# Neurobiology of Chronic Pain and Opioid Analgesic Dependence and Addiction

# 112

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**Abstract**

Pain is a highly prevalent worldwide issue, affecting 20 % of all adults. With increasing use of opioid analgesics over the past decade, there has been a concomitant rise in opioid analgesic abuse and dependence, particularly in the United States, Australia, and New Zealand. Many frontline clinicians receive little, if any, training or education in pain management or opioid analgesic pharmacology. In an effort to address this educational gap, the purpose of this chapter is to provide a basic and broad overview of (1) the neurobiology of pain (including classification and pathophysiology of acute and persistent pain), (2) the processes that occur naturally and pathologically when opioid analgesics are used for pain (including analgesia, tolerance, physical dependence, and addiction), and (3) an overview of the neurobiology specific to opioid analgesic addiction. The goal of this chapter is to improve the basic understanding of pain and opioid analgesic addiction for frontline clinicians.

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## 112.1 Introduction

Pain is an enormous worldwide problem. Twenty percent of adults in the world suffer from pain and 10 % of adults are newly diagnosed with chronic pain each year (Goldberg and McGee 2011).

Though controversial, opioid analgesics are often prescribed for pain. In 2009, the estimated worldwide prevalence of current opioid use was between 0.5 % and 0.8 %, approximating 24–35 million people, including nearly 18 million people (5.9 % of the population) in the United States (United Nations Office on Drugs and Crime 2011).

Although not a uniquely American issue, US citizens, constituting less than 5 % of the world's population, have been consuming 80 % of the global opioid supply, including 99 % of the global hydrocodone supply (Manchikanti and Singh 2008). This places opioid analgesics as the most commonly prescribed medication of any category in the United States (Kuehn 2007). In Australia, there was a 60 % increase in prescriptions for opioid analgesics and a 180 % increase prescriptions for oxycodone from 2002 to 2009 (Hollingworth et al. 2013; United Nations Office on Drugs and Crime 2011). In New Zealand, pharmaceutical opioids diverted from the medical system have been known to be a central source of opioids for injecting drug users since the regular supply of heroin was disrupted in the 1970s (Wilkins et al. 2011).

With regard to opioid abuse and addiction, this too is a global problem, with between 13 and 22 million people worldwide abusing opioids in the past year (United Nations Office on Drugs and Crime 2011). However, when we separate opioid abuse into heroin and opioid analgesic abuse, we again see substantial regional differences. In the majority of Europe, Africa, and Asia, heroin remains the most prevalent illegally consumed opioid. In the Americas, Australia, and New Zealand, illegally diverted or misused prescription opioids (e.g., codeine, hydrocodone, morphine, hydromorphone, oxycodone, meperidine, tramadol) are the primary opioids of abuse. In 2009, 1.9 million people in the United States were addicted to prescription opioid pain relievers and 359,000 addicted to heroin (United Nations Office on Drugs and Crime 2011). Morphine and methadone have become the "street" opioids of choice in New Zealand, with the number of opioid substitution treatment centers increasing from 650 in 1990 to more than 4,000 in 2011 – despite the shortage of heroin (Robinson et al. 2011). Additionally, some African and Asian nations have also reported a surge in opioid analgesic abuse in the last decade (United Nations Office on Drugs and Crime 2011; van den Brink and Haasen 2006).

In contrast to other commonly abused substances, prescription opioids are unique in that their consumption is prescribed and endorsed by healthcare professionals. Because of this, some individuals develop a false sense of safety regarding prescription opioids and erroneously believe that the severity and risk of negative side effects is lower with prescription opioids as compared to other substances. Nonmedical prescription opioid use, however, is associated with increased rates of unintentional overdose, significant physical and mental

health problems, and staggering societal cost (e.g., emergency room admissions, lost productivity) (McLellan and Turner 2008).

The purpose of this chapter is to provide a broad overview of the basic neurobiology of pain, the processes that occur naturally and pathologically when opioid analgesics are used for pain, and neurobiology specific to opioid analgesic addiction.

