Endogenous opioids and pain: a review[1]

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A variety of methods is now available for producing analgesia in man (Adams 1976, Boureau *et al.* 1980) and antinociception in animals (Akil *et al.* 1976, Chesher & Chan 1977, Lewis & Gebhart 1977) through the activation of endogenous mechanisms. It is now clear that many different neurotransmitter systems are involved and that no single simple hypothesis will explain the experimental observations that have so far been published. The role of monoamines, particularly of 5-hydroxytryptamine and noradrenaline, is now well established (Mayer & Price 1976), largely because a number of pharmacological tools are available to aid the investigation of the relevant pathways. Since the discovery of endogenous opioids within the central nervous system (Hughes 1975) and pituitary (Bradbury *et al.* 1976, for review *see* Beaumont & Hughes 1979), the objective of many researchers has been to establish a role for these substances in pain control. Our knowledge of synthetic and degradative pathways for opioids is at a very elementary stage and at present we have no suitable drugs that will specifically deplete or lesion opioid peptide-containing neurones and few that will prevent degradation of released opioid (Beaumont & Hughes 1979, Sullivan *et al.* 1980). The only group of substances readily available as tools are receptor antagonists, the best example of which is naloxone (Sawynok *et al.* 1979), and most of the evidence for a physiological function for the opioids that we have to date depends on antagonism of analgesia or antinociception by naloxone.

Naloxone was developed as an agent for reversing the effects of opiates in the clinical situation. In this role it has been very successful and has no undesirable effects in humans at the doses needed to reverse narcotic overdosage (Evans 1973). In animal experiments the actions of systemically administered opiates are readily reversed by naloxone given by a variety of routes, and this reversal extends to a whole range of effects from antinociception (Lewis & Gebhart 1977) through to endocrine (Grandison & Guidotti 1977) and haemodynamic changes (Belenky & Holaday 1979, for review *see* Sawynok *et al.* 1979). It therefore seems logical to employ naloxone in attempts to antagonize the effects produced by the physiological release of endogenous opioids. Indeed, naloxone played a large part in their discovery and was one of the agents used in the binding studies (Pert & Snyder 1973) on the opiate receptor that led to the endogenous ligands. When Hughes, Kosterlitz and colleagues announced the discovery of the enkephalins, one of their criteria for the identification of these first endogenous opioids was that the effects they produced on bioassay preparations should be reversed by naloxone (Hughes 1975, Beaumont & Hughes 1979). Mpre recently isolated peptides have been subjected to the same tests and in most cases have been shown to produce naloxone-reversible effects (Lowney *et al.* 1979).

When used on isolated tissues such as the mouse vas deferens, guinea-pig ileum or cultured mammalian neurones, naloxone is a potent and specific antagonist of the effects produced by application of extracted endogenous ligands or by synthetic opioids (Crain *et al.* 1978, Kosterlitz & Leslie 1978, Kosterlitz *et al.* 1980) and, indeed, has been referred to in the literature as a pure antagonist. As might be expected, results obtained in behavioural experiments are less homogeneous, but there is now a convincing body of evidence to show that the antinociceptive effects produced by the electrical stimulation of central (Adams 1976, Akil *et al.* 1976) and peripheral sites (Boureau *et al.* 1980, Chapman & Benedetti 1977) and by

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behavioural stimuli such as stress (Amir & Amit 1978) and reward (Dum & Herz 1980) will be at least partially attenuated by prior systemic or central administration of naloxone. Some of the most convincing evidence has been obtained in clinical studies and it is noteworthy that, in terms of the dose required to reverse a narcotic overdose, man is amongst the most sensitive of animals to the effects of naloxone (Martin 1967).

