Endogenous opiates and pain

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A WIDE RANGE OF techniques has been used in the past to manage pain, and nurses, with other members of the health team, have long struggled with the complex and often frustrating dilemma of helping patients in pain. Pharmacological manipulation, psychotherapy, surgical intervention, and physiological stimulation are a few examples of techniques often used. Unfortunately, these and other methods have had two common problems: The physiological mechanisms of their effects are not precisely understood, and permanent success is rarely achieved. The discovery of the endogenous opiate peptides offers hope that the physiological mechanisms of pain will be further elucidated. The importance of this recent advance in nursing is that the study of endogenous opiates may lead to more precise measurement of the effects of existing nursing interventions for pain, as well as suggest new methods of pain control.

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THE CONCEPT OF PAIN

The activity of endogenous opiates, as a new physiological dimension of pain, fits well into the framework of current understanding of the pain process. Nursing science subscribes to a holistic concept of humans as biopsychosocial beings. Similarly, pain can be conceptualized as a biopsychosocial phenomenon. For example, fear and anxiety are typical *emotional* responses to acute pain. Likewise depression is a common feature in chronic pain patients. Cultural differences in pain interpretation and response are evidence of the *social* component of pain, as are environmental reinforcers of the behavior of people in pain. The *physiological* responses to pain are well described but vary markedly among individuals. If two people are subjected to the same painful procedure, their rating of the amount of physical pain experienced will be different. What accounts for the difference? What occurs in the nervous system prior to the cognitive interpretation (perception) of the pain? The difference may lie in the individual's endogenous opiate system. Concomitantly, how the endogenous opiate system responds is influenced by the level of emotional arousal.

ENDOGENOUS OPIATES

Definition

Endogenous opiate peptides are substances produced by the body that have properties similar to those of morphine. The term *endorphins* combines the words *endogenous* and *morphine* and is sometimes used as a general term for endogenous opioid factors. However, use of the general term *endorphins* can be confusing because it refers to two separate groups of peptides. One is the enkephalins, consisting of the pentapeptides methionine-enkephalin and leucine-enkephalin, which are widespread throughout the central and peripheral nervous system. The other group consists of three larger polypeptides called alpha-, beta-, and gamma-endorphin. Beta-endorphin is the most active of the three and has been the subject of the most research. Although the latter group of peptides is found in small amounts in the brain, the largest concentration is in the pituitary gland.

Discovery

The history of endogenous opiate research is short. The serendipitous discovery of opiate receptors reported in the early 1970s prompted the search for an endogenous ligand.[1] (A ligand is a molecule that binds to a particular site on another molecule.) Opiate receptors in the nervous systems of animals exhibited stereo-specific binding that was antagonized by naloxone, a known morphine antagonist. When Kuhar, Pert, and Snyder determined the density of opiate receptor sites in the monkey brain, they found that the most dense areas were the amygdala and periaqueductal gray matter.[2] The heterogenous receptor distribution corresponded

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roughly to pathways that were believed to mediate the motivational-affective components of pain.[3] The discovery of the opiate receptor raised an intriguing question: Why had a receptor evolved for which the only known binding particles were poppy plant alkaloids? Did the body produce its own morphine? The search for an endogenous ligand began.

In 1975 Hughes reported the isolation of a substance that had a morphine-like effect on two animal tissues known to have morphine receptor sites: the mouse vas deferens and the guinea pig ilium. In addition, the morphine-like effect was reversed by naloxone.[4] A Swedish group simultaneously reported similar findings.[5] In a short time, Hughes et al identified the endogenous ligand as two pentapeptides, which they called *enkephalins* from a Greek work meaning *in the head.*[6] The discovery of three more peptides with morphine-like biological properties was reported in 1976. Named alpha-, beta-, and gamma-endorphin, these substances were isolated mainly from the anterior and intermediate lobes of the pituitary gland.[7,8]

