The analgesic effects of morphine and other opiates have long been recognized, but the mechanisms underlying these effects have only recently been uncovered. First, opiate receptors were discovered and their distribution throughout the central nervous system mapped. Then endogenous morphine-like compounds, called endorphins and enkephalins, were identified. One of the most promising aspects of understanding the physiology and pharmacology of these endogenous opiates is conquering control over pain.

Key Words: Neuroanatomy, Neurophysiology, Pain.

Morphine and other opiates have been used for the relief of pain and other medicinal purposes for centuries. Only very recently has the mechanism by which morphine produces its analgesic effects been elucidated.

Animal experiments have shown that injection of morphine into the periaqueductal area of the brain is far more effective in producing analgesia than are injections in any other part of the brain. These results raised the question: What underlies the topical specificity of this brain region?

It was proposed that morphine and other opiates might act on specific membrane receptors and so a search for such receptors was initiated. Radio-labelled opiates, injected into the brain, combined with the putative receptors and made it possible to determine the distribution, density, and characteristics of “opiate” receptors. These opiate binding sites are concentrated on the synaptic membrane, are specific for opiates, and mediate all pharmacological effects of opiates. Furthermore, the receptors have striking stereospecificity; that is, the opiate or drug must have the proper shape to bind to the receptor surface. In fact, it has been demonstrated quantitatively that the receptors bind with a “tightness” or “affinity” comparable to their pharmacological potency.

DISTRIBUTION OF OPIATE RECEPTORS

Biochemical assays have revealed opiate receptors throughout the brain and neuroaxis. However, there may be as much as a 40-fold difference in receptor density from one region to another. The brain areas with the highest receptor count are the midline and intralaminar nuclei of the thalamus, which are the sites of termination of the paleospinothalamic and spinoreticulothalamic fibers. The amygdala, the periaqueductal gray matter, the hypothalamus, and the medial thalamus also have a very high receptor density. In contrast, the white matter of the brain and the cerebellum are essentially devoid of opiate receptors.

Within the brain stem, opiate receptors are highly concentrated in the solitary nuclei. Here the receptors are localized to vagal nerve fibers themselves. Within the spinal cord, opiate receptors are localized in the dorsal horn to laminae I to III, with the white matter being devoid of opiate receptors. In fact, the narrow streak outlining the dorsal gray matter is the richest part of the spinal cord in opiate-receptor content.

Opiate receptors are mostly confined to the CNS, but some peripheral tissues such as the gut respond to opiates and have opiate receptors. These peripheral tissues have provided a convenient test preparation for doing bioassays to evaluate the effectiveness and potency of synthetic opiates.

If the dorsal roots are sectioned in an experimental animal and three weeks are allowed for the afferent fibers to degenerate, the opiate receptors on the lesioned side decrease by 50 percent. This loss accompanying afferent-fiber degeneration suggests that the opiate receptors are located on the primary afferent terminals. If, like other synaptic receptors, opiate...
conductance in cat spinal neurons. One cur- 

phine, however, has been shown to alter sodium 

ently, opiate receptors are postsynaptic units that 

bind rapidly with the opiate receptor and block the 

access of the opiate agonist, but they are incapable of 

producing the action of morphine or other agonists. 

Naloxone is one such substance and is commonly 

used to block the effects of morphine. 

ACTION OF OPIATES AT RECEPTOR SITES

The exact action of opiates is not known. Mor­

phine, however, has been shown to alter sodium 

conductance in cat spinal neurons. One cur- 

rent hypothesis proposes that the opiate receptor os- 

cillates between two forms: in one form it binds 

sodium and in the other it releases sodium. Appar- 

ently, opiate receptors are postsynaptic units that 

combine with a neurotransmitter that functions by 

altering the membrane’s conductance to sodium. 

The opiate receptor’s action on the sodium conductance of 

subsynaptic membrane seems quite analogous to 

the glycine receptor’s action on chloride conduct- 

ance. 

ENDOGENOUS OPIATES—THE ENKEPHALINS 

AND β-ENDORPHIN

The foregoing observations raised the questions: “Why does the brain have specific receptors for mor- 

phine, a plant alkaloid? Are there morphine-like sub- 

stances in the body?” The immediate and striking 

answer for these questions was the discovery of en- 

dogenous compounds with morphine-like proper- 

ties. In 1975, opiate-like substances were discov- 

ered as natural constituents of the brain. The 

generic term for these compounds is endorphin (from “endogenous” and “morphine”). The discovery of 

endogenous endorphin led to a research explosion 

whose consequences are altering our understanding of pain, mental health, and drug addiction. 

All endorphins thus-far discovered are peptides. 

The major endorphins identified in the brain to date 

are methionine enkephalin, leucine enkephalin, 

and β-endorphine. Although these substances 

have qualitatively similar actions, they differ in 

molecular size, site of origin, site of action, physiology, 

and pharmacology. 

The enkephalins are small peptide molecules con- 
sisting of five amino acids. They have been identified 
in many brain regions and in the dorsal horns of the 

spinal cord. In fact, the distribution of the enkephalins 
corresponds to that of the opiate receptors. The 

highest concentrations of the enkephalins are in the 

caudate nucleus, the anterior hypothalamus, the cen- 
tral gray matter, and the substantia gelatinosa—the 
same regions of the CNS in which the opiate receptors 

are found in the highest densities. 

