REVIEW ARTICLE

ENDORPHINS IN CLINICAL MEDICINE

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The concept of specific receptor sites for opiate drugs evolved from extensive studies of the relationship between their chemical structure and **in vivo** pharmacological activity(1, 2). In 1967, Martin(3) discussed the possibility in an extensive review that opioids mimic a naturally ongoing process. Subsequently in 1971, Goldstein **et al**(4) put forward a set of criteria for the demonstration of specific opiate receptors in neuronal membranes. Later Collier(5) gave theoretical arguments in favour of the existence of endogenous ligands for opiate receptors. This was followed by successful demonstration of stereospecific opiate binding sites in brain tissue by four laboratories simultaneously(6-9). Two naturally occurring penta-peptides with amino acid sequences Tyr-Gly-Gly-Phe-Met and Tyr-Gly-Gly-Phe-Leu which have been named Met^5-Enkephalin and Leu^5-Enkephalin respectively were identified hy Hughes and Co-workers(10). Later, other endogenous ligands, the C-fragment(11), B-endorphin(12, 13) were described. All these peptides have known structures and are believed to have functional roles in living organisms. There are other peptides of known structure, such as α-endorphin, β-endorphin(14) Leu^5-endorphin(15), β-casomorphin(16), kyotorphin(17), and dynorphin(18) whose functions are yet to be known. In addition there are other peptides of known structure, which might be functionally important or artefactual. The latter include anodynin(19), Fraction I and II(20), "enkephalin-like" immuno-reactive substance(21), "big-big" β-endorphin(22), multiple forms of β-endorphin(23), "calcitonin-like" peptide(24), "big" enkephalins(25), Met^5-Enkephalin-Arg^6-Phe^7(26), morphine-antagonistic agents from human CSF(27), Humoral endorphin(28), peptides related to -endorphin(29), "dynorphin-like" peptide(30), and BAM-12P and BAM 22P(31). In addition to all these peptides, there might be peptides which are yet to be indentified.

The localization of opioid receptors and endogenous opioid peptides and their effects suggest that they are involved in many functions such as the regulation of nociception, gastrointestinal motility, behavioural patterns, learning and memory, extrapyramidal motor effects, cardiac and respiratory rate, appetitie and thirst, pathology of some forms of epilepsy, labour, foetal distress, parturition, itching and certain endorcrinological effects. In the present review, attention will be drawn on the role of endogenous morphines in some aspects of clinical medicine, taking into account the multiplicity of receptors and ligands.

Endogenous morphines and their receptors are unevenly distributed in the brain with highest concentrations in the striatum, midlbrain, pons and medulla. None was found in the cerebellum, lungs and liver. Enkephalins have been found in nucleus accumbens, pre-optic nuclei, periaqueductal grey, thalamus, hypothalamus, amygdala, globus pallidus, caudate nucleus and substantia nigra. In addition to these areas of brain, met^5-

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Enkephalin is also found in CSF, in spinal cord with dense distribution in the marginal zone. Outside the CNS, concentrations of met^5-Enkephalin are found in the pituitary, in the adrenal glands, circulating plasma and in the carotid body. These locations suggest that met^5-Enkephalin might have some role in the regulation of endocrine and circulatory functions. Leu^5-Enkephalin is found in many of the same places as Met^5-Enkephalin but the relative distributions within the individual and among species are by no means identical. The functional correlates of these differences in distribution of the two enkephalins are yet to be established. Although there are relatively high concentrations of enkephalins in the pituitary, it is most unlikely that they are synthesized there to be later transported to other parts of the CNS. Enkephalins appear to be synthesized locally from precursors which are locally produced. This is supported by experimental evidence that hypophysectomy does not effect the amount of enkephalins in brain.