## 112.2 Neurobiology of Pain and Opioid Addiction

### 112.2.1 Pain

Pain can be defined as an unpleasant sensation which is localized to a part of the body. Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The function of the pain sensory system is to detect, localize, and identify tissue-damaging processes. Whether characterized as a symptom, sign, or syndrome, the common denominator of pain is suffering. In this regard, pain is both sensation and emotion. Pain of moderate or higher intensity is often accompanied by anxiety and an urge to escape or end the feeling. When acute, pain can be associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. Additionally, local muscle contraction is often present.

#### 112.2.1.1 Types of Pain

Pain is often initially categorized as being nociceptive or neuropathic (Portenoy 1989). Nociceptive pain is perceived by a highly specialized subset of nerve fibers (nociceptors) that respond only to painful or noxious stimuli or stimuli that become painful if prolonged. These fibers are present in nerves to the skin and deep somatic and visceral structures. The most painful stimuli activate a variety of nociceptor types in the affected area, which are summed into one nociceptive input, and ultimately lead to the subjective sense of pain.

##### Nociceptive Pain

Nociceptive pain is generally caused by tissue damage (e.g., injury, surgery) and can be further divided into somatic and visceral pain. Somatic pain, caused by injury to body tissues, is well localized but variable in description and experience. Visceral pain, caused by injury to internal organs, is mediated by stretch receptors and generally characterized as poorly localized, deep, dull, and cramping (e.g., pain associated with pancreatitis, cholecystitis, or nephrolithiasis).

Nociceptive pain can also be divided into musculoskeletal pain, inflammatory pain (e.g., inflammatory arthritis, postoperative pain, tissue injury, infection), or mechanical/compressive pain (e.g., low back pain, neck pain, visceral pain from expanding tumor masses).

### Neuropathic Pain

Neuropathic pain is caused by abnormal neural activity due to disease, injury, or dysfunction of the nervous system. It generally persists without ongoing disease (e.g., diabetic neuropathy, trigeminal neuralgia, or thalamic pain syndrome). Depending on which type of neural injury and the location of the neural injury, neuropathic pain can be further subdivided into peripheral neuropathy, sympathetically mediated pain, and central pain.

Peripheral neuropathy is caused by damage to a peripheral nerve (without associated autonomic change, e.g., postherpetic neuralgia and neuroma formation). Sympathetically mediated pain arises from injury to a peripheral nerve which does have associated autonomic changes (e.g., complex regional pain syndrome, causalgia). Central pain arises from abnormal central nervous system activity (e.g., phantom limb pain, pain from spinal cord injuries, and poststroke pain).

Mononeuropathy affects only one nerve; mononeuropathy multiplex affects several nerves in different areas of the body; and polyneuropathy describes diffuse and bilateral neuropathy.

## 112.2.1.2 Pathogenesis of Pain

### Acute Pain

Any pain sensation begins with a noxious stimulus sensed by peripheral nociceptors. A-delta fibers are relatively fast-conducting myelinated nociceptors. They respond to thermal and mechanical stimuli and are responsible for the first (immediate) sharp pain. Unmyelinated C-fibers make up most of the peripheral nociceptors. These slow-conducting fibers respond to thermal, mechanical, and chemical stimuli, recover from fatigue more slowly than the A-delta nociceptors, and mediate delayed or longer-lasting pain, typically characterized as dull.

The pain signal is transmitted from the peripheral A-delta and C-fibers to the dorsal horn of the spinal column via primary afferent neurons. The primary ascending pathway for pain from the dorsal horn of the spinal column to the brain is the spinothalamic tract, which projects contralaterally within the spinal cord and synapses in the thalamus. Neurons from the thalamus then project to multiple brain areas in the primary and secondary somatosensory cortex, cingulate cortex, prefrontal cortex, insular cortex, amygdala, and the cerebellum. It is important to note that the spinothalamic tract axons also connect to thalamic and cortical regions linked to emotional responses, such as the cingulate gyrus and frontal lobe. This pathway is thought to mediate the unpleasant emotional aspect of pain.

