Psychological Medicine, 1979, **9**, 1–4
Printed in Great Britain

EDITORIAL

Endogenous opioid peptides and the control of pain[1]

In recent years it has become evident that peptides of relatively small molecular weight play an important role not only in the regulation of endocrine function but also in the control of certain pathways in the central nervous system. The discovery of peptides which mimic the actions of morphine is of particular interest since it may give an insight into the physiological modulation of responses to painful experiences. Two such pentapeptides, methionine-enkephalin (tyrosine-glycine-glycine-phenylalanine-methionine) and leucine-enkephalin (tyrosine-glycine-glycine-phenylalanine-leucine) were identified in extracts of pig brains (Hughes *et al.* 1975) and of other species. It is of interest that the sequence of methionine-enkephalin is present in the pituitary peptide β-lipotropin as amino acid residues 61–65.

Present evidence indicates that there are 2 independent peptidergic systems: one is characterized by the presence of the short-chain peptides, methionine-enkephalin and leucine-enkephalin, and is widespread throughout the central and peripheral nervous systems (Elde *et al.* 1976; Hughes *et al.* 1977; Simantov *et al.* 1977), whereas the other system contains the long-chain peptide, β-endorphin (β-lipotropin$_{61-91}$) and is centred around the hypothalamus–pituitary axis with extensions into the thalamus, midbrain, medulla and pons (Rossier *et al.* 1977*b*).

The investigation of the analgesic, or rather antinociceptive, properties of the opioid peptides is made difficult by the high sensitivity of the pentapeptides, the enkephalins, to the very rapid degrading actions of aminopeptidases and carboxypeptidases, whereas the long-chain peptides are resistant to these enzymes and have their activity more slowly reduced by an endopeptidase cleaving the molecule between amino acid residues 77 and 78. This property of the enkephalins makes the use of the ordinary antinociceptive tests unreliable, even if the peptides are administered directly into the cerebral ventricles. On the other hand, β-endorphin is a very strong and long-lasting antinociceptive agent (Feldberg & Smyth, 1977), even after intravenous administration to mice but not to rats (Tseng *et al.* 1976; Rossier *et al.* 1977*a*). In this context it is of interest that the affinity of β-endorphin to the receptor represented by [^{3}H]leucine-enkephalin or [^{3}H]methionine-enkephalin binding in brain homogenate is similar to that of methionine-enkephalin and leucine-enkephalin, whereas its affinity to the receptor represented by [^{3}H]naloxone or [^{3}H]naltrexone binding is considerably greater than that of methionine-enkephalin and particularly of leucine-enkephalin. In contrast to the opioid peptides, morphine has a much lower affinity to the binding site of [^{3}H]leucine-enkephalin than to that of [^{3}H]naloxone or [^{3}H]naltrexone (Lord *et al.* 1977).

The evidence that methionine-enkephalin and possibly leucine-enkephalin play an important role in the control of the modulation of the transmission of noxious and painful stimuli is based on electro-physiological experiments, on the relationship between substance P and enkephalin in the central nervous system and the antagonism by naloxone of the analgesic effects of electrical stimulation of the pericentral grey in intractable pain and of those of electro-acupuncture.

It has been shown (Duggan *et al.* 1977) that methionine-enkephalin and its amide have different effects on the responses of neurones of spinal laminae IV and V of spinal cats to noxious and innocuous skin stimuli. When administered in the substantia gelatinosa, the enkephalins predominantly reduce the responses to noxious stimuli with little effect on the responses to non-nociceptive stimuli. These observations are in good agreement with the immunohistochemical findings that methionine-enkephalin and substance P have a similar distribution in areas related to pain and analgesia (Hökfelt *et al.* 1977). Such areas are the periaqueductal grey, the marginal layer of the spinal trigeminal nucleus and the substantia gelatinosa of the dorsal horn of the spinal cord

[1] Address for correspondence: Professor H. W. Kosterlitz, University of Aberdeen, Unit for Research on Addictive Drugs, Marischal College, Aberdeen AB9 1AS, Scotland.