The pituitary has been shown to possess large concentrations of β-endorphin in the anterior and intermediate lobes, suggesting an endocrinal role at least in part for that peptide. The target organs of the pituitary endorphins are not clearly known. The tumour tissues of the pituitary contain large amounts of β-endorphin. In the CNS, there are also large amounts of β-endorphin suggesting a neuronal role. Thus, the putuitary and brain endorphin systems are probably acting independently. In human subjects, chemical hypophysectomy by instillation of ethyl alcohol into the sella tursica has been reported to produce dramatic pain relief(33) but the mechanism is not known since naloxone did not reverse pain relief(34) and CSF endorphins remain unaltered(35). Interestingly it has also been observed that hypopituitary function is not associated with lowered CSF β-endorphin levels(36). Outside the CNS, β-endorphin is usually found in low concentrations in human plasma. It is believed that β-endorphin is formed from a precursor molecule called pro-opiocortin. The splitting of this molecule results in the formation of ACTH and β-lipotropin; the latter might then generate β-endorphin. It appears that the ACTH and β-lipotropin are released in approximately equimolar amounts, and only in certain pathological states such as Addison's disease, Cushing's Syndrome or chronic renal failure, the levels of β-endorphin become significant(35). High levels of β-endorphin are reported in the third trimester of pregnancy. This might arise from pituitary as well as placenta(36, 37).

However more detailed studies on the distribution of endogenous opioid peptides in humans is required, as the data obtained from experimental animals cannot be simply extrapolated.

Functions of endorphins:

In the evaluation of functions of endorphins, two types of approaches were quite commonly employed. The first one is to examine the actions by using an opioid receptor antagonist e.g. naloxone or naltrexone. The second approach involves the measurement of endorphins by suitable methods in tissue or body fluids under appropriate conditions.

The pharmacologic approach using a receptor antagonist and observing the changes in functions holds good only when highly specific receptor antagonists are used(38). The opioid antagonist, naloxone normally shows little morphine-like activity, but it might not be absolutely specific and might produce non-specific pharmacological effects unrelaed to opioid receptor interaction. Further, the antagonism by naloxone suggests but does not prove that a behavioural or physiological response is mediated by endorphins(39). In addition to these problems, at high doses it might produce some morphine-like effects by itself(38) and/or through its N-dealkylated metabolites. This is further complicated by the existence of multiple opioid receptors such as μ, κ, σ and δ. Furthermore naloxone less easily antagonises the effects of enkephalins than that of opiates and β-endorphin, and enkephalins are less readily displaced by naloxone from the opioid binding sites(40).

The chemical approach presents difficulties because of problems of access to the tissues and samples can be obtained only on autopsy. It might be possible to measure endorphins in blood or urine, but this measure is of little value since their origin whether from brain or intestinal tissues or elsewhere cannot be clearly ascertained. Measurement of endorphin levels in CSF might indicate their activity in CNS, even though it is difficult to determine whether it is derived from brain or locally in the spinal cord.

I. Pain Control:

One of the important pharmacological effects of morphine is analgesia and therefore much attention has been paid on the role of endorphins in pain control. Several studies have attempted to investigate the role of endorphins in the adaptation to pain. In some early studies, naloxone produced no significant effect when healthy volunteers were subjected to pain by electrical stimulation(41) or ischaemia(42). In these two studies, the method of ascending limits has been followed, which is not a reliable indicator of pain sensitivity(34). However naloxone has been shown to produce significant increase in pain sensitivity to radiant heat, when sensory-discriminatory function and the response factors were considered. Inter-individual differences in pain sensitivity were also observed; under these circumstances, pain insensitive subjects responded with an increase in pain sensitivity after the administration of naloxone, whereas in pain-sensitive subjects naloxone did not produce any significant effect(43). In fact, a bidirectional effect of naloxone on pain sensitivity has been described earlier(44). It has also been suggested that endorphins mediate the diurnal variation in the perception and reaction to pain, as naloxone has been shown to produce hyperalgesia in the morning but not in the afternoon(45). This point has some relevance to the clinical observation that patients suffering from chronic pain report more intense pain during evening hours(34). It has also been observed in patients suffering from chronic pain syndromes of psychogenic and organic aetiology that there was a significant circannual variation in the concentration of Fraction I endorphins, with the highest concentrations in January and February and the lowest concentrations in July and August(46). This aspect relates to circannual differences in the intensity of symptoms in chronic pain syndromes and affective disorders. All these studies point out that provided the experimental conditions are adequately maintained, naloxone will certainly modify the response to experimentally-induced pain, suggesting a physiological role of endorphins in the regulation of pain. In this context it must be remembered that clinical pain is quite different from experimental pain.