In addition to ascending pain pathways, descending inhibitory and facilitatory pathways exist that modulate the experience and sensation of pain. For example, circuits from the prefrontal cortex and anterior cingulate cortex may decrease nociceptive input, indirectly augmenting analgesia. These descending fibers may also interact with the opioid system, noradrenergic system, and serotonergic system and can significantly inhibit responses to noxious stimuli. Descending facilitatory pain pathways are also present.

### 112.2.1.3 Mechanisms for Persistent Pain

Several mechanisms modulate the progression of acute pain to chronic pain. These include peripheral and central sensitization as well as other mechanisms (ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition).

#### Sensitization

Peripheral sensitization and central sensitization are the major causes of pain hypersensitivity after injury.

#### Peripheral Sensitization

When painful stimuli are intense, repeated, or prolonged, cells become damaged. These damaged cells can release their intracellular contents as well as synthesize substances including cytokines, chemokines, bradykinin, histamine, prostaglandins, and growth factors. As part of the inflammation process, leukotrienes are also engaged. These substances, among others, can directly activate the nociceptor terminal or sensitize the terminal so that it becomes hypersensitive to subsequent stimuli. These substances can also indirectly facilitate the sensitization process by recruiting other inflammatory substances and propagating the cycle. Therefore, in the presence of damaged tissue or inflammation, the threshold for activating nociceptors is lowered and the frequency becomes higher for all stimulus intensities. Additionally, in the presence of injury and inflammation, nociceptors themselves can begin to express new channels, further facilitating the sensitization process. A good example of peripheral sensitization is sunburn. The decreased threshold for activating the nociceptors in the damaged area serves to protect the area from further injury through avoidance of pain.

#### Central Sensitization

Central sensitization is caused by an increase in excitability of central nociceptor transmission neurons of the spinal cord (at the level of the synaptic transfer from the nociceptor terminal to dorsal horn neurons). Initially, strong nociceptive input, which may come from acute injury, chronic pain syndromes, or peripheral sensitization, activates the dorsal horn neurons and causes a massive release of glutamate and co-regulatory peptides. Glutamate, a major excitatory neurotransmitter, modulates synaptic transmission in the dorsal horn in several ways. First, glutamate binds alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropioninc acid (AMPA) receptors on dorsal horn neurons, which mediates fast excitatory transmission. Additionally, glutamate interacts with N-methyl-D-aspartic acid (NMDA) receptors. During a normal, physiologic pain transmission, the NMDA receptor is physically blocked by a magnesium ion so that no current flows if glutamate binds the receptor. Massive release of glutamate in the dorsal horn, which can occur with acute or persistent injury, not only activates AMPA receptors, facilitating fast excitatory transmission, but also causes strong membrane depolarization resulting in removal of the magnesium blockade to the NMDA receptor,

thereby increasing the time the channel is open. Additionally, the NMDA receptor is phosphorylated, which increases its distribution in the synaptic membrane and its responsiveness to glutamate. The increase in excitability of the dorsal horn cell means that it can be activated by normally subthreshold inputs, with increased response to suprathreshold inputs, leading to the process of central sensitization.

### Other Mechanisms for Persistent Pain

In the face of injury, multiple changes in the functioning and structure of nociceptors and their pathways can lead to persistent pain. When sensory neurons are injured, they can become altered such that they begin to spontaneously initiate action potentials independent of a stimulus, similar to a pacemaker. These pacemaker-like action potentials are postulated to arise due to upregulation of voltage-gated sodium channels (or their subunits), upregulation of receptors in myelinated neurons, or downregulation of potassium channels on nociceptors. Additional alterations in the sensory neurons from nerve injury can lead to actual physical rearrangement and new growth in the circuitry of the dorsal horn and for normally quiescent glial cells in the spinal cord to become activated, producing cytokines and chemokines that alter patterns of gene transcription in neurons. Moreso, neuromodulators that are normally expressed only in C-fibers (like brain-derived neurotrophic factor and substance P) may begin to be expressed in large-diameter A fiber neurons.

