Endogenous Opioid Systems in Brain

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Despite the extensive use of opiates since ancient times, their molecular mechanisms of action are only now being unravelled. The past six years have seen the unfolding of an endogenous opioid neurotransmitter system whose activation mimics opiate action. Although the existence of such a system had been postulated for many years, the discovery of the opiate receptor, a stereospecific binding site localized to nerve terminals, was the first step in the discovery of this system.

The intense interest in analgesic agents over the years has resulted in the synthesis of thousands of opiate drugs and derivatives, including meperidine (Demerol®), propoxyphene (Darvon®), oxycodone (Percodan®), the mixed agonist-antagonist pentazocine (Talwin®) and the antagonist naloxone (Narcan®). In addition to the strict structural requirements for potency, these synthetic efforts defined the three classes of opiate drugs: agonists, antagonists and mixed agonist-antagonists. Agonists, such as morphine, are analgesic and produce tolerance and physical dependence. Antagonists like naloxone are devoid of analgesic activity and are capable of reversing or blocking agonist action. In dependent animals they will produce withdrawal. The mixed agonist-antagonists combine many aspects of both classes of drugs. At low concentrations they produce analgesia whereas at high concentrations they antagonize it. These drugs, such as pentazocine (Talwin), are said to have less abuse potential than pure agonists. However, there are clinical limitations in their use. They have a markedly increased incidence of hallucinations and euphoric reactions and can produce withdrawal in patients dependent on pure agonists because of the increased sensitivity to the antagonist properties of this class of drugs in dependent patients. Despite the dramatic differences in pharmacologic activity, small substitutions change agonists into antagonists. The best example is the conversion of the potent agonist oxymorphone to the antagonist naloxone by replacing an N-methyl group with an N-allyl group. These strict structure-activity relationships and specific antagonists led pharmacologists to suggest that opiates act by binding to very specific recognition sites, or receptors, which in turn produce the biologic effects.

Demonstration of these receptor binding sites experimentally came years later [1–3]. The difficult separation of relevant high affinity binding from nonspecific low affinity binding required radioactive drugs of high specific activity and specialized filtration techniques for sensitive assays of opiate receptor binding. Early studies clearly established this binding as pharmacologically relevant [4]. Localized to nerve terminal membranes, the receptor binding of a large series of narcotics correlated very well with their relative clinical potency. Clinically active levo stereoisomers were up to 50,000 times more potent in binding assays than their clinically inactive dextro isomers and non-narcotic compounds, including many putative neurotransmitters and nonopiate analgesics, and did not bind to the receptor at reasonable concentrations. Differences between agonist and antagonist opiate receptor binding seen with a series of biochemical treatments also helped to explain their different pharmacologic actions.

Opiate receptor binding within the brain showed marked regional differences. High levels of opiate binding were found in grey areas, specifically the periaqueductal grey, hypothalamus, basal ganglia, medial thalamus and amygdala whereas little binding was detected in white matter. Autoradiologic methods [5] were even able to localize receptors to specific nuclei within the brain, like the substantia gelatinosa which has pain fiber synapses. Thus, opiate receptors are associated with the paleospinothalamic tract, which carries the slowly conducted deep, burning pain sensitive to morphine. The presence of receptors in the solitary nuclei of the brainstem has been postulated to be responsible for other opiate actions, such as cough suppression and orthostasis. Although the function of receptors in the amygdala and basal ganglia are still not well understood, they have been implicated in some
emotional states and in dopaminergic mechanisms and movement disorders. The hypothalamic receptors appear responsible for the dramatic effects of opiates on release of pituitary hormones, such as prolactin.

A series of biochemical and pharmacologic investigations of opiate binding suggested the presence of several types of opiate receptors, analogous to alpha and beta noradrenergic and muscarinic and nicotinic acetylcholinergic receptors [6-8]. Recent experiments have implicated one class of receptors with analgesia and another with those factors responsible for mortality in opiate overdose. The possibility that distinct subpopulations of opiate receptors mediate different clinical effects, such as sedation, analgesia and respiratory depression, offers the additional possibility of drugs specific for one pharmacologic effect.

