The term 'endorphin' (a combination of endogenous morphine) is used to designate the entire group of peptides found in the brain and pituitary that mimic the biological properties of opiates. 'Endogenous opioid peptides', 'endogenous opioids', 'opioid peptide' and 'endopioids' can be considered as synonymous.

Since the identification of stereospecific opiate receptors and the pentapeptides methionine and leucine enkephalin, more than 20 endogenous peptides have been discovered and additional synthetic analogues have been developed. Although their precise function remains unknown, evidence suggests they may act as neurotransmitters, neurohormones or neuromodulators.

The link between endorphins and the pathogenesis of schizophrenic and affective states has been made on the observations and findings of:

1. endogenous opiates produce mood changes and schizophrenic-like symptoms,
2. anecdotal evidence of their prophylactic use against psychotic symptoms in heroin users,
3. the distribution of these peptides follows closely pathways involved in the mediation of pain and emotional behaviour,
4. depressive and schizophrenic patients have higher pain thresholds.

Two seemingly paradoxical hypotheses have been advanced following the observation that intracerebral administration of B-endorphin produced catatonic-like state in rodents. Bloom et al. speculated that the catatonia was similar to motor abnormalities characteristic of some schizophrenias and was related to an excess of endorphin levels at receptor binding sites. Jacquet and Marks, on the other hand, compared the catatonia with the extrapyramidal rigidity produced by neuroleptics. They suggested a deficiency of endorphin activity in schizophrenia.

The evidence in support of either hypothesis is inconclusive. Administration of B-endorphin, enkephalins or synthetic analogues to test the deficiency hypothesis has resulted in symptomatic improvement, deterioration or no change. A similar confused picture has emerged following the administration of the opiate antagonists, naloxone and naltrexone, to reduce assumed high endorphin levels. Factors contributing to this confusion are the varied doses used on diagnostically heterogenous patients, the concurrent medication taken by some patients, the small sample sizes and the adequacy of assessment measures or procedures used. Gerner et al., for example, investigated the effects of B-endorphin infusion in 10 depressed and eight schizophrenic subjects. While several measures were used and changes rated by different assessors at different times, only the overall ratings of psychopathology as determined by one scale, the modified Bunney-Hamburg scale, were reported on and discussed. The reader is left to assume that changes in other measures remained insignificant. Whether double-blind investigations were maintained in these studies is also open to question. Administration of B-endorphin led 75% of Gerner et al.'s sample to report spontaneously mood or somatic changes on infusion. The possibility of biased ratings remains.

Marked clinical changes may not occur after a single-dose administration of endorphins or opiate antagonists. As with neuroleptics, improvement may manifest itself only after a period of time and following repeated doses and such studies should be conducted before any definitive statement can be made.

The determination of optimal B-endorphin dose for infusions, and the monitoring of induced behavioural changes, are major problems. The dose must be sufficiently large to ensure diffusion across the blood-brain barrier, and induce observable behavioural changes. For example, Gerner et al. infused 10 mg IV at a constant rate over 30 to 35 minutes. Since the optimal dose is unknown and could well be exceeded, high affinity opiate receptors might have been
saturated and binding to low affinity receptors such as those of dopamine might have occurred.\textsuperscript{11} Any observed behavioural changes may therefore be due to secondary effects mediated through unspecified receptor binding. Moreover, the effect of infused doses on humoral systems needs to be investigated. For instance, it is well documented that B-endorphin exhibits significant trophic effects on other hormones including those of the thyroid, adrenal and gonadal endocrine glands.\textsuperscript{12} Gerner et al.'s 10 mg infused B-endorphin produced peak plasma levels of greater than 100,000 pmol/l. This would undoubtedly produce considerable secondary effects but Gerner et al. failed to consider this possibility. In theory a better method would be the injection of much smaller doses into intraventricular spaces, a technique used in rodents but unacceptable, of course, in human studies.

Naloxone reversal is an essential test to determine specificity of opiate action.\textsuperscript{13} The omission of this procedure, not only in Gerner et al.'s study but in many others, makes it uncertain that observed responses are caused specifically by B-endorphin action.

Studies measuring plasma and CSF endorphin levels have not clarified the issue. Increased CSF endorphin levels have been reported during mania and depression. Plasma and CSF levels have been reported as elevated, normal or decreased in schizophrenic patients.\textsuperscript{14} Reported levels for subtypes of schizophrenia and chronicity of illness have also varied considerably.

These conflicting findings may be accounted for by the differing assay procedures employed, patient groups used, concomitant medication and failure to differentiate between B-endorphin and B-lipotropin in assays. This latter point is important since cumulative measures may obscure specific changes in one or other of the peptides.

The findings of Brambilla et al.\textsuperscript{14} are pertinent. They found a wide variability in B-endorphin, B-lipotropin and ACTH levels in 37 chronic schizophrenic patients. Sex, age, age of onset, chronicity, hallucinations, sub-type of schizophrenia and previous therapy were not related to these levels. These authors concluded that no typical opioid secretion pattern characterised schizophrenias but that two biochemically different types existed; one with normal and the other with elevated peptide levels. The confused findings may therefore be related to the averaging of group data masking significant results in subgroups. The two-phase design introduced by the Russians\textsuperscript{15} may overcome this problem. Responders to endorphins or antagonists are initially identified and then investigated by use of repeated doses to determine consistency of responding and its relationship to symptomatology.

Not until the methodology of studies is improved will the contradictory results be clarified. Issues such as increased sample size, homogeneous patient groups, repeated B-endorphin administration and demonstration of effect-reversal by opiate antagonists, sensitive measures for symptomatic change, true double-blind conditions and replication by different researchers must be considered. A greater understanding of opiate and opiate antagonist action at the molecular level, and their effects on normal subjects, is needed before an understanding of the role of endorphins in schizophrenia and affective disorders is achieved.

References


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