Nerve injury can also decrease inhibitory pain pathways in the dorsal horn. Excessive glutamate release, failure of glutamate uptake, or TNF-alpha released from microglia can lead to selective apoptosis of GABAergic inhibitory synaptic currents. This loss in inhibitory GABA function can recruit previously absent A-beta fiber activity, effectively unmasking a previously silent pathway.

### Pain Modulation: How Psychological Factors Can Contribute to Chronic Pain

In clinical work with patients experiencing pain, it is clear that the pain produced by similar injuries can be remarkably variable in different situations and in different people. Some patients with back injuries, for example, can have a full recovery, while others can become severely disabled with a seemingly minor injury. Furthermore, even the suggestion of relief can have a significant analgesic effect (placebo) in certain patients, whereas others can find even minor injuries (such as venipuncture) unbearable. It is known that the expectation of pain can induce pain without a noxious stimulus (anticipatory pain), whereas merely having perceived control over pain can decrease pain substantially.

The powerful effect of expectation and other psychological variables on the perceived intensity of pain implies the existence of brain circuits that can modulate the activity of the pain-transmission pathways.

Although there are probably several circuits that can modulate pain, one has been studied extensively. This circuit has links in the hypothalamus, midbrain, and medulla and selectively controls spinal pain-transmission neurons through a descending pathway. There is good evidence that this pain-modulating circuit also contributes to the pain-relieving effect of opioid analgesic medications.

Each of the component structures of the pathway contains opioid receptors and is sensitive to the direct application of opioid drugs. Furthermore, lesions to the system reduce the analgesic effect of systemically administered opioids such as morphine. Along with the opioid receptor, the component nuclei of this pain-modulating circuit contain endogenous opioid peptides such as enkephalins and **β**-endorphin.

The most reliable way to activate this endogenous opioid-mediated modulating system is by prolonged pain and/or fear. There is evidence that pain-relieving endogenous opioids are released following operative procedures and even in patients given a placebo for pain relief.

Pain modulation is bidirectional. Pain-modulating circuits not only produce analgesia but are also capable of increasing pain. Both pain-inhibiting and pain-facilitating neurons in the medulla project to and control spinal pain-transmission neurons. Since pain-transmission neurons can be activated by modulatory neurons, it is theoretically possible to generate a pain signal with no peripheral noxious stimulus. Such mechanisms could account for the finding that pain can be induced by suggestion alone and may provide a framework for understanding how psychological factors can contribute to chronic pain.

## 112.2.2 Neurobiology of Opioid Analgesia, Tolerance, and Dependence

Most of the commercially available opioid analgesics act at the mu (μ) opioid receptor, differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Opioid agonists produce analgesia through direct action in brain and spinal cord regions involved in the transmission and modulation of pain. Additionally, some effects may be mediated by opioid receptors on peripheral sensory nerve endings.

### 112.2.2.1 Receptor Types

There are three major classes of opioid receptors: mu (μ), delta (**δ**), and kappa (**κ**). All are members of the G protein-coupled family of receptors. Multiple receptor subtypes have been proposed based on pharmacologic criteria, including μ1, μ2; **δ**1, **δ**2; and **κ**1, **κ**2, and **κ**3. Since an opioid may function with different potencies as an agonist, partial agonist, or antagonist at more than one receptor class or subtype, it is not surprising that these agents are capable of diverse pharmacologic effects.

### 112.2.2.2 Cellular Actions and Neural Mechanisms for Central and Peripheral Opioid Analgesia

At the molecular level, opioid receptors are physically coupled to G proteins. Opioid peptides have two well-established direct G protein-coupled actions on the opioid receptors of pain neurons: (1) they inhibit voltage-gated (N-type) calcium channels in the presynaptic membrane of primary sensory neurons,

thereby preventing the release of neurotransmitters, and (2) they hyperpolarize, and thus inhibit, postsynaptic secondary neurons by activating potassium channels, preventing the onset of action potentials. The presynaptic action – depressed transmitter release – has been demonstrated for a large number of neurotransmitters, including acetylcholine, norepinephrine, serotonin, substance P, and glutamate (the principal excitatory amino acid released from nociceptive nerve terminals).

