# Understanding How Opioids Contribute to Reward and Analgesia

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Opioids acting at the mu opioid (MOP) receptor produce powerful analgesia. They also produce an intensely rewarding effect that can lead to addiction. The analgesic effect of MOP receptor agonists derives from a direct inhibitory effect on pain transmission at the spinal-cord level and through activation of a descending pain-modulatory pathway. The rewarding effect of MOP agonists is the result of their actions in the mesostriatal dopamine pathway classically associated with both natural and drug rewards. Both the analgesic and rewarding effect of MOP agonists are best understood in the context of decision making under conditions of conflict. Pain is one of many competing motivational states, and endogenous opioids suppress responses to noxious stimuli in the presence of conflicting motivations, such as hunger or a threatening predator. When a food reward is available, MOP agonists microinjected into the mesostriatal circuit promote its consumption, while concomitantly suppressing responses to noxious stimulation. The mesostriatal "reward" circuit, thus, appears to perform a function critical to decision making and can either amplify or suppress responses to noxious stimuli. *Reg Anesth Pain Med 2007;32:242-246.*

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Because pain is ubiquitous and is associated with robust objective and subjective responses, it has been conceptualized in many different ways. One broadly accepted concept is that pain is the sensation that results from somatic stimuli of sufficient intensity to threaten tissue damage (see Sherrington, p. 229[1]). According to this view, the relevant events for understanding pain revolve around the properties of the noxious stimulus. Because stimulus intensity typically correlates with the likelihood of significant tissue injury, this view has been affirmed by careful psychophysical studies that demonstrate human reports of perceived pain intensity are a robust and reproducible function of stimulus intensity.[2] Furthermore, when one studies the neurons of the afferent pathways that mediate pain sensation, their firing rate is also a reliable function of stimulus intensity.[3]

These study results are all well and good; however, in the real world, when tissue injuries occur, factors other than the properties of the stimulus play a major role in determining what an individual experiences. Clinicians who see patients with long-standing pain problems are often struck by exacerbations and remissions in the severity of the patient's pain that are independent of objective changes in a peripheral pathologic process. To the contrary, these fluctuations in pain level are often correlated with life stresses or changes in mood. Some painful conditions (e.g., migraine headache or fibromyalgia) have no identified tissue-damaging process. The opposite also occurs; individuals (athletes during a competition or soldiers in battle[4,5]) commonly sustain a significant acute injury without experiencing any immediate pain. Furthermore, placebo treatment often gives potent analgesia.[6,7]

These seemingly disparate observations show that a comprehensive framework for understanding pain must encompass not only the reliable responses to controlled stimuli observed in the psychophysical laboratory but also the perplexing variability that is seen by physicians in clinical practice. An important step toward such a comprehensive view begins by asking the following question: What biological purpose could possibly be served by having such variable responses to similar tissue-damaging stimuli? One simplifying framework that moves us in that direction is to consider that pain is just one of the many motivations that determine the behavior of an individual. Within this larger framework, pain can be conceptualized as a motivation that often occurs in the setting of other conflicting motivations. For example, consider that

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you are hanging on a ledge by your fingers, the pain in your hands and arms is growing, but if you let go, the consequences are extreme, so survival demands that you tolerate much greater pain. Consider a less extreme example: You are sitting in an uncomfortable chair. However, dessert is about to be served, and it is your favorite. Chances are, you will endure the discomfort a little while longer.

Ethologists and experimental psychologists have studied such conflict situations in simplified form in animals. They have demonstrated that behavioral responses to pain can be suppressed under a variety of conditions; for example, during micturition,[8] in the presence of a predator, or when confined to an environment in which severe pain has previously been experienced.[9,10] Pain responses are also suppressed in situations in which rodents anticipate reward.[11] Under many circumstances, such suppression of pain responses can be prevented by administration of nonselective opioid-receptor antagonists such as naloxone. Interestingly, in this regard, placebo analgesia can also be reversed by naloxone.[7,12] This finding indicates that endogenous opioids are a key signaling molecule for pain suppression and that pain suppression often occurs in clinical situations in which the patient believes a treatment effective for pain has been given.

This critical role of endogenous opioids in pain suppression provides an important insight about the biology of opioid analgesics. Opioid analgesics such as morphine do not simply inhibit pain-transmission pathways; they mimic the action of endogenous opioids that are released in response to *specific conflict situations*; that is, when a noxious stimulus is present, but a compelling reason exists to avoid responding. These compelling reasons include the threat of even greater injury or death or the possible loss of some highly desired reward. In this article, I will briefly describe current views of where and how opioids act to reduce responses to pain.

