neurons in the brain and spinal cord secrete peptides derived from prodynorphin. Some of these peptides appear to be endogenous ligands for κ-opioid receptors. Dynorphin$_{1-13}$, isolated from porcine pituitary by Goldstein *et al.* (1979), contains within its sequence Leu-enkephalin, which appears to be one of the products of posttranslational processing (Zamir *et al.*, 1984; Palkovits *et al.*, 1983). Dynorphin$_{1-13}$ is 700 times more potent than the enkephalins in inhibiting electrical contractions of the guinea pig ileum longitudinal muscle (Goldstein *et al.*, 1979).

The third prohormone from which opioid peptides are derived is proopiomelanocortin, which yields a number of nonopioid and opioid peptide products (O'Donohue and Dorsa, 1982). Of these products, β-endorphin, an untriakontapeptide isolated from camel pituitary gland by Li and Chung (1976), is thought to interact primarily with μ- and δ-opioid receptors.

1.3. Evidence for Specific PCP/σ-Opioid Receptors

In recent years, several investigators have reported the presence of a class of high-affinity binding sites for phencyclidine [1-(1-cyclohexylphenyl)piperidine, PCP], a dissociative anesthetic with psychotomimetic properties. This binding was shown to be saturable, reversible, and selective (Vincent *et al.*, 1979; Zukin and Zukin, 1979; Quirion *et al.*, 1981a; Vignon *et al.*, 1982) as well as stereoselective (Quirion *et al.*, 1981a). Also, the binding of [^{3}H]PCP was rapidly inactivated by heat and destroyed by proteases, indicating that the PCP receptor is a protein (Vignon *et al.*, 1982). Receptor densities using [^{3}H]PCP (Quirion *et al.*, 1981b) and [^{3}H]TCP {N-[1-(2-thienyl)cyclohexyl[3,4[3,4[^{3}H]piperidine} (Contreras *et al.*, 1985a) to label the binding sites were reported to be highest in cortical regions and hippocampus, indicating that the distribution of PCP binding sites correlates well with the psychotomimetic properties of the drug. [^{3}H]Phencyclidine appeared to label PCP