Endogenous opioid peptides are the major inhibitory neurotransmitters in the dorsal horn of the spinal cord, and pharmaceutical opioids have been developed in order to mimic this action in order to provide pain relief. The majority of currently available opioid analgesics act primarily at the μ-opioid receptor. As μ-opioid receptors are also expressed in the medullary respiratory control center, the medullary chemoreceptor zone, and the gastrointestinal tract, opioids may also produce respiratory depression, nausea, vomiting, and constipation. Therefore, both the analgesic effects of opioid analgesics and the primary side effects and physical dependence result principally from actions at μ-receptors. The primary spinal involvement of the pain-relieving aspects of opioids has been exploited clinically by direct application of opioid agonists to the spinal cord. This can provide regional analgesic effects without causing the systemic effects of respiratory depression, nausea, vomiting, and sedation that may occur from the supraspinal actions of systemically administered opioids.

It is important to note that systemic opioid analgesic effects are complex and also include interaction with **δ** and **κ** receptors, both directly and through activation of endogenous opioid peptides. For example, when opioid analgesics are given systemically, part of the pain-relieving action involves the release of endogenous opioid peptides. All three receptor subtypes (μ, **κ**, **δ**) are present in high concentrations in the dorsal horn of the spinal cord and modulate supraspinal and spinal analgesia, but each receptor subtype responds with different affinity to endogenous opioid peptides. **δ** receptors are thought to have high affinity to the endogenous opioid class of enkephalins and are also thought to modulate hormone and neurotransmitter release. **κ-**receptors have high affinity for dynorphins and are thought to be responsible for psychotomimetic effects and slowed gastrointestinal transit of exogenous opioids. An exogenous opioid agonist (e.g., morphine) may act primarily and directly at the μ-receptor, but this action may evoke the release of endogenous opioids that additionally act at **δ**- and **κ**-receptors, causing both additional pain relief and additional side effects. Thus, even a receptor-selective ligand can initiate a complex sequence of events involving multiple synapses, transmitters, and receptor types.

In an effort to develop opioid analgesics with reduced side effect profiles, especially related to respiratory depression, tolerance, and addiction, there has been development of compounds that show preference for **κ**-opioid receptors, such as butorphanol and nalbuphine. However, these agents have been limited in their clinical success as analgesics due to dysphoric reactions and limited potency. It is interesting that butorphanol has been shown to cause significantly greater analgesia in women than in men. In fact, gender-based differences in analgesia mediated by μ- and **δ**-receptor activation have been widely reported.

Partial-agonists at the μ-opioid receptor, such as buprenorphine, have also been shown to have less propensity for tolerance than full opioid agonists.

Under most circumstances, exogenous opioid analgesics are given systemically and so act simultaneously at multiple sites. These include not only the ascending pathways of pain transmission through nociceptors detailed above but also descending (modulatory) pathways. As opioids directly inhibit pain neurons, there is a simultaneous activation of descending inhibitory neurons that send processes to the spinal cord and inhibit pain neurons. This activation has been shown to result from the inhibition of inhibitory neurons in several locations. Taken together, interactions at these sites increase the overall analgesic effect of opioid agonists.

In addition to actions in the central nervous system, animal and human clinical studies have demonstrated that endogenous and exogenous opioids can produce opioid-mediated analgesia at sites outside the central nervous system. The activation of peripheral μ-receptors on sensory terminals results in a decrease in sensory neuron activity and transmitter release and inhibition of the pain signal. Endogenously, **β**-endorphins released by immune cells within injured or inflamed tissue represent one source of physiologic peripheral μ-receptor activation. Peripheral administration of exogenous opioids, for example, into the knees of patients following arthroscopic knee surgery, has shown clinical benefit up to one day after administration.