The CSF endorphin levels as measured by methionine-enkephalin equivalents in patients with postoperative pain (0.42 pmol/ml) and chronic pain due to lumbar disc syndrome (1.44 pmol/ml) were very low compared to the levels in control patients with no history of pain (4.4 pmol/ml)(47). However, in the acute postoperative pain group, the influence of other factors such as anaesthesia and/or surgical stress might be involved and they were not examined in this study. In addition to the above findings, in a recent paper to assess the relation between postoperative demand for analgesics in relation to individual levels of en-

dorphins and substance P in CSF, Tamsen **et al**(48) reported that there was a significant and inverse relationship between preoperative Fraction I endorphin concentrations in CSF and the individual mean pethidine concentrations in plasma in CSF during self-administration. During the 24 h period encompassing surgery and postoperative self-administered analgesia, substance P decreased in some patients, when the concentration of pethidine in CSF was high (> 200 ng/ml). These results suggested a role of endorphins in the modulation of acute pain and are compatible with experimental evidence for an inhibitory role of opiates on substance P release.

Any evaluation of the pharmacological treatment of pain is complicated by the placebo reaction, which by itself may be a powerful tool in pain control, particularly in a clinical situation(34). Levine **et al**(49) considered that placebo response might be mediated via the release of endorphins, because in their study naloxone decreased pain ratings in placebo reactors. In fact it is well-known that patients reporting severe pain tended to respond better to a placebo and this could could explain why a placebo is more effective in clinical pain than against experiemental pain. All these studies argue favourably for the participation of endorphins in a placebo response. Other factors such as prior suggestions and interindividual differences might also take part in such responses. Activation of endorphinergic systems is also possible under conditions of stress or arousal in battlefield or sport situations, where the subjects show paradoxical insensitivity to pain(50).

Psychological approaches to management of pain such as behaviour therapy or hypnosis can produce beneficial effects in some individuals. However the involement of endorphins in hypnosis-induced analgesia (HIA) remains controversial, as in some cases administration of naloxone failed to antagonize HIA(51) and in one report, it was shown to effectively attenuate HIA(52). These opposite results reveal that such investigations might depend on the experimental design. For example, all such studies concern volunteer subjects. Experiments in patients need to be carried out. Much work remains to be done on the role of endorphins in mood and behaviour.

a) Intracerebral electrical stimulation:

Intracerebral electrical stimulation produce analgesia in humans suffering from intractable pain(53-55). The clinical success rate is fairly high which merits its use in the treatment of cases resistant to conventional therapy. The most effective site for electrical stimulation lies in the areas adjascent to the posterior wall of the third ventricle. Electrical stimulation of areas such as periaqueductal grey might lead to painful and/or unpleasant symptoms(56). In most of the cases(53-55), where intracerebral electrical stimulation produced powerful analgesia, high doses of naloxone reversed the effects and it is not unreasonable to assume that pain relief is related to activation of endorphinergic systems. This does not mean that non-opiate analgesic mechanisms are not involved in this process. Another fact that supports the involvement of endorphins in the mediation of pain relief is the development of tolerance, a characteristic phenomenon of morphine. Tolerance develops rapidly if there is repetitive and frequent stimulation and for a long period(54). Furthermore there are also reports that electrical stimulation can substitute for opioid analgesics in chronic users. The development of tolerance can largely be abolished, if the stimulation sessions are shorter and given at longer intervals of time. Quantitative estimation of endogenous opioid peptides after electrical stimulation of brain indicated elevated levels of enkephalin-like immunoreactivity or endorphins(55). Certainly, the physiology of endogenous pain inhibiting systems activated by intracerebral stimulation remains exceedingly complex and still. insufficiently understood(55).

b) Peripheral stimulation:

Acupuncture analgesia under strict double blind conditions was reduced by naloxone(57). There are at present two types of peripheral stimulation which can produce pain relief. The first one is electroacupuncture which employs low frequency and high intensity electrical stimulation. The second one is transcutaneous electrical stimulation, which uses high frequency and low intensity stimulation. In acupuncture, deep fibres are activated and a long period of stimulation (> 30 min) is required. Electroacupuncture is accompanied by an increase in the levels of CSF endorphins and reversed by naloxone and might involve structures at both spinal and supraspinal levels. The transcutaneous electrical stimulation might possibly act via non-endorphinergic mechanisms. This procedure offers advantages of shorter sessions of stimulation and less discomfort during the stimulation period. Administration of naloxone in such patients with maximum pain relief after transcutaneous electrical stimulation produced either no antagonism(58) or only partial(59) antagonism. Hence it is clear that all types of peripheral stimulation might not trigger endorphinergic systems. These studies also emphasize that there might be non-endorphinergic pain-inhibitory systems(55, 60) and the role of endorphins in such a concerted action of several inhibitory systems is difficult to define.

