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Pharmacology of Narcotic Analgesics

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Abstract: Opioid receptors are described and differentiated by their affinities for specific agonists and antagonists. Their sites of action and receptor activities are discussed. Tachyphylaxis and tolerance are described and methods for overcoming these problems are recommended. Suggestions are made regarding future drugs to act at specific receptors. **Key Words:** Opiate receptors—Spinal opioids—Agonist-antagonists.

Opiate analgesics, (natural or synthetic compounds that have morphine-like analgesic effects) are the mainstay in the treatment of acute and certain types of chronic pain. Clinically, this family of drugs is recognized as providing pain relief over a wide range of useful doses without loss of touch, temperature, or proprioception modalities.

Pharmacologists have extensively investigated opiates to establish if endogenous products and exogenous opiates produced effects at similar receptors in the central nervous system and in the spinal axis. Identification and localization of opiate receptors was made possible by the development of radioactive ligand displacement technique in the early 1970s (1). In addition, endogenous morphine-like activity was identified from specific body peptides, many of which are part of the β-lipoprotein molecule that is secreted in the pituitary. The larger fractions of this molecule having analgesic effects are classified as endorphins, whereas the smaller pentapeptides are classified as enkephalins. High concentrations of opiate receptors have been identified in the periaqueductal gray matter of the limbic system, in the medial thalamus, in the amygdala, in the posterior pituitary gland, and in the substantia gelatinosa of the dorsal horn in the spinal cord.

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Chemically, the exogenous opiates can be related to morphine, as they can fit into the basic morphine T structure requirement for receptor binding.

Over the years, a number of active drugs related to morphine have been synthesized. These substances vary in potency and in the duration of their effects, but all had effects similar to those of morphine, including addiction and respiratory depression. In addition, derivatives of morphine were synthesized, which antagonized the effects of morphine. Some of these antagonists also exhibited agonist-analgesic effects, which led to the development of the agonist-antagonist class of drugs exemplified by nalorphine.

To account for the pharmacologic effects of these agonist-antagonist drugs, a multiple receptor hypothesis was postulated. Martin (2), in his investigations, presented evidence to support the presence of three opiate receptors (μ, κ, and σ). The μ receptor was associated with central analgesia and respiratory depression. The κ receptor was associated with spinal cord analgesia, and the σ receptor was associated with dysphoric and psychomimetic effects. In addition, Martin postulated that, when administered, these substances can have effects on more than one opiate receptor and postulated that nalorphine antagonized morphine at the μ receptor while producing analgesia at the κ receptor. Nalorphine was also observed to have significant dysphoric effects at high doses by an effect at a third (σ) receptor. The realiza-

tion that the same drug could bind and produce effects at two different opiate receptor sites led to the development of other drugs which, like nalorphine, had both agonist and antagonist effects. The general characteristic of this group of drugs is that each produces maximal effect (a ceiling effect) in both analgesia and respiratory depression.

When opiates are administered, the site of action, i.e., the brain or spinal axis, depends upon the mode of drug administration and thus the concentration of analgesic at the receptor site. Therefore, when the opiate is injected systemically, the concentration of drug at the brain receptors is high, whereas that in the spinal cord is low. In contrast, the reverse situation occurs when the drug is injected into the spinal neuraxis. In the spinal axis, opiates inhibit nociceptive impulses. These impulses are carried by the slow conducting A and C fibers to the spinal cord where they synapse at junctions in the substantia gelatinosa of the dorsal horn. This action of opiates in the spinal cord is believed to be at the synapses where they inhibit the release of excitatory neurotransmitters such as substance P or somatostatin, which are believed to be responsible for the postsynaptic transmission of pain impulses. Pain perception is intrinsically regulated by the release of endogenous endorphins and enkephalins in the substantia gelatinosa. The dorsal horn synapses are also modulated by descending impulses from the brain, and the putative neurotransmitters at the dorsal horn for this effect appear to be monoamines 5-hydroxytryptamine (5-HT) and epinephrine (3). In the central nervous system, the analgesic effect of opiates acts on μ, κ or other analgesic receptors.