The existence of stereospecific opiate receptors throughout the brain implied endogenous ligands with opiate activity. Enkephalin was the first substance isolated and purified from brain [9]. A five amino acid peptide existing in two forms (tyr-gly-gly-phe-met and tyr-gly-gly-phe-leu), enkephalin binds to the opiate receptor with high affinity and produces analgesia and other opiate actions which are naloxone-reversible [10]. Its regional distribution corresponds quite closely to opiate receptor binding with high levels in the anterior hypothalamus, basal ganglia, periaqueductal grey and raphe regions. In addition, enkephalins are localized within synaptic vesicles in nerve terminals and are released by a variety of physiologic and pharmacologic techniques.

A second endogenous opioid with pharmacologic properties similar to enkephalin, beta-endorphin, has been isolated from pituitary glands [11]. Beta-endorphin is produced from beta-lipotropin (amino acids 61-91), which in turn is a cleavage product of “big ACTH,” the precursor peptide for ACTH. Immunohistochemical techniques have confirmed the presence of both ACTH and beta-endorphin within the same cells; additional studies show that both peptides are released from the pituitary together. Despite the similarity between the five N-terminal amino acids of beta-endorphin and enkephalin, each peptide appears to be a distinct transmitter agent on the basis of different regional distributions, and the absence of beta-endorphin and ACTH in enkephalin cells and the lack of enkephalin in beta-endorphin and ACTH cells. Like enkephalin, beta-endorphin binds to the opiate receptor with high affinity and produces analgesia and a variety of other morphine-like effects in animals and in man which are reversed by naloxone.

The enkephalin/endorphin system appears to be intimately involved in pain modulation. Electrical stimulation of the periventricular grey produces naloxone-reversible analgesia (stimulation analgesia) [12] which shows cross tolerance with morphine analgesia and releases endogenous opioid peptides into the cerebrospinal fluid. Interestingly, the site of stimulation analgesia is rich in opiate receptors as well as enkephalin-containing neurons.

The interrelationships of neurons within the central nervous system are complex, and it is simplistic to assume that the opioid peptides are the only neurotransmitters involved with pain perception. Extensive studies with a variety of biochemical, pharmacologic and physiologic techniques on morphine analgesia have established important relationships between morphine’s potency and various aminergic, cholinergic and peptide neurotransmitters. Treatments which increase serotonin and its release, such as L-tryptophan administration or raphe nuclei stimulation, potentiate morphine analgesia whereas serotonin depletion by reserpine, p-chlorophenylalanine or raphe lesions lessen morphine’s potency. Although dopamine has effects similar to serotonin, alpha noradrenergic agents inhibit morphine analgesia. In fact, several studies have suggested that alpha blockers like phentolamine and phenoxybenzamine are analgesic when given alone. Since stimulation analgesia is affected by these treatments in a similar manner, it is not surprising that centrally active agents, such as the antidepressants, reserpine, L-dopa and L-tryptophan, can have dramatic effects on pain perception. The future use of these nonaddictive analgesic adjuncts may play a major role in the future therapy of pain.

The actions of opioid peptides are not restricted to analgesia. Prolactin release is partially mediated by opiate receptors since its release by many physiological stimuli can be blocked by naloxone. Genetically obese Zucker rats and Ob/Ob mice with extremely high pituitary beta-endorphin levels are lean litter-mates have been discovered. Naloxone suppresses their eating and produces weight loss. Endotoxin shock and even hypotension from spinal cord trauma have been effectively reversed in rats with naloxone. These nonanalgesic actions of the opioid peptides and their receptors are only a few examples of the growing importance of the enkephalin/endorphin system in clinical medicine.

REFERENCES