II. Pathological states:

(a) Chronic pain:

Patients with chronic pain seem to be classified into at least two categories differing diagnostically and in endorphin involvement. In patients suffering from organic and somatogenic pain, particularly caused by deafferentation, CSF endorphin levels were low and these patients had low pain thresholds(61). Although the casual relationships are not known, it may be that such a pain might arise from the loss of sensory input and an inadequate activation of endogenous control mechanisms regulating pain sensitivity. In this regard endogenous opioid peptides might play an important role. In patients suffering from psychogenic pain, there is a tendency for higher endorphin activity(61). This has been observed in the primary diagnosis of endogenous depression and emphasizes the close relationship between depression and pain syndromes.

(b) Congenital insensitivity to pain:

Certain pathologic conditions are characterized by abnormal insensitivity to pain. Patients with congenital insensitivity to pain might have a central defect(62) and these patients responded to naloxone with a lowering of pain threshold or return of pain responsiveness(63, 64), strongly suggesting that they could have excessive endorphin production or activity. It is also frequently observed that some patients with psychiatric disorders may be insensitive to painful stimuli.

(c) Migraine headache:

Sicuteri **et al**(65) suggested that migraine and other forms of recurrent headache are probably due to a central dysfunction of endorphins. This is supported by two lines of observations; the first one is phenomenological, the similarity between a classic migraine attack and the morphine abstinence syndrome(66); a similarity which seems to be quite striking. The second line of approach was based on endor-

phin measurements in the CSF of headache patients(67). Several patients could be followed both when experiencing headache and during pain-free states. The lowest endorphin concentration was found during the attacks. Sicuteri **et al**(65) therefore proposed that recurrent pain of the migraine type depends on variation in endorphin activity and the attack is precipitated by a sudden drop in endorphin activity. The connection with the serotoninergic system is also important since the vascular changes associated with the headache are related to the supersensitivity of vascular serotonin receptors. This hypothesis for the mechanism of migraine headache can easily be tested by administering naloxone to precipitate an attack and curing the attack by injecting morphine or an opioid peptide.

(d) Psychiatric disorders:

Several lines of evidence support the hypothesis that schizophrenia reflects a deficiency of endorphins. FK-33824, a synthetic analogue of methionine enkephalin (0.5-1 mg for 2 days) has been reported to decrease the psychotic symptoms in schizophrenic patients lasting from one to seven days and a strikingly postive effect on hallucinations(68). Because intracerebro-ventricular injection of β-endorphin produced muscular rigidity and stiffness in rats, it was thought that β-endorphin was an endogenous neuroleptic(69) and schizophrenic symptoms might reflect an endorphin deficiency. In this context, it was reported that some schizophrenic patients benefitted from intravenous doses of β-endorphin (1.5 to 9 mg) in a single-blind study. However double-blind studies indicated that following β-endorphin for the treatment of schizophrenia, there was either no clinical improvement or transient worsening of schizophrenic symptoms (68). Thus further investigations, possibly using multiple injections of β endorphin are needed to categorically determine whether or not β-endorphin is useful against schizophrenia.

In contrast to studies suggesting an endorphin deficiency in schizophrenia, some investigations indicate an increase in endorphin activity in schizophrenia. In a double-blind cross-over study(70), the condition of some schizophrenic patients(71). When these patients were medicated, the increased concentrations returned to normal. An increase in CSF levels of β-endorphin in some schizophrenic patients have also been reported. The reported improvement in schizophrenic symptoms following haemodialysis(72, 73) is an evidence in favour of excess endorphin hypothesis in schizophrenia and the improvement was attributed to the removal of leucine^5 β-endorphin. Unfortunately the haemodialysis trial was not double-blind, and there has been no confirmation of elevated leucine^5 β-endorphin either in the dialysate or plasma of schizophrenic patients (74). Following intravenous injection of naloxone, improvement in the symptoms of schizophrenic patients, such as a decrease in unusual thought contents(75), schizophrenic hallucinations(76-79), or overall amelioration of psychotic symptoms(80) have been reported.