Amino Acid Sequences of Beta-Lipotropin

H-Glu-Leu-Thr-Gly-Gln-Arg-Leu-Arg-
10
Gln-Gly
Asp-Gly-Pro-Asn-Ala-Gly-Ala-Asn-
20
Asp-Gly-
Glu-Gly-Pro-Asn-Ala-Leu-Glu-His-
30
Ser-Leu-
Leu-Ala-Asp-Leu-Val-Ala-Ala-Glu-
40
Lys-Lys-
Asp-Glu-Gly-Pro-Tyr-Arg-Met-Glu-
50
His-Phe-
Arg-Trp-Gly-Ser-Pro-Pro-Lys-Asp-
60
Lys-Arg-
61 65*
Tyr-Gly-Gly-Phe-Met-*Thr-Ser-Glu-*
70
Lys-Ser-
Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-
80
Lys-Asn-
Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-
90 91†
Lys-Gly-Glu-OH.

*Sequence of methionines-enkephalin (61-65)
†Sequence of beta-endorphin (61-91)

Composition and distribution

The five endorphin and enkephalin peptides have similar structures. Methionine-enkephalin and leucine-enkephalin vary by one amino acid. Methionine-enkephalin is identical to the N-terminal sequences of the 31-amino-acid beta-endorphin. Beta-endorphin is contained in the 91-amino-acid compound of beta-lipotropin (see boxed material). Despite the chemical similarities, it is believed that the enkephalins and the endorphins have a different biosynthetic origin. Results of immunocytochemical studies demonstrate that neurons containing beta-endorphin exist separately from those containing enkephalin. Furthermore, beta-endorphin in the brain appears to be regulated independently from beta-endorphin in the pituitary gland.[9,10]

The significance of the variation in origin and distribution may lie in the different functional roles of beta-endorphin and the enkephalins. In the central nervous system, beta-endorphin is found in the hypothalamus, midbrain, and pons/medulla. Outside

the CNS beta-endorphin is found in the intermediate and anterior lobes of the pituitary gland (see Fig 1). The high concentration of beta-endorphin in the pituitary gland and the long duration of its effect (in brain tissue it can induce analgesia for hours) suggests that it has a neuromodulator or hormone function in the CNS and periphery.

The distribution of the enkephalins, on the other hand, varies markedly from that of beta-endorphin. The enkephalins are widely distributed in the central nervous system, with high concentrations in the limbic system and in areas associated with pain: the dorsal horn of the spinal cord (see Fig 2), the spinal trigeminal nucleus, the raphe nuclei, and the periaqueductal gray matter (see Fig 1).[11] In addition, enkephalins have been found in parts of the gastrointestinal tract and in peripheral nerves.[12] Although enkephalins do not meet all rigorous criteria required to be proven neurotransmitters, some of their properties, such as short duration of action and widespread distribution, suggest that they do function as neurotransmitters in the central and peripheral nervous system.[13]

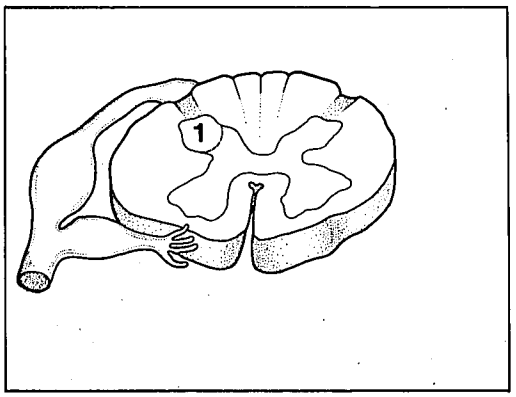

Fig 1. Sites of concentration of endogenous opiates in the brain. A = Anterior and intermediate lobes of pituitary, high concentration of B-endorphin. 2 = Periaqueductal gray, High concentration of met-enkephalin. 3 = Raphe nuclei, High concentration of met-enkephalin.