and, to a lesser extent, the medullary raphe nuclei. From lesion experiments it would appear that the enkephalinergic neurones in the dorsal horn are interneurones or propriospinal neurones with nerve terminals in laminae I and II, areas which are also very rich in substance P containing nerve terminals arising from primary afferent neurones. On the basis of these observations and the fact that D-Ala^2-methionine-enkephalin amide inhibits the K^+-induced release of substance P from slices of spinal trigeminal nerve nuclei, the hypothesis has been put forward that presynaptic enkephalinergic neurones reduce the release of substance P from small diameter primary afferent fibres and thus modulate the transmission of nociceptive stimuli (Jessell & Iversen, 1977).

If the opioid peptides present in the central nervous system play a physiological role, it would follow that the opiate antagonists, naloxone and naltrexone, should increase pain perception in man and in animals. Perhaps surprisingly, the results of such investigations have not been consistent. Some authors have reported negative findings (El-Sobky *et al.* 1976; Goldstein *et al.* 1976), whereas others obtained increases in nociceptive responses (Jacob *et al.* 1974; Frederickson *et al.* 1976). Analysis of the reasons for these discrepancies should give an important insight into the nature and physiological significance of the postulated pain modulation by the enkephalinergic neurones.

More information on the effects of naloxone has been obtained from its interaction with the antinociception induced by electrical stimulation of different areas of the brain. For instance, the antinociceptive effect of stimulation of the periaqueductal grey of the brain stem of rats is blocked by naloxone (Akil *et al.* 1972), although this finding has not been unequivocally confirmed by other authors (Pert & Walter, 1976; Yaksh *et al.* 1976). Further, it has been shown that the analgesia produced by electrical stimulation of the periventricular and periaqueductal grey in patients with intractable pain is reversed by naloxone (Hosobuchi *et al.* 1977). Important findings were that an intensity of stimulation sufficient to induce pain relief does not seem to alter the acute pain threshold and that indiscriminate repetitive stimulation leads to tolerance to the analgesic effect of electrical stimulation and of narcotic analgesics. In cases of successful electrical stimulation, there is often an increase in the amount of opioid peptides in the cerebrospinal fluid (Terenius, 1978; J. Miles, J. Hughes & H. W. Kosterlitz, unpublished observations). Finally, it has been reported that the analgesic effects of acupuncture on the pain caused by electrical stimulation of teeth in man are abolished by naloxone (Mayer *et al.* 1977). On the other hand, naloxone has no effect on analgesia induced by hypnosis (Goldstein & Hilgard, 1975; Mayer *et al.* 1977).

The role of β-endorphin in physiological modulation of pain is still as uncertain as that of the enkephalins. As already mentioned, this peptide has powerful antinociceptive effects and it has been shown that in conditions of stress it is released from the pituitary into the blood stream together with corticotrophin (Guillemin *et al.* 1977). Under such conditions, the content of β-endorphin decreases in the hypothalamus but does not change in other areas of the brain. From a consideration of the levels of β-endorphin in the plasma, it is unlikely that the β-endorphin released into the blood stream is correlated with the mechanisms underlying pain suppression (Rossier *et al.* 1977*a*).

As far as therapeutic usefulness is concerned, the long-chain peptides have the disadvantage of the expense of their synthesis. Since the naturally occurring pentapeptides, methionine- and leucine-enkephalin, cannot be used because of their short biological survival, a very large number of analogues have been synthesized in numerous pharmaceutical laboratories. Such analogues may be potent antinociceptive agents after administration into the cerebral ventricles (e.g. D-Ala^2-Met-enkephalin amide, Pert *et al.* 1976; NCH_3-Tyr-Gly-Gly-Phe-Met amide, Feldberg & Smyth, 1977; Tyr-D-Ala-Gly-Phe-D-Leu, Baxter *et al.* 1977). Other analogues are active after intravenous and subcutaneous injection (e.g. Tyr-D-Met-Gly-Phe-Pro amide, Székely *et al.* 1977), but only one or two compounds have an antinociceptive effect after oral administration (e.g. Tyr-D-Ala-Gly-NCH_3Phe-Met(*O*)-ol or FK 33–284, Sandoz; Roemer *et al.* 1977). In this context it is of importance that there are in the central nervous system several opiate receptors with different pharmacological characteristics; for instance, the δ-receptors have a higher affinity for the enkephalins than for morphine, whereas the μ-receptors have a higher affinity for morphine than for the enkephalins (Lord *et al.* 1977). It should be noted that most of the published analogues have a lower affinity for the δ-receptors than the natural enkephalins and a higher affinity for the μ-receptors; one of the few

