CHAPTER 2
THE ENDOGENOUS OPIOID SYSTEMS

The complex effects, both beneficial and adverse, of opioid analgesics can be traced to the interaction of these agents with endogenous opioid systems. Opioid compounds and their receptors exist throughout the central and peripheral nervous systems and in other tissues. Opioid systems are involved in a diverse array of homeostatic functions and movement control as well as the processing of noxious sensory input. The antinociceptive system, involved in pain modulation, is itself exceedingly complex. Information about this system is useful background for an understanding of the effects of opioid analgesics.

Mechanisms of opioid analgesia

Pain transmission in the spinal cord is regulated by a balance of facilitatory and inhibitory influences operating on the neural circuits of the somatosensory system. Noxious stimuli activate high-threshold primary sensory neurons in the periphery. This activity is conducted to their central terminals, which synapse on second-order nociceptive neurons in the spinal cord. Although opioid compounds are active in the periphery as well, they produce analgesia primarily by inhibiting nociceptive transmission in the central nervous system (CNS).

Opioid receptors located presynaptically and postsynaptically at the first central synapse in the spinal cord have been most extensively studied. Those located on the presynaptic nerve terminal decrease the release of excitatory neurotransmitters from nociceptive neurons, specifically the neurons that send small C-fibers and A-delta fibers into the periphery and respond to a variety of noxious stimuli. This presynaptic inhibition is caused by the effects of opioid receptor activation on ion channels. Specifically, opioid activation leads to hyperpolarization of the terminal through the opening of potassium channels or closing of calcium channels. These hyperpolarized neurons are less likely to have spontaneous discharge or evoked responses.

Opioid receptors located postsynaptically have similar effects on the second-order neuron. Hyperpolarization caused by changes in ion fluxes leads to a reduced response of this neuron as it receives excitatory input from first-order nociceptive neurons.

Signal transduction from opioid receptors occurs through binding to inhibitory G proteins. One opioid receptor can regulate several G proteins, and multiple receptors can activate a single G protein. Likewise, a single G protein can regulate several effectors, and a single effector can be activated by several G proteins. Through these mechanisms, a cascade of complex processes can be initiated, involving activation of protein kinases, stimulation of genes, and generation of other neuromodulators. These processes in turn alter the response characteristics of the neuron and lead to synthetic processes that can change various receptors or other structures. The interactions and outcomes remain poorly understood and are undergoing intensive investigation.

Endogenous opioid systems and analgesia

Opioids exert their analgesic effects by binding to and activating receptors that comprise part of an endogenous opioid system. This system normally operates to modulate sensory input caused by noxious stimuli, its response activated by endogenous peptide neurotransmitters. Opioids mimic and amplify the actions of these neurotransmitters.

Endogenous opioid peptides

The endogenous opioid system includes a large number of opioid peptides that are ligands for numerous types of opioid receptors. Some of these naturally occurring peptides produce morphinelike effects and can be displaced from their binding sites by opioid antagonists.

Three distinct families of endogenous opioid peptides have been well characterized: the endorphins, the enkephalins, and the dynorphins, which derive from the precursor polypeptides pro-opiomelanocortin, proenkephalin, and prodynorphin, respectively. More recently, 2 additional short peptides that display a high affinity and selectivity for μ opioid receptors have been identified. These peptides, endomorphin-1 and endomorphin-2, produce potent and prolonged analgesia in animals. However, the gene coding for them is yet unknown.

The endogenous opioid peptides bind to opioid receptors. In the CNS, there are 3 primary opioid receptor types that mediate analgesia, which are designated μ, κ, and δ (see table 3). Preferentially, enkephalins interact with the δ receptor, dynorphins interact with the κ receptor, and endorphins bind to both μ and δ receptors with comparable affinity. As noted previously, these peptides have diverse physiologic functions, one of which involves antinociception. In different systems and settings, they

can appear to function as neurotransmitters, neuromodulators or, in some cases, neurohormones. Research during the past 3 decades has only just begun to elucidate the physiologic roles of these peptides and the receptors with which they interact.