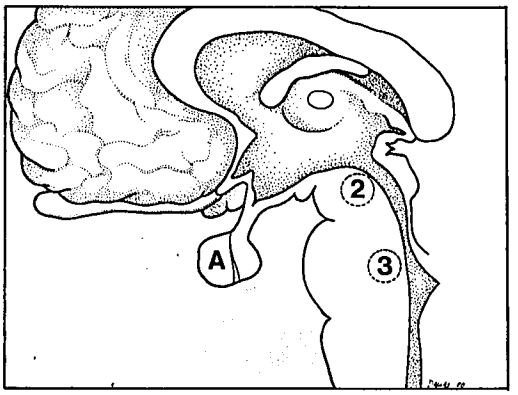

Fig. 2. Dorsal horn of spinal cord, illustrating a site of concentration of met-enkephalin.

ENDOGENOUS OPIATES AND PAIN

The anatomical distribution and the morphine-like effects on receptor tissue indicate an obvious role for endogenous opiates in inhibiting pain. Experimental investigation has involved mainly three approaches: (1) studying the effects of narcotic antagonists on clinical and experimental pain states, (2) inducing analgesia via electrical stimulation of the brain and testing for reversal using antagonists, and (3) attempting to measure directly endogenous opioid levels in pain patients.

Effects of narcotic antagonist

Naloxone is a morphine antagonist, meaning that it competes for binding sites on the opiate receptor, thus blocking the

narcotic effects of morphine. If endorphins and enkephalins act on opiate receptors to inhibit pain transmission, then blocking the receptor site with an antagonist would prevent the inhibitory effect, resulting in accentuation of pain. Ethical considerations limit the testing of naloxone on acute pain states in humans, so its use has largely been confined to animal experimentation and to experimental pain situations in humans. Results have been inconsistent.

A naloxone injection was found to increase pain sensitivity in animals.[14] A naloxone injection also caused a significant increase in pain intensity in individuals following tooth extraction.[15] However, in an experimental pain situation, paid healthy volunteers reported no change in pain threshold after naloxone administration.[16] To explain the negative naloxone effect, Grevert and Goldstein hypothesized that endogenous opiates are not activated in the low-stress experimental pain situation. On the other hand, in a clinical pain study using ten chronic pain patients, Lindblom and Tegner found that naloxone did not alter levels of pain or heat pain thresholds.[17]

These seemingly paradoxical findings, in light of the distribution of endogenous opiates within pain pathways, are puzzling. However, when one recalls that morphine also has little effect on pain threshold, the findings seem less contradictory. Patients report that after morphine administration, pain is still perceived, but tolerance is increased.[18] Thus, morphine seems to act on the reactive or emotional component in acute pain states. One may, therefore, conclude that the endogenous opiates modulate pain in clinical pain states when pain is associated with high levels of fear and anxiety, whereas they are neither significantly active in experimental pain states (as suggested by Grevert and Goldstein) nor active in some clinical states of chronic pain.

Stimulation-produced analgesia

Another approach to the study of the relationship of endogenous opiates to pain is via stimulation-produced analgesia (SPA), which is analgesia that is induced by electrical stimulation of selected areas of the brain. Reynolds first demonstrated that electrodes implanted in midbrain central gray areas of rats induced analgesia sufficient to perform surgery on the rat.[19] Work with SPA has been extended to humans, with intriguing results. In a series of experiments on 13 patients with intractable pain, electrical stimulation of the periventricular gray matter of the brain resulted in relief of pain.[20,21]

Naloxone reverses SPA in both animals and, at least partially, in humans.[22,23] The naloxone-reversibility of analgesia at midbrain sites that are richly endowed with enkephalin-containing nerve terminals suggests that SPA is mediated by endogenous opiates. In further support of this hypothesis, Akil et al found that the levels of an enkephalin-like substance in cerebrospinal fluid samples from eight chronic pain patients were below normal. Levels of the enkephalin-like material in these patients began to rise after 20 to 30 minutes of brain stimulation.[24]

Measurement of endogenous opioid levels

A third avenue of study has been the attempt to directly measure endogenous

opioid levels in body fluids. Opioid levels in cerebrospinal fluid (CSF) have been of particular interest because presumably these levels would reflect CNS activity of the substance. Morphine-like factors in the CSF of headache patients were measured, comparing levels during headache episodes to levels at pain-free periods. The lowest level of the factor occurred during episodes of headache; during pain-free states, the CSF concentrations of morphine-like factors were three to four times higher than at pain-free periods.[25]

Terenius and Wahlstrom developed a method of estimating enkephalin activity in cerebrospinal fluid by a fractionation procedure followed by measurement by radioreceptor assay.[26] In a series of experiments comparing chronic pain patients with patients not suffering from pain and healthy persons, they found that CSF levels of the morphine-like substance varied, with the lowest levels occurring in the chronic pain patients.