exceptions is Tyr-D-Ala-Gly-Phe-D-Leu (Lord *et al.* 1977; unpublished observations). This change in relative affinity may be of particular importance with regard to the non-analgesic actions of these compounds, such as their effects on respiration, mood, gastrointestinal motility and endocrine functions. At present, it is not possible to allocate different physiological roles to the different types of receptors.

As far as is known at present, all natural and synthetic opioid peptides are liable to produce tolerance and dependence. There is no evidence, however, that under physiological conditions animals or man are tolerant to, and dependent on, their own endogenous opioid peptides. The mechanisms which appear to prevent occurrence of such dependence are the sequestration of the opioid peptides in subcellular structures and the rapid destruction, particularly of the short-chain enkephalins, 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 (Kosterlitz & Hughes, 1977).

H. W. KOSTERLITZ

REFERENCES

Akil, H., Mayer, D. J. & Liebeskind, J. C. (1972). Comparison chez le rat entre l'analgésie induite par stimulation de la substance grise peri-aqueducale et l'analgésie morphinique. *Comptes rendus hebdomadaires des séances de l'Académie des Sciences, Paris* **274**, 3603–3605.

Baxter, M. G., Goff, D., Miller, A. A. & Saunders, I. A. (1977). Effect of a potent synthetic opioid pentapeptide in some antinociceptive and behavioural tests in mice and rats. *British Journal of Pharmacology* **59**, 455–456P.

Duggan, A. W., Hall, J. G. & Headley, P. M. (1977). Enkephalins and dorsal horn neurones of the cat: effects on responses to noxious and innocuous skin stimuli. *British Journal of Pharmacology* **61**, 399–408.

Elde, R., Hökfelt, T., Johansson, O. & Terenius, L. (1976). Immunohistochemical studies using antibodies to leucine-enkephalin: initial observations on the nervous system of the rat. *Neuroscience* **1**, 349–351.

El-Sobky, A., Dostrovsky, J. O. & Wall, P. D. (1976). Lack of effect of naloxone on pain perception in humans. *Nature* **263**, 783–784.

Feldberg, W. & Smyth, D. G. (1977). C-fragment of lipotropin – an endogenous potent analgesic peptide. *British Journal of Pharmacology* **60**, 445–453.

Frederickson, R. C. A., Nickander, R., Smithwick, E. L., Shuman, R. & Norris, F. H. (1976). Pharmacological activity of met-enkephalin and analogues *in vitro* and *in vivo*. In *Opiates and Endogenous Opioid Peptides* (ed. H. W. Kosterlitz), pp. 239–246. North-Holland: Amsterdam.

Goldstein, A. & Hilgard, E. R. (1975). Failure of the opiate antagonist naloxone to modify hypnotic analgesia. *Proceedings of the National Academy of Sciences, Washington* **72**, 2041–2043.

Goldstein, A., Pryor, G. T., Otis, L. S. & Larsen, F. (1976). On the role of endogenous opioid peptides: failure of naloxone to influence shock escape threshold in the rat. *Life Sciences* **18**, 599–604.

Guillemin, R., Vargo, T., Rossier, J., Minick, S., Ling, N., Rivier, C., Vale, W. & Bloom, F. (1977). β-Endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* **197**, 1367–1369.

Hökfelt, T., Ljungdahl, A., Terenius, L., Elde, R. & Nilsson, G. (1977). Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: enkephalin and substance P. *Proceedings of the National Academy of Sciences, Washington* **74**, 3081–3085.