The enkephalins have been isolated from the syn- 

aptosomal fractions of brain homogenates and they 
have been identified in specific nerve terminals by 
immunoochemical methods. When released from 

nerve terminals they are either rapidly destroyed by 
specific inactivating enzymes or they combine with 
opiate receptors of the postsynaptic membrane and 

alter the activity of the cell bearing the receptors. All 
of this accumulated experimental evidence suggests that 
the enkephalins are neurotransmitters. 

When the enkephalins combine with the opiate 

receptors, usually the action of the cell bearing the 

receptors is depressed. For example, in the spinal 

cord, where the action of enkephalin is most clearly 

understood, small enkephalin-containing interneu- 

rons of the substantia gelatinosa make axo-axonic 
synapses on the primary afferent terminals conveying 
pain impulses (Fig. 11). Substance P is the transmitter 
of these primary afferent neurons. Activation of the 
enkephalinergic neurons reduces the amount of sub- 

stance P released by the action potentials in the 

primary afferent fiber. The functional consequence is 
a reduction in the postsynaptic potentials in the sec- 

ond-order neurons. It remains to be determined 

whether all depressant effects of enkephalin are medi- 

ated by this presynaptic type of inhibition at axo- 

axonic synapses. At some sites in the brain, enkeph-
Fig. 11. An axo-axonic synapse. A small enkephalinergic interneuron of the substantia gelatinosa terminating on the opiate receptors of a primary afferent terminal.

Enkephalin appears to exert direct postinhibitory or excitatory effects at axosomatic or axo-dendritic synapses. As suggested above, the localization of enkephalinergic neurons in the brain and spinal cord has been mapped out. These neurons presumably make up specific neuronal systems that mediate the integration of sensory information relating to pain and emotional behavior.

β-endorphin is a very large peptide molecule consisting of a long sequence of amino acids. It is contained in virtually all cells of the intermediate lobe of the pituitary gland and in scattered cells of the anterior lobe. In fact, β-endorphin has been extracted only from the pituitary gland.

Like the enkephalins, β-endorphin binds firmly to opiate receptors but unlike the enkephalins it is not inactivated rapidly by tissue enzymes. The half-life of β-endorphin is four hours, whereas that of the enkephalin is two minutes. This difference in rate of inactivation probably accounts for β-endorphin's being more potent in its morphine-like characteristics than are the enkephalins.

β-endorphin produces a wide spectrum of relatively long-lasting effects. This and other evidence suggests that β-endorphin serves as a chemical messenger rather than as a neural transmitter. Its actions include analgesia, catatonia, and behavioral disturbances.

The pituitary cells that contain β-endorphin also contain the antibody against corticotrophin (ACTH). The pituitary gland appears to synthesize and release these two hormones together as a single large molecule ("Big ACTH"), which is subsequently separated into β-endorphin and ACTH. Although it is known that these hormones are released in response to stress, the possible target organs or functions of β-endorphin are as yet unknown. It has been suggested they are involved in the response to severe trauma.

The properties of the enkephalins and β-endorphin are summarized in the Table. New information about these endogenous opiates is coming to light daily. Perhaps no field of neurobiology is moving at as fast a pace. Although current reviews are provided in the references, they will be outdated by the time this paper is in print. Nonetheless, it is these substances—and probably others yet-to-be discovered—that account for the success of the new procedures evolving for the management of pain as described in Part III of this series.

### Table

<table>
<thead>
<tr>
<th>Physiological Property</th>
<th>Enkephalins</th>
<th>β-endorphin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Throughout CNS; concentration in any region correlates with density of opiate receptors; absent from white matter</td>
<td>Confined to the pituitary gland</td>
</tr>
<tr>
<td>Intracellular Location</td>
<td>In nerve terminals and synaptosomal fraction of brain homogenates</td>
<td>Contained within pituitary cells as very large molecule</td>
</tr>
<tr>
<td>Molecular Size</td>
<td>Small peptides (5 amino acids)</td>
<td>Large peptides (long sequences of amino acids)</td>
</tr>
<tr>
<td>Mode of Action</td>
<td>Combine with opiate receptors on postsynaptic membrane to alter sodium conductance</td>
<td>Released as &quot;Big ACTH&quot; in response to stress; acts as chemical messenger (hormone); target organ unknown</td>
</tr>
<tr>
<td>Rate and Means of Inactivation</td>
<td>Rapidly inactivated by specific inactivating enzymes; half life is two minutes</td>
<td>Not inactivated rapidly by tissue enzymes; half life is four hours</td>
</tr>
<tr>
<td>Hypothesized Function</td>
<td>Neurotransmitter: 1) at axo-axonic synapses, induces presynaptic inhibition and 2) at axo-dendritic synapses, induces postsynaptic inhibition or excitation</td>
<td>Produces a wide spectrum of long-lasting effects, including analgesia in severe trauma; catatonia and behavioral disturbances</td>
</tr>
<tr>
<td>Relative Potency of Morphine-like Properties</td>
<td>Weaker and less enduring</td>
<td>Most potent of the endogenous opiates and long enduring</td>
</tr>
</tbody>
</table>

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