#### 112.2.2.3 Pharmacogenetics

There is wide interindividual variability among patients in response to opioid analgesics. The majority of exogenous opioids are metabolized by the cytochrome P450 2D6 (CYP2D6) pathway or by glucuronidation. Codeine, oxycodone, and hydrocodone undergo O-methylation to produce metabolites that have a stronger μ-receptor affinity. Therefore, they exert their analgesic properties mainly through their metabolites. The O-methylation step is controlled by CYP2D6. CYP2D6 polymorphisms have been associated with altered enzyme activity that could result in altered drug effects. For example, poor metabolizers, or individuals who do not express functional CYP2D6, can only form trace amounts of O-methylated products and may experience reduced analgesia. For example, in poor metabolizers who take codeine, a prodrug that is metabolized to morphine, only trace amounts of morphine will be detected. Conversely, drugs like morphine, oxymorphone, and hydromorphone are already O-demethylated, so they will be less effected by metabolism and have smaller interindividual variability of opioid effects.

#### 112.2.2.4 Tolerance and Dependence

With frequently repeated therapeutic or recreational doses of morphine or its surrogates, there is a gradual loss in effectiveness which requires higher doses of the substance to get the same effect; this is termed tolerance. Along with tolerance, physical dependence develops, which is defined as a characteristic withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered.

The mechanism of development of tolerance and physical dependence is not completely understood, but persistent activation of μ-receptors, such as what occurs with the treatment of severe chronic pain, appears to play a primary role in its induction and maintenance. It is also interesting to note that tolerance develops to most side effects of opioids such as euphoria, respiratory depression, and nausea, but not to the side effect of constipation.

### Withdrawal (Dependence)

The locus ceruleus, located in the upper pons, is a major source of norepinephrine for the brain and an important mediator of tolerance to opioids. There are opioid receptors in the locus ceruleus, and when activated, they suppress the release of norepinephrine, contributing to the classic symptoms of opioid intoxication, including drowsiness, slowed breathing, and low blood pressure. With repeated exposure to opioids, the locus ceruleus increases alternative paths of norepinephrine production in order to maintain a homeostatic alertness. When opioids are subsequently withdrawn, there is a relative surge of norepinephrine. This leads to subjective symptoms of withdrawal, including increased anxiety and tremor, among other symptoms. This is the site of action of clonidine when given to relieve symptoms of opioid withdrawal.

Other brain areas in addition to the locus ceruleus also contribute to the production of withdrawal symptoms, including the mesolimbic reward system. For example, opioid receptors are located in the ventral tegmental area, and when tolerance develops, there is a decrease in the release of dopamine into the nucleus accumbens. In addition to becoming tolerant to the euphoric effects of the drug, this may also prevent the patient from obtaining pleasure from normally rewarding activities such as eating. These changes in the ventral tegmental area and dopamine reward systems, though not fully understood, form an important brain system underlying craving and compulsive drug use.

### Tolerance

On a molecular level, chronic opioid administration results in an upregulation of the intracellular cyclic adenosine monophosphate (cAMP) system at multiple levels in the locus ceruleus. These changes include increased levels of Gi and Go proteins (alpha subunits), adenylate cyclase, and cAMP-dependent protein kinase. Given the location of these changes in the locus ceruleus, it is postulated that the upregulation of the adenylate cyclase system may play a role in the development of tolerance. It is less clear whether the specific changes in the second-messenger function in the locus ceruleus persist beyond the period of chronic opioid administration.

Although the process of upregulation of the cAMP system is associated with tolerance, more recent theories suggest it is not sufficient to explain it. Another hypothesis for the development of opioid tolerance and dependence is based on the concept of receptor recycling. Normally, activation of μ-receptors by endogenous endorphins results in endocytosis followed by resensitization and recycling of the receptor to the plasma membrane. This process is thought to be an important component of tolerance. It is known that morphine, a drug known to be susceptible

to tolerance, fails to induce endocytosis of the μ-opioid receptor, whereas methadone, which is less susceptible to tolerance and used for the treatment of chronic pain and opioid addiction, does induce receptor endocytosis. This suggests that maintenance of normal sensitivity of μ-receptors requires reactivation by endocytosis and recycling at the plasma membrane. A related hypothesis suggests that receptor uncoupling is involved with tolerance due to a dysfunction of structural interactions between the μ-receptor and G proteins, second-messenger systems, and their target ion channels. This uncoupling and recoupling of μ-receptor function is likely linked to receptor recycling.