Hosobuchi, Y., Adams, J. E. & Linchitz, R. (1977). Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. *Science* **197**, 183–186.

Hughes, J., Smith, T. W., Kosterlitz, H. W., Fothergill, L. A., Morgan, B. A. & Morris, H. R. (1975). Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* **258**, 577–579.

Hughes, J., Kosterlitz, H. W. & Smith, T. W. (1977). The distribution of methionine-enkephalin and leucine-enkephalin in the brain and peripheral tissues. *British Journal of Pharmacology* **61**, 639–647.

Jacob, J. J., Tremblay, E. C. & Colombel, M.-C. (1974). Facilitation de réactions nociceptives par la naloxone chez la souris et chez le rat. *Psychopharmacologia* **37**, 217–223.

Jessell, T. M. & Iversen, L. L. (1977). Opiate analgesics inhibit substance P release from rat trigeminal nucleus. *Nature* **268**, 550–551.

Kosterlitz, H. W. & Hughes, J. (1977). Peptides with morphine-like action in the brain. *British Journal of Psychiatry* **130**, 298–304.

Lord, J. A. H., Waterfield, A. A., Hughes, J. & Kosterlitz, H. W. (1977). Endogenous opioid peptides: multiple agonists and receptors. *Nature* **267**, 495–499.

Mayer, D. J., Price, D. D. & Raffii, A. (1977). Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. *Brain Research* **121**, 368–372.

Pert, A. & Walter, M. (1976). Comparison between naloxone reversal of morphine and electrical stimulation induced analgesia in the rat mesencephalon. *Life Sciences* **19**, 1023–1032.

Pert, C. B., Pert, A., Chang, J.-K. & Fong, B. T. W. (1976). [D-Ala^2]-Met-enkephalinamide: a potent, long-lasting synthetic pentapeptide analgesic. *Science* **194**, 330–332.

Roemer, D., Buescher, H. H., Hill, R. C., Pless, J., Bauer, W., Cardinaux, F., Closse, A., Hauser, D. & Huguenin, R. (1977). A synthetic enkephalin with prolonged parenteral and oral analgesic activity. *Nature* **268**, 547–549.

Rossier, J., French, E. D., Rivier, C., Ling, N., Guillemin, R. & Bloom, F. E. (1977*a*). Foot-shock induced stress increases β-endorphin levels in blood but not brain. *Nature* **270**, 618–620.

Rossier, J., Vargo, T. M., Minick, S., Ling, N., Bloom, F. E. & Guillemin, R. (1977*b*). Regional dissociation of β-endorphin and enkephalin contents in rat brain and pituitary. *Proceedings of the National Academy of Sciences, Washington* **74**, 5162–5165.

Simantov, R., Kuhar, M. J., Uhl, G. R. & Snyder, S. H. (1977). Opioid peptide enkephalins: immunohistochemical mapping in the rat central nervous system. *Proceedings of the National Academy of Sciences, Washington* **74**, 2167–2171.

Székely, J. I., Rónai, A. Z., Dunai-Kovács, Z., Miglécz, E., Bertzétri, I., Bajusz, S. & Gráf, J. (1977). (D-Met², Pro⁵)-Enkephalinamide: a potent morphine-like analgesic. *European Journal of Pharmacology* **43**, 293–294.

Terenius, L. (1978). Significance of endorphins in endogenous antinociception. In *Advances in Biochemical Psychopharmacology*, vol. 18 (ed. E. Costa and M. Trabucchi), pp. 31–44. Raven Press: New York.

Tseng, L. F., Loh, H. H. & Li, C. H. (1976). β-Endorphin as a potent analgesic by intravenous injection. *Nature* **263**, 239–241.

Yaksh, T. L., Yeung, J. C. & Rudy, T. A. (1976). An inability to antagonize with naloxone the elevated nociceptive thresholds resulting from electrical stimulation of the mesencephalic central gray. *Life Sciences* **18**, 1193–1198.

https://doi.org/10.1017/S0033291700021498 Published online by Cambridge University Press