A slightly more controversial area is the consideration of whether or not naloxone will produce hyperalgesia. Many published reports, including most of those in which stimulus-evoked analgesia was reversed by naloxone, state that baseline nociception thresholds are not influenced by naloxone (Akil *et al.* 1976, Boureau *et al.* 1980, Chesher & Chan 1977). However, it is now clear that, under selected experimental conditions, hyperalgesia can be produced in rodents by naloxone and various other opiate antagonists (Bonnett *et al.* 1978, Jacob & Ramabadran 1977). Similar studies have been attempted in man and it is noteworthy that postoperative pain following dental surgery can be exacerbated by naloxone (Levine *et al.* 1978*b*), that placebo analgesia appears to be naloxone-sensitive (Levine *et al.* 1978*a*), and that one case of congenital insensitivity to pain was reversed by naloxone (Dehen *et al.* 1978). It would be wrong to pretend that there were not considerable difficulties in interpreting the results of the above studies and it is clear that the observed results are likely to involve a mixture of neurotransmitter and endocrine effects. For example, the naloxone-reversible electroacupuncture seen in man (Sjölund & Erikson 1979) is likely to operate at a segmental level as it is accompanied by a release of low molecular weight opioids into the cerebrospinal fluid overlying the spinal cord segment being stimulated (Terenius & Wahlström 1979), whereas electroacupuncture antinociception in the mouse, although similarly naloxone-sensitive, is not seen in hypophysectomized animals (Pomeranz & Chiu 1976). Paradoxically, hypophysectomy in man often produces analgesia in intractable pain states and recent evidence suggests that this too may be naloxone-sensitive (Yanagida *et al.* 1979). There is now some evidence that the action of anaesthetic agents with no structural resemblance to opioids, e.g. nitrous oxide, may be naloxone-reversible (Berkowitz *et al.* 1978). This adds support to the postulate of an endogenous opioid operated pain-modification system that can be stimulated by many different inputs.

If some of the observations of naloxone-reversible analgesic mechanisms are attributable to the action of endogenous opioids as inhibitory neurotransmitters, then electrophysiological experiments should reveal such actions at the level of the single neurone. Surprisingly, few such studies have been reported, in comparison with the large number of behavioural and biochemical publications on this topic, but some positive evidence is now emerging. A number of workers report that naloxone, locally or systemically applied, will enhance the nociceptive responses of neurones in the dorsal horn and elsewhere (Bell & Martin 1977, Henry 1980, Rivot *et al.* 1979), but, strangely, this effect is most readily seen following the exposure of the neurone to an exogenous opioid (Duggan *et al.* 1977). Stimulation of the putative β-endorphin containing pathway originating in the arcuate nucleus produces an inhibition of locus coeruleus neurones that is attenuated following the intravenous administration of naloxone (Strahlendorf *et al.* 1980). Peripheral noxious stimuli produce inhibition of the firing of a proportion of neurones in nucleus reticularis ventralis (NRV) of the rat caudal medulla and this too is reduced by intravenous naloxone (Hill 1980), as are the electroacupuncture-induced inhibition of the nociceptive responses of cat dorsal horn neurones (Pomeranz *et al.* 1977) and the reduction in the ventral root response produced by Lissauer's tract stimulation (Wall & Yaksh 1978).

Drug interaction studies may also shed light on the role of the endogenous opioids and, for example, potentially opioid-operated effects may show cross tolerance to opiates (Berkowitz *et al.* 1978, Chesher & Chan 1977, Lewis & Gebhart 1977) and specific brain lesions have been shown to attenuate both the effects of an administered opiate and stimulus-evoked analgesia (Basbaum *et al.* 1976, Lewis & Gebhart 1977). In one recent investigation the weak analgesia produced by diazepam was initially thought to be naloxone-insensitive, but when the peptidase inhibitor bacitracin was administered concurrently then the antinociceptive effect of diazepam was increased and became naloxone-sensitive (Wüster *et al.* 1980). This approach

may have a wider application, particularly as it now seems that an endogenous substance, kyotorphin, may act indirectly by releasing opioids rather than binding directly to opiate receptors (Satoh *et al.* 1980).

Much evidence is thus accumulating to support the idea that endogenous opioids have an important role in pain control mechanisms. It is likely that as our knowledge of this field increases then improvements in the therapy of pain will follow; but, as with other fields of study, the more that this area is investigated the more complicated it seems to be and it will be some considerable time before our understanding of this fascinating phenomenon is complete.

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