Another interesting theory involves the NMDA-receptor ion channel complex, which has been shown to play a central role in the development and maintenance of tolerance in that NMDA-receptor antagonists such as ketamine can block tolerance development. Although a role in endocytosis is not yet clearly defined, the development of novel NMDA-receptor antagonists or other strategies to recouple μ-receptors to their target ion channels provides hope for achieving a clinically effective means to prevent or reverse opioid analgesic tolerance. One last hypothesis suggests that the **δ**-opioid receptor is involved with tolerance and functions as an independent component in the maintenance of tolerance.

In addition to the development of tolerance, persistent administration of opioid analgesics has been observed to increase the sensation of pain leading to a state of hyperalgesia. This phenomenon has been observed with several opioid analgesics, including morphine, fentanyl, and remifentanil. Spinal dynorphin and activation of the bradykinin receptor have emerged as important candidates for the mediation of opioid-induced hyperalgesia.

### 112.2.3 Neurobiology of Opioid Addiction

The pleasure derived when opioids activate the brain's natural reward system promotes continued drug use during the initial stages of opioid addiction. Subsequently, repeated exposure to opioid drugs induces the brain mechanisms of dependence, which leads to daily drug use to avert the unpleasant symptoms of drug withdrawal. Further prolonged use produces more long-lasting changes in the brain that may underlie the compulsive drug-seeking behavior and related adverse consequences that are the hallmarks of addiction. Drug addiction is characterized by a pathological motivation for drug-seeking and drug-use behaviors that is associated with the inability to stop such behaviors, even despite negative consequences related to drug use (Kalivas and Volkow 2005). Recent scientific research has generated several models to explain how habitual drug use produces changes in the brain that may lead to drug addiction. In reality, the process of addiction probably involves components from each of these models, as well as other features.

The general neurobiology of addiction has been detailed in previous chapters of this text. To understand the neurobiology of addiction specific to opioids and prescription opioids, we will review animal models that most closely mimic "drug-seeking behavior" (drug reinforcement studies) and relapse and

reinstatement (conditioning homeostatic models), involving opioids. We will also review more recent literature describing structural brain changes associated with prescription opioid use and dependence.

#### 112.2.3.1 Behavioral Neurobiology of Opioid Reinforcement ("Drug-Seeking Behavior")

Opioid tolerance, dependence, and addiction are all manifestations of brain changes resulting from chronic opioid use and abuse. It is known, however, that one does not have to be physically dependent upon opioids to experience primary reinforcing properties of opioids. Decades ago, Bozarth and Wise (1984) demonstrated the neurobiology of this phenomenon in a study on drug-naive rats that learned to press a lever in order to receive direct injections of morphine into the ventral tegmental area (mimicking drug-seeking behavior in humans). The rats were then exposed to a challenge with naloxone (a direct opioid antagonist), which did not precipitate signs of withdrawal following the morphine injections. Moreover, signs of withdrawal were not seen after long-term morphine infusion into the ventral tegmental area but were observed after chronic infusion into the periventricular gray region. The data strongly suggested that the pathways mediating opioid reinforcement (e.g., the ventral tegmental area) were independent of pathways mediating the signs of opioid withdrawal (e.g., the locus ceruleus).

The pathways for opioid reinforcement and dependence, however, are clearly overlapped in some areas of the brain where opioids can act as both reinforcers and cause dependence. In the nucleus accumbens, a brain area important for reward and pleasure, and in the locus ceruleus, an area of the pons associated with physiologic response to stress and panic (and producer of norepinephrine), opioids can acts as reinforcers. But studies have also shown that with direct placement of naloxone in the nucleus accumbens of morphine-dependent rats, withdrawal can cause the disruption of food-mediated behaviors and conditioned place aversion. The locus ceruleus is also sensitive to the acute reinforcing effects of opioids (resulting in a suppression of locus ceruleus activity), as well as to the effects of opioid withdrawal (as characterized by a large increase in locus ceruleus activity). Thus, it is clear that some neurons are affected both by the acute reinforcing effects of opioids as well as by opioid withdrawal. The data are consistent with the view that although opioids will serve as reinforcers in the absence of physical dependence, the "motivation" for opioid self-administration is enhanced during opioid withdrawal.