## The Pain Sensory System and Spinal Opioid Analgesia

Throughout the body are primary afferent nociceptors with terminals that contain receptor molecules sensitive to mechanical deformation, temperature extremes, lowering of pH, and a variety of activating substances released by inflammation or other pathologic processes.[13] With appropriate stimuli, these receptor molecules depolarize the peripheral terminals of unmyelinated and small-diameter myelinated primary afferents. The depolarization induces action potentials that propagate to the central terminals of the afferents in the superficial layers (I, II, and V) of the gray matter of the spinal cord.[3] When active, the spinal-cord terminals of primary afferent nociceptors release glutamate, and many also corelease a peptidergic neurotransmitter. These neurotransmitters combine to produce prolonged firing of the second-order and third-order neurons in the dorsal horn. Activity in these spinal-cord projection neurons then propagates to the brain stem and thalamus, where their axons terminate. The brain-stem and thalamic neurons that receive the nociceptive message from the spinal cord project to a variety of forebrain structures, including the amygdala, the hypothalamus, and the somatosensory, anterior cingulate, and insular cortices.[14,15] Imaging studies have shown robust correlations between stimulus intensity, activation of these cortical areas, and patient reports of pain.[16]

Opioids control the pain-transmission pathway directly through actions in the superficial layers of the dorsal horn.[17] Both primary afferent terminals and second-order dorsal-horn neurons bear mu opioid (MOP) and delta opioid (DOP) receptors.[18] Spinal application of MOP agonists reduces excitatory neurotransmitter release from primary afferent terminals by inhibiting a voltage-gated calcium channel.[19,20] Opioids also directly depolarize second-order dorsal-horn neurons by opening an inwardly rectifying potassium channel.[21] These actions of opioids in the dorsal horn make a major contribution to the clinical efficacy of spinal application of MOP agonists such as morphine.

## Opioids and Pain-Modulatory Systems

Although spinal opioids are highly effective for pain relief, the opioid story has much more to it. Very early on, investigators discovered that supraspinal sites contribute to the analgesic effect of systemically administered opioids.[17] In fact, careful mapping of the forebrain by microinjection of MOPs showed very significant hot spots for analgesia in cortex, hypothalamus, midbrain periaqueductal gray (PAG) matter, and rostral ventromedial medulla (RVM).[17,22,23] Furthermore, either lesions or microinjection of opioid antagonists into some of these same sites blocked the analgesic effect of systemic MOPs. These studies demonstrated that when morphine is given systemically, it acts in a distributed and simultaneous manner at multiple supraspinal sites. Furthermore, cutting the dorsolateral funiculus of the spinal cord blocks the analgesic effect of low-dose systemic morphine.[23] This finding showed that, in addition to its direct action on the spinal cord, systemic morphine also activates supraspinal structures that project down and control pain transmission at the level of the spinal cord.

Subsequent work demonstrated a "top-down" pain modulatory circuit that includes such structures as frontal-lobe cortical regions and the hypothalamus and amygdala. These regions project to the PAG, which, in turn, relays via the RVM to the superficial layers of the dorsal horn.[23] This anatomic arrangement enables the descending system to control nociceptive transmission at the first central synapse, where the nociceptive primary afferents terminate. The component nuclei of this pain-modulatory pathway contain MOP receptors and a relatively high concentration of the endogenous opioid peptides leucine and methionine enkephalin. Furthermore, activation of the descending pathway at rostral sites leads to release of endogenous opioids in downstream regions.[24]

## Activation of the Opioid Pain-Modulatory Pathway by Expectation of Harm or Expectation of Reward

When rodents encounter a threat, such as a predator or an environment in which they have received a significant and inescapable noxious stimulus, they typically freeze and become transiently analgesic. This form of stress-induced analgesia can be blocked by lesions of the central nucleus of the amygdala and by opioid antagonists (e.g., naloxone), given either systemically, into the PAG, or into the RVM.[10,25,26] In this case, the analgesic effect of being placed in a threatening context can be conceptualized as a "decision" to not respond to an imposed noxious stimulus. Its biological significance is illustrated by placing a rat in proximity to a predator, such as a cat. In this case, the value to the rat of avoiding movement is obvious because the predator is "judged" by the rat to be the greater threat than the noxious stimulus.[9,27] This "do not respond to pain" decision is implemented by the opioid-mediated, pain-modulatory pathway described above. A "do not respond" decision has also been demonstrated under conditions of anticipated reward. Dum and Herz[11] trained rats by feeding them on a hot plate held at room temperature. Of 2 groups of rats, the first group was fed regular laboratory chow, and the second group was fed highly palatable chocolate treats. After several feeding sessions, the rats were simply placed on the hot plate, which was then turned on. The rats fed regular chow jumped off the hot plate at about 5 seconds, whereas those that had been fed the chocolate remained on the hot plate almost twice as long. When given before the hot plate was turned on, naloxone had no effect on rats that had been fed regular chow, whereas it shortened the escape latency for the chocolate-fed rats, completely eliminating the difference between them and the chow-fed group.