In a further study involving 37 chronic pain patients, subjects were divided into two groups: (1) those having pain of a mainly organic origin, that is, a somatic lesion was the basis for the pain, and (2) a group of psychogenic pain patients for whom no somatic lesion could be found. Patients with organic pain syndromes were found to have significantly lower levels of an enkephalin-like substance as compared to the psychogenic pain patients. Additionally, depressive symptomatology was correlated with levels of the enkephalin-like substance: Higher levels of the enkephalin-like substance correlated significantly with higher scores of depressive symptomatology.[27]

In a later review of this series of experiments with chronic pain patients, one of the authors commented that the most appropriate observation to be made was that deviations from normal occur in pathological conditions. The significance of the variability among patients remains unclear. Localized pain may be the result of a localized deficiency of endorphins, or pain itself may activate inhibitory mechanisms, suppressing endorphin production.[28]

ENDOGENOUS OPIATES AND THE GATE CONTROL THEORY OF PAIN

As the biochemical pathways of enkephalins and endorphins become clearer, many questions remain about how pain is perceived and how psychosocial factors affect pain. In 1965 Melzack and Wall proposed the "gate control" theory, which integrates both physiological and psychological components of pain. According to this theory, central inhibitory mechanisms act to modulate pain impulse transmission.[29] How are endogenous opioids involved in the gate control theory?

The gate control theory proposes that pain impulses are modulated at the level of the dorsal horn of the spinal cord. The modulation is dependent on complex feedback systems located in higher centers, especially those located in brain stem retic-

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ular structures. Pain impulses are carried from the periphery by two types of fibers: (1) small diameter fibers that on entering the spinal cord form synapses in laminae I of the dorsal horn, and (2) large diameter fibers that enter more medially, penetrate the dorsal horn at laminae IV and V, then sweep up into laminae II and III (also called the substantia gelatinosa). In the gate control model, the small neurons in the substantia gelatinosa are the site of the spinal "gate" and play a major inhibitory role in pain transmission. In addition to input from the small nociceptive fibers and the large non-nociceptive fibers, cells in the substantia gelatinosa are thought to be influenced by pathways originating in higher centers—in the sensorimotor cortex as well as in the periventricular, periaqueductal, and raphe areas.[30] After modulation by cells in the substantia gelatinosa, pain impulses ascend from the dorsal horn, some terminating in the brainstem reticular formation and others proceeding to the thalamus.

Since the dorsal horn and the originating sites of the descending pathways are rich in enkephalin neurons, enkephalins may be the inhibitory neurotransmitter—which are modulating pain impulses at the spinal gate. What do they inhibit? Although the answer to this question is not entirely clear, morphine, beta-endorphin, and enkephalin have been found to inhibit the release of Substance P from the rat trigeminal nucleus.[31] Substance P has been implicated as a sensory transmitter of the primary afferent small-diameter fibers in the dorsal horn of the spinal cord. Furthermore, there is immunohistochemical evidence that met-enkephalin and Substance P have a similar distribution in areas associated with pain and analgesia, such as the substantia gelatinosa of the spinal cord dorsal horn and the spinal trigeminal nucleus.[11] The role of Substance P remains controversial, since it seems to have a dual nociceptive action. Frederickson et al concluded that at low doses, Substance P acts to release endorphins and thus inhibits pain transmission, whereas at high doses, it excites nociceptive neurons.[32]