(e) Addiction:

It is logical to assume that endorphin mechanisms may be influenced by drugs of abuse and the process of addiction is related to the alterations in endorphinergic systems. Genetic factors and consequently biochemical mechanisms might be involved in drug-dependence. It may not be unreasonable to believe that there is an attenuated endorphin function, if we consider endorphins as "reward transmitters". In fact it was recently reported that the plasma β-endorphin levels as measured by radioimmuno-assay were low in individuals dependent on heroin(81) and thus abnormally low levels of endorphins might be at least partly responsible for the protracted signs of heroin abstinence known to persist for a long time after cessation of the more dramatic signs of acute withdrawal(82). In this regard, even prior to the discovery of endorphins, Dole and Nyswander (83) suggested that some type of metabolic disease may underlie the phenomenon of opiate dependence. Recently it was suggested that some changes in endorphin homeostasis might occur as a conseuqence of alcohol intoxication or chronic abuse of alcohol(84).

(f) Labour, foetal distress and parturition:

It is of interest to know that immunoreactive β-endorphin levels increase during labour(85, 86, 87) and foetal distress(88) and, the degree of elevation of β-endorphin is correlated with the degree of foetal distress. Birth might be a painful process and a source of stress to the foetus. The foetus may endure pain during labour because the endorphins aid the foetus in withstanding such a stress, and so, agents like naloxone may be detrimental to foetal welfare through counteracting their endorphins. The elevated levels of endorphins uder such circumstances suggest that they might play a role in foetal pain tolerance and cardiovascular asphyctic responses. With regard to the origin of amniotic β-endorphin, it is most likely to arise from foetal pituitary gland rather than foetal CNS. The elevated levels of amniotic immunoreactive β-endorphin found in premature labour may be a consequence of an increase in output from the foetal and/or placental compartments associated with parturition(89). The possibility that these elevations may arise as a result of tocolytic agents in the management of labour cannot be excluded and further studies are needed before a role can be assigned to β-endorphin in parturition.

(g) Itch:

Itching produced by opiates and opioid peptides may involve receptors in CNS as, in a few case reports it was shown that administration of naloxone produced a relief from generalized itch of unknown origin(90, 91) and in patients with liver diseases(92). Also it can prevent butorphanol-induced pruritus(93). Further studies with control subjects on placebo are necessary to confirm the efficacy of naloxone and to define the role of endorphins in these disorders.

Conclusion and perspectives:

A lot of work remains to be done with regard to various aspects of endorphin and in particular on pain control. This is because of the existence of a wide variety of the endogenous opiates such as enkephalins endorphins, kyotorphin, dynorphin, various enkephalin-like and endorphin-like peptides in the CNS, each of which require separate assessment. The presence of multiple receptor types also poses many difficulities particularly in relation to the partial or total resistance to naloxone, although the μ receptors involved in nociception are considered to have a high affinity for the opiate antagonists. In the field of pain control, the evidence available at present indicates not only the importance of endogenous opiates but also other substances such as other peptides and classical neurotransmitters such as acetylcholine, catecholamines and serotonin and it appears the inter-

relationships between these transmitters and the endorphinergic systems are complex. It is important to note that hyperalgesia has been observed not only with naloxone but also with various other drugs like α-adrenoceptor antagonists, serotonin receptor antagonists, muscarinic receptor antagonists, dopamine receptor antagonist and ACTH.

There are a number of pathological conditions which appear to involve the endorphinergic systems. However, there are several difficult problems which need to be resolved because the pathological conditions may result from factors such as variations in the number and affinity of multiple opioid receptors: the turn-over of one or more endogenous opioids; modification in the release processes; the ontogenic development of the pathways and the production of various peptides. Other conditions relating to the genetic background and environmental influences have also to be considered. These two aspects appear to be important with respect to predisposition to euphoria and dependence.

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