As with other drugs of abuse, there is evidence that opioid reinforcement involves activation of dopamine neurons, with an increase in extracellular dopamine concentrations in the nucleus accumbens. With repeated administration, more opioid is needed to stimulate the ventral tegmental area brain cells of the mesolimbic reward system to release the same amount of dopamine in the nucleus accumbens. Therefore, more opioid is needed to produce pleasure comparable to that provided in previous drug-taking episodes. Interestingly, although the lesioning of dopamine neurons in the nucleus accumbens eliminates stimulant self-administration, it fails to eliminate opioid self-administration in rats (Koob and Bloom 1988). Opioids may also indirectly increase the firing of

dopamine neurons by activating μ-opioid receptors in the ventral tegmental area and nucleus accumbens, producing local disinhibitory effects on the dopamine neurons. Not surprisingly, naloxone blocks the effects of opioids on the ventral tegmental area (Britt and Wise 1983).

It is interesting to note that with chronic administration of opioids, an increased sensitization to their reinforcing properties (reverse tolerance) can be seen. It is hypothesized that chronic opioid administration can affect gene expression of guanine-nucleotide binding proteins (G proteins) and the cyclic adenosine monophosphate (cAMP) system. These changes in the molecular biology of second-messenger function may be related to the development of sensitization to the reinforcing properties of opioids.

#### 112.2.3.2 Models for Progression to Addiction

Theories on the neurobiologic basis of addiction are not unique to opioid addiction and have been reviewed in previous chapters. We will provide a brief review of the neurobiologic theories of addiction as they apply to opioid and prescription opioid addiction.

#### 112.2.3.3 The "Changed Set-Point" Model in Relation to Prescription Opioid Dependence

The "changed set-point" model of drug addiction postulates that drug abuse alters a biological or physiological setting or baseline of the dopamine reward system. This model has several variants based on the altered neurobiology of the dopamine neurons in the ventral tegmental area, the nucleus accumbens, and the locus ceruleus during the early phases of withdrawal and abstinence. One variant of the changed set-point model, by Koob and LeMoal (2001), is based on the idea that neurons of the mesolimbic reward pathways are naturally "set" to release enough dopamine in the nucleus accumbens to produce a normal level of pleasure. Koob and LeMoal suggest that repeated doses of opioids initiate a vicious cycle of changing this set point which results in decreased release of dopamine during normally pleasurable activities (in the absence of opioids).

#### 112.2.3.4 Molecular, Genetic, and Structural Changes with Acute and Chronic Opioid Exposure

On a molecular level, it is known that the dopamine receptor, which uses cAMP as its second messenger, is affected by chronic morphine administration (Beitner-Johnson and Guitart 1992). Chronic morphine treatment results in decreased levels of the G protein that inhibits adenylate cyclase, with increases in adenylate cyclase and cAMP-dependent protein kinase. Ultimately, these changes can alter the structural features of mesolimbic dopamine neurons so as to reduce the ability of these cells to transmit dopamine signals to postsynaptic cells in the nucleus accumbens. This leads to an effective resetting of the set point of the mesolimbic dopamine neurons.

Chronic morphine treatment also results in a decrease in the phosphorylation state of tyrosine hydroxylase in the nucleus accumbens (the rate-limiting enzyme in

the synthesis of dopamine) (Bietner-Johnson and Guitart 1992). This results in decreased functional activity of the enzyme in the nucleus accumbens, whereas there is upregulation (and increased phosphorylation) of the enzyme in the ventral tegmental area.

Bronstein and colleagues (1990) have reported that there is a decline in pro-opiomelanocortin (POMC) messenger ribonucleic acid (mRNA) levels with chronic morphine treatment. Because POMC yields several biologically active peptides, including **β**-endorphin, ACTH, melanocyte-stimulating hormone, and B-lipotropin, morphine may also affect the biosