

## BRAIN'S OWN OPIATES

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'Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings none is so universal and so efficacious as opium (Thomas Sydenham 1680).' Opium has been used in medical practice since prehistoric times however, it was only with the recent discovery, in the human brain, of the endogeneous peptides with morphine like actions that it was realized nature had also provided human body with its 'own opium' to deal with the stressful and painful stimuli, so common in one's day to day life. The discovery of endogeneous opoid peptides and the establishment of the concept of opiate receptors in the body during the 1970s marks the recent advance in neuropharmacology. The physiological role of these peptides and their possible therapeutic implications are being widely studied.

### The Opoid Peptides and the Opiate Receptors

All the peptides with opiate like actions are polypeptides. The first opoid peptide to be identified was Enkephalins. Enkephalins are pentapeptides which may be either Methionine enkephalin (met-enkephalin) or Leucin-enkephalin (Leu-enkephalin). Endorphins are another group of opoid peptides with 31 amino acid sequence. In fact beta-lipotropins are the precursors of all these peptides and a hormone called 'Melanocyte Stimulating Hormone' (MSH)<sup>6</sup>. The opoid peptides are synthesized in various parts of the body and are widely distributed.

They are found in the hypothalamus, pituitary, substantia nigra and periaqueductal gray matter of midbrain, cerebellum and cerebral cortex of the brain, substantia gelatinosa in the posterior horn of the spinal cord, G. I. tract and the adrenal medulla. They are also found human placenta where they regulate placental Acetyl choline release<sup>8</sup>. It has been

found that all the neurons of the hypothalamus and anterior pituitary containing beta-endorphins contain ACTH as well, suggesting their synthesis in a common cell.<sup>10</sup> Thus they are secreted parallel with ACTH in response to stress.

The opoid peptides are synthesized in the brain and the G. I. tract.<sup>6</sup> Recent evidence suggest that most met-enkephalin in circulation originates from the adrenal medulla. Pullan et al have reported the ectopic production of met-enkephalin and beta-endorphins from the hormone producing carcinoid tumours of the lung and thymus.<sup>14</sup>

The enkephalins are highly unstable in vivo because of rapid enzymatic hydrolysis by a specific peptidase called 'enkephalinase'. Even though it is subjected to enzymatic degradation the beta-endorphin is very much more stable than enkephalins. These enkephalin degrading peptidase (enkephalinase) are found in the vicinity of the opiate receptors in the brain<sup>12</sup>. Thus the naloxone (opiate antagonist) inhibitable analgesia produced by aprotinin, a broad-spectrum inhibitor of protease, could be due to its inhibitory action on the hydrolytic breakdown of endogenous opoid peptides, thereby increasing their concentration and duration of action.<sup>13</sup>

The term 'opiate receptor' was used to designate areas of the brain having specific affinity for opiate agonists (Morphine, pethidine, opoid peptides) and antagonists (Naloxone). Endogenous peptides can react with these receptors to produce analgesia.<sup>5</sup> Three types of opiate receptors called mu, kappa and sigma receptors have been described to be distributed in the brain synaptosome membrane, spinal cord and ileum. A special delta receptor has been found for the beta-endorphins in the vas deferens.<sup>17</sup>

### Physiological and Pathological roles

1). Enkephalins and Endorphins are modulators of neurotransmitter release in the nervous tissue. Endogeneous opoids inhibit dopaminergic activity in the hypothalamus while stimulating serotonergic neurons. Opiates inhibit the firing of noradrenergic neurons of the brain.<sup>4</sup> Withdrawal of the opiate leads to massive neuronal discharge which is associated with the symptoms and physiological changes of the 'opiate abstinence syndrome'.

### 2). Endogeneous Opioid peptides and the control of pain<sup>9</sup>

The most important physiological role of these endogeneous opioide peptides is the

modulation of painful and other unpleasant stimuli. There are several evidences in its favour. High concentrations of enkephalins are found in the posterior horn of the spinal cord and periaqueductal gray matter of the brain stem. Electrical stimulation of these areas is known to produce profound naloxone reversible analgesia, accompanied by an apparent increase in enkephalins and endorphin like peptides in CSF. The intrathecal administration of beta-endorphin is found to produce profound analgesia in man by reacting with the opiate receptors in the substantia gelatinosa of the spinal cord.<sup>19</sup> Beta-endorphin has powerful antinociceptive effect and it has been shown that in conditions of stress it is released from the pituitary into the blood stream together with corticotrophin.

There is evidence to suggest that the endogenous opioids mediate acupuncture induced analgesia, which is reversible by naloxone. It is very likely that acupuncture is associated with the release of enkephalins and endorphins into CSF. Acupuncture has also been found to alleviate the symptoms of opiate withdrawal.

- 3). There are various confusing and contradictory reports about the association of opioid peptides with psychiatric disorders. Excess of beta-endorphin levels in CSF of schizophrenic patients have been found and there are reports of naloxone reducing auditory hallucinations in these patients. On the contrary, substantial number of schizophrenics and depressed patients were found to have improvement following administration of gamma-endorphins and other synthetic opioid analogues.

The presence of an abnormal peptide resembling beta-endorphin was found in higher concentration in the plasma of psychotic patients resistant to neuroleptic drug. Further study will have to be done to ascertain whether this is the cause or the effect of the biochemical disturbance associated with psychiatric diseases.

#### 4). Neuroendocrine Regulation

The presence of the opioid peptides in the hypothalamus and pituitary makes it probable that these peptides have some role in neuro-endocrine regulation. The parallel release of beta-endorphins and ACTH from the pituitary during stress and pain has already been mentioned. Raised beta-endorphin levels have been found during parturition and there is evidence to suggest that they play a specific role in pregnancy and labour.<sup>7</sup> The

opoid peptides modulate lutenizing hormone secretion and have a physiological role in the endocrine events leading to sexual maturation.<sup>2</sup>

There are various other controversial physiological and pathological roles that have been attributed to these endogenous opoids. Their role in temperature regulation, food intake, learning and memory, and involvement in some sort of motor control have been described. However, the hitherto believed involvement of the endorphins in sexual arousal and orgasm in man has been denied by Avram Goldstein et al.<sup>1</sup> The inclusion of naloxone in the therapeutic management of septic shock, spinal shock and ethanol induced coma, have been advocated by some on the possible involvement of endorphins in the pathogenesis of these conditions.

Before concluding, their possible role in exogenous narcotic dependence should be briefly mentioned. Administration of enkephalin has been shown to enhance the development of acute tolerance and dependence to morphine.<sup>20</sup> As far as is known at present, tolerance and dependence to the natural opoid peptides, although a possibility, does not occur. There is no evidence that under physiological conditions animals or men are tolerant to, and dependent on their own endogeneous opoid peptides. The mechanisms which appear to prevent occurrence of such dependence are the sequestration of opoid peptides in subcellular structures and their rapid destruction after their release from the nerve endings. These circumstances would limit the duration of exposure of the receptors to their ligands, thus avoiding the development of tolerance and dependence.<sup>9</sup>

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