Opioid receptors

Opioid receptors, like other G protein–coupled receptors, are characterized by 7 transmembrane domains. High densities of opioid receptors are located in all areas of the CNS known to be involved in integrating information about pain—the brainstem, the medial thalamus, the spinal cord, the hypothalamus, and the limbic system. Opioid receptors also have been identified in the periphery. Recently, the μ, κ, and δ receptors have been cloned and their cDNA sequenced, yielding invaluable information about receptor structure and function.

Drugs that bind to opioid receptors are classified as agonists, partial agonists, mixed agonist-antagonists, and antagonists. Receptor activation by an agonist initiates pharmacologic actions (table 3), whereas an antagonist occupies the receptor without these effects. In patients with physical dependence, displacement of an agonist drug by an antagonist is associated with abstinence (withdrawal). The ability of the drug-receptor complex to initiate a pharmacologic effect is defined by the intrinsic activity of a drug. The intrinsic activity is further

Table 3. Opioid receptors, their location, and responses mediated by them

Receptor	CNS location	Response on activation
μ	Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)	μ_1: supraspinal analgesia, physical dependence; μ_2: respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
κ	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
δ	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria, physical dependence

CNS, central nervous system.

Adapted, with permission, from Yaster M, Kost-Byerly S, Maxwell LG. Opioid agonists and antagonists. In: Schechter NL, Berde CB, Yaster M, eds. Pain in infants, children, and adolescents. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2003:181-224.

described by the receptor occupancy required to yield a defined effect. If a drug has a sufficiently low intrinsic activity, high receptor occupancy still produces less than a maximal response, these drugs are called partial agonists. Partial agonists may also have antagonistic properties, because they compete with pure agonists for occupancy of opioid receptor sites. The degree to which they compete is determined by their affinity for the receptor. Buprenorphine hydrochloride, an analgesic now also used for addiction therapy, is a partial agonist with very high affinity for the μ receptor; it can compete for the receptor and have antagonist properties and also is difficult to displace from the receptor once bound.

The opioid analgesics most commonly used in clinical practice bind selectively to the μ receptor and are called μ-agonists. Morphine is considered the prototypical μ-agonist. Although there are many similarities between morphine and the other μ-agonists, the different drugs can produce varied effects in the individual patient. For example, when a patient who is chronically exposed to one μ-agonist is switched to another, pain can often be controlled by doses of the second drug that are far lower than predicted by their relative potencies, and both the pattern and severity of nonanalgesic effects can be distinct. This observation, now known as incomplete cross-tolerance, suggests that these μ-agonists are not acting through identical receptors.

Pharmacologic studies completed more than a decade ago demonstrated that there were at least 2 μ receptors, which were labeled μ_1 and μ_2 receptors. After the cloning of the μ receptor, MOR-1, investigators have evaluated the possibility of different alleles in the gene coding for MOR-1 and different phenotypes from these genes based on single nucleotide polymorphisms (so-called splice variants). Studies have confirmed the existence of different alleles in the population, and antisense mapping of gene-coding fragments known as exons has established the existence of multiple polymorphisms. To date, 15 splice variants of the original gene encoding the μ receptor (*Oprm*) have been identified, and at least 10 show high affinity and selectivity for μ opioids in receptor-binding assays.

Considering the potential for both multiple opioid receptors distinguished by gene sequence (alleles) and multiple receptors distinguished by gene expression (polymorphisms produced by splice variants), it is likely that the μ receptor actually comprises literally dozens of versions within the population. In an individual, different μ-agonists may lead to different clinical effects, depending on the predominating form of the receptor. Recent studies

using ultra-low doses of μ-antagonists have identified an intriguing paradox. At these doses the antagonists are actually analgesic and they reverse opioid tolerance. Combined with a μ-agonist, they provide enhanced analgesia. These findings have suggested that the opioid receptor, which is widely recognized as a mediator of inhibitory actions, can exist in a form that is excitatory. This excitatory opioid receptor is blocked by ultra-low doses of the antagonist. Further research into this mechanism may lead to the use of antagonists at ultra-low doses in clinical practice.