At present, at least two other opiate receptors have been reported, a δ and an ϵ receptor (4–6). Specifically, the δ receptor is believed to be an enkephalin receptor that may act to modulate the μ receptor. The ϵ receptor is believed to be responsive to the endogenous endorphins.

As the receptor information unfolds, evidence has now been presented by Pasternak (7) that the μ receptor needs to be subdivided into μ_1 and μ_2 receptors. This conclusion is based upon the finding that two drugs, naloxonazine and naloxazone antagonize morphine analgesia but do not antagonize the respiratory depression of morphine in animals. These drugs then would be classified as μ_1 antagonists and the respiratory depressant effects of morphine would be through the μ_2 receptor effects.

In addition to the above observations, the enkephalins have also been noted to have high affinity for the μ_1 receptor, which is similar to that seen with morphine. The enkephalins also have a low affinity for the second opiate receptor, the δ receptor, which is postulated to modulate the μ-opiate response. In summary, morphine acts as a high-affinity μ_1-receptor agonist and a low-affinity μ_2-receptor agonist whereas enkephalins behave as μ_1- and δ-receptors agonists.

Common problems encountered during administration of opiates are the development of tachyphylaxis and tolerance. Currently, it appears that tachyphylaxis is directly related to the duration of the time that the receptor is exposed to high concentrations of opiates and that the development of tolerance can be delayed by the use of continuous low infusion drug rates that lower the concentration of drug at the receptor sites to minimally effective analgesic concentration. This speaks strongly for the use of patient-controlled analgesia (PCA) where drug levels are consistently low rather than the use of intermittent bolus doses with resultant variable high and low concentrations of drug at the receptor. Another method of obtaining lower concentrations of opiates at any one receptor is through the use of agonist drugs that produce analgesia at a different receptor, i.e., δ- or κ-receptor agonists or by using drugs that modulate the opiate response. At present, κ- or δ-specific drugs are being investigated but none are clinically available.

A second approach is to use drugs such as clonidine, which can act to modulate nociceptive input at the spinal cord and in the brain by increasing the monoamine influence at synaptic sites. Coombs (8) has demonstrated that the α_2 agonist, clonidine, modulates the release of monoamines, especially 5-HT and norepinephrine, both centrally and at the dorsal horn, producing an additive analgesic effect.

A further observation relating to tolerance is the finding that cross tolerance between receptors does not appear to occur. For example, tolerance at the μ receptor does not cause tolerance at κ or δ receptors; therefore, use of drugs active at a second receptor in a tolerant patient appears to "restore" μ-receptor sensitivity. Furthermore, in selecting specific receptor agonists when they become available one should also consider the observation of Schauss (9) that visceral pain was more responsive to κ-receptor agonists than to δ-receptor agonists, whereas cutaneous electrical and thermal stimulation, which approximates somatic pain, responds best to μ-and δ-receptor ag-

onists. As δ- and υ-specific drugs become available, the intermittent use of these agents, depending upon the site of origin of pain, should help to effectively treat the patient who becomes tolerant and should also delay or prevent the development of tolerance.

In the future, it would appear that specific drugs could be developed that would minimize the undesirable side effects of opiates, i.e., respiratory depression and dysphoria. The future drugs could be any of the following: (a) A μ_1-specific agonist; (b) a mixed agonist-antagonist drug with agonist action at $\mu_1$and antagonist effect at μ_2; (c) a μ_2-specific antagonist that could be given with opiates having μ_1 and μ_2 actions; or (d) a potent κ- or δ-specific drug.

In summary, as the pharmacology of opiates becomes clearer and drugs are developed with specific receptor actions, patients with acute pain will be more effectively medicated.

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