CLINICAL IMPLICATIONS

It is easy to see why the mechanisms of pain have been so elusive for so long, given the complexity of such a small but significant component as the function of endogenous opiates. Nevertheless, the biochemical mechanisms underlying the transmission of pain are being carefully studied, and the management of acute and chronic pain patients by the health team continues. Will an understanding of the activity of endogenous opiates lead to the development of an analgesic that controls pain without the concomitant problems of tolerance and dependence? That rapid degradation of the naturally occurring pentapeptides methionine-enkephalin and leucine-enkephalin limits their therapeutic usefulness. Synthetic analogues are being developed. Unfortunately, thus far, both natural and synthetic opioids produce tolerance and dependence.[33,34] There is no evidence that individuals are tolerant of or dependent on their own endogenous opiates, however. The reason that dependence does not occur is probably because of sequestration of the peptides in subcel-

lular structures and the rapid breakdown of the peptides, particularly the short-chain enkephalins, after their release from nerve terminals.[35]

Opiate analgesics may be developed that do not have other side effects (respiratory depression, eg). Subpopulations of opiate receptors exist, some of which mediate the analgesic effects of morphine and others that mediate the lethal effects (presumably cardiovascular functions and respiratory depresssion).[36] The discovery of opiate receptors that mediate specific effects offers hope of developing narcotics that can produce analgesia without respiratory depression.

Another implication of endogenous opiate research is further development and wider use of electrical stimulation for chronic pain patients. At the University of California, San Francisco, selected chronic pain patients are being treated with "neuroaugmentation," which means using stimulation devices to augment functions of the CNS. Chronic pain patients who are selected for this treatment are divided into two groups: those with pain of a central origin and those with peripheral pain. For central pain patients, electrodes are implanted into the somatosensory area, the internal capsule, or thalamus. For patients with peripherally evoked pain, electrodes are implanted into the periaqueductal/periventricular gray matter. Presumably analgesia produced by stimulation of the latter sites is mediated by endogenous opiates. A 60% to 75% success rate is reported for peripheral pain syndromes, and a 40% success rate is achieved with patients having pain of a central origin.[37]

An alternative to implantation of brain electrodes is analgesia produced by stimulation of peripheral sites. Use of transcutaneous nerve stimulators (TNS) is a method of pain control familiar to nurses. Some patients who do not get relief of pain using conventional high-frequency TNS devices report more success with acupuncture-like low-frequency TNS, suggesting that the mechanisms of action are different.[38] Analgesia from acupuncture-like TNS is reversible by naloxone, whereas conventional TNS analgesia is not. This would seem to indicate that acupuncture-like methods may stimulate endogenous opioids.[39]

Although electrical stimulation is helpful for some patients with somatogenic pain, patients with no objective signs of somatic illness and who are deemed *psychogenic* pain patients are poor candidates for peripheral conditioning stimulation.[37] Somatogenic and psychogenic pain patients have different levels of enkephalin-like material,[26] but the significance of these differences is not known. Regardless of the etiology of pain, from the patient's viewpoint the subjective experience of pain may not be different. Pain is after all a conscious sensation and, therefore, involves higher cognitive structures. It is the task of the clinician to assist the individual to achieve a psychological state (distracted or relaxed, eg) such that when noxious impulses arrive, the endogenous opiate system can respond maximally to inhibit the pain.

There is hope that further research on endogenous opioids will answer questions about physiological mechanisms of pain as well as provide additional tools for relief of pain. Research questions from a nursing perspective would be: How do endoge-

nous opiate levels change in response to nursing interventions such as relaxation and massage in the patient experiencing moderate pain? Would it be possible to use an individual's endogenous opiate level to determine amounts of exogenous opiates necessary for effective pain relief? Is there a relationship between endogenous opiate levels and anxiety in patients with nociceptive pain? How do levels of endogenous opiates change in response to nonpainful stressors?

Finally, research on endogenous opiates may lead to the development of models for determining the psychophysiological basis for some illnesses. A more complete understanding of endogenous opioids and solutions to other complexities of mind-body interaction provide a challenge for the future.

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