## Bidirectional Control of Pain: Brain-Stem ON and OFF Cells and Behavioral Decision

Clearly, under certain conditions of conflict, the "do not respond to the noxious stimulus" decision is implemented by activation of a descending pain-modulatory pathway that depends on endogenous MOP agonists. Interestingly, in this regard, the component neurons of this descending modulatory pathway are of two distinct types: OFF cells that are activated by MOP agonists and inhibit responses to noxious stimuli and ON cells that are activated by noxious stimuli, are inhibited by MOP agonists, and facilitate responses to noxious stimulation.[22] ON and OFF cells are found in the PAG, the dorsolateral pons, and the RVM. RVM ON and OFF cells project directly to the dorsal horn, where they modulate pain transmission. Because lesions of the RVM do not inhibit responses to noxious stimuli, removal of facilitation is insufficient to block behavioral responses to noxious stimulation. This observation means that *activation* of RVM OFF cells (rather than inhibition of ON cells) is critical for suppressing responses to noxious stimuli. On the other hand, ON cells can be activated under a variety of conditions associated with hyperalgesia. These conditions include acute opioid abstinence and tonic noxious stimuli. I propose that when the individual makes a "do not respond to pain" decision, OFF cells are activated. In contrast, when the decision is to respond, ON cells are activated.

## Mesolimbic Dopamine Pathways and the "Decision Circuit"

These examples clearly show that under circumstances in which anticipated harm or reward conflict with the motivation to escape from a noxious stimulus, the decision to respond to the greater threat or to the reward involves inhibition of the response expected from the noxious stimulus. This "do not respond to pain" decision is typically implemented by the opioid-mediated, descending pain-modulatory system via the PAG and RVM projection to the dorsal horn. Conversely, the decision to respond to the noxious stimulus is promoted by activation of the descending facilitatory pathway, with activation of ON cells. Although interesting and informative, this observation leaves open a more interesting and more general question: How and where in the nervous system is the "respond" versus "do not respond" decision made?

The answer to this question is, as one might expect, quite complicated, and it appears to depend upon the nature of the drive state that is competing with noxious input for access to the motor system. For the sake of this short review, I will focus on the conflict between a palatable food reward and a concomitant noxious stimulus. Several studies have confirmed the competitive interaction between feeding (approach) and escape (avoidance) behaviors. Food consumption raises escape thresholds for noxious stimuli, and noxious stimuli will interrupt feeding.[28,29] Furthermore, as discussed above,[11] animals that expect a highly palatable food reward in a specific context have significantly higher pain thresholds when they are in that context. Importantly, their ability to wait for the expected reward was blocked by the opioid antagonist naloxone.

Although the specific brain circuitry that underlies the analgesic effect of reward expectancy is not known, a reasonable hypothesis is that the mesostriatal circuit implicated in drug and food reward is involved. Microinjection of MOP agonists directly into the ventral striatum (specifically the nucleus accumbens [NAc]) selectively enhances consumption of palatable food[30] and suppresses responses to noxious stimuli.[31] MOP agonist injection into the NAc activates neurons in the lateral hypothalamus and in the dopaminergic brain-stem region, the ventral tegmental area.[32] Furthermore, injection of addicting drugs such as morphine or cocaine into these regions produces both reward and analgesia.[33,34] These studies link anticipated reward to analgesia and are consistent with the idea that mesostriatal dopamine neurons are critical for this effect.

Electrophysiologic studies of the NAc yield some insight into the decision-making process. The NAc appears to contain multiple subsets of neurons. Some of these subsets encode the relative reward value or the expected reward value of a palatable food.[35,36] Evidence also suggests that neurons that encode anticipated reward promote reward approach and consumption.[37] Other subsets of NAc neurons appear to inhibit these approach behaviors, and I, along with other investigators, have proposed that they promote competing behaviors.[36,37] One possibility is that the NAc neurons that promote the response to pain inhibit those that promote consumption of palatable food. In any case, these studies indicate that the ventral striatum is a critical element in the circuitry involved in action selection under conditions of conflict. Furthermore, MOPs in this region promote the selection of actions that lead to consumption of palatable foods and, concomitantly, suppress the selection of actions that lead to escape from noxious stimuli.

In summary, conceptualizing pain as a motivational state that typically occurs in the setting of conflicting motivations leads to a deeper understanding of both the biological meaning and the neural mechanism of opioid analgesia. Threat or anticipated reward can elicit the release of endogenous opioids that inhibit pain responses through activation of a descending pain-modulatory pathway. Opioids also directly affect the decision process through an action in the mesostriatal dopamine pathway, where they concomitantly promote reward seeking and raise the threshold for responding to noxious stimulation.

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