Most recently, a receptor that is structurally similar to the opioid receptor was discovered. This receptor has been classified as opioid-receptor-like 1 (ORL_1). The natural ligand has been termed orphanin FQ (OFQ), or nociceptin. The physiology of this system is yet poorly understood. It appears to be involved in the central modulation of pain but does not appear to be implicated in respiratory depression.

Clinical implications

In the future, it may be possible to "type" a patient according to the predominant opioid receptor and select the drug that is most likely to have favorable effects. Combinations of opioids may ultimately be preferred in some patients to optimally activate the opioid system (some clinicians are empirically trying such combination therapy now). It is even possible that studies may allow development of opioids that activate antinociceptive systems without involving the "reinforcement and reward" brain systems that become problematic in persons genetically predisposed to addiction.

Research into the interaction between specific pain pathophysiologies and opioid systems may illuminate the phenomenon of poor opioid sensitivity and allow development of therapies that can convert a patient's poor response into a beneficial one. Studies have already shown that neuropathic pain is relatively less responsive to opioid therapy than pain of other types, a phenomenon that may be due, at least in part, to involvement of the N-methyl-D-aspartate (NMDA) receptor in the pathogenesis of neuropathic pain. Activation of the NMDA receptor has been shown to lessen the sensitivity of the opioid receptor, and NMDA receptor blockers reverse opioid tolerance in animal models. Further study of these interactions may yield useful combinations of drugs or preferred opioid treatment approaches in patients with relatively poor opioid responsiveness.

As receptors continue to be identified and characterized, the potential for development of highly selective agents increases. These drugs may have fewer unwanted effects or a better therapeutic index. For example, some agents have more affinity for the

μ or κ receptor and thus might be expected to have different actions on the gastrointestinal tract. At present, knowledge of the complexity of the opioid system involved in analgesia should be a continuing reminder of the need for clinical flexibility. Opioid rotation, the process of switching opioid drugs in an effort to identify the one with the most favorable balance between analgesia and side effects, is a rational approach, given the multiple phenotypes of the μ receptor.

Peripheral opioid mechanisms

Recently, opioid receptors that are capable of mediating analgesia in humans have been discovered on peripheral sensory nerve terminals. The prevailing peptides found in the periphery are the endorphins and enkephalins. Pharmacologic experiments indicate that the characteristics of receptors located in the periphery are very similar to those of receptors in the brain.

This peripheral opioid system interacts with immune functions. During inflammation, opioid peptides secreted by immune cells can activate opioid receptors on sensory nerve terminals to inhibit nociception. In addition, humans have been shown to possess a peptide called enkelytin (proenkephalin A), which has a potent antibacterial action. It has been suggested that immune or neural signaling leads to enhanced proenkephalin proteolytic cleaving, thereby causing the release of both opioid peptides and enkelytin simultaneously. These findings constitute a new concept of intrinsic pain control that involves mechanisms traditionally used by the immune system for mounting a host response to fight pathogens. The potential effects of exogenously administered opioids on the immune system require further study.

Existence of peripheral opioid mechanisms has suggested the potential utility of peripherally administered opioid medications. For example, some placebo-controlled studies have demonstrated that relatively low doses of morphine, when administered into a site of peripheral injury (eg, a joint space after surgery), can produce analgesia. Other studies suggest a similar outcome from morphine applied topically to painful wounds, a result that is independent of systemic drug uptake. Further studies are needed to clarify the efficacy of peripherally administered opioid medications and to explain why there is such interindividual variance in responses.

Conclusion

The physiologic modulation of noxious stimuli involves a highly complex system that integrates the actions of multiple opioid

receptors and endogenous opioid peptides. The interaction of this system with different opioids is similarly complex. Future research that elucidates the pharmacology and molecular biology of the endogenous system holds great promise for development of new selective drugs, rational selection of treatments for individual patients, and fashioning of novel drug combinations to optimize the benefit and minimize the risks associated with opioid therapy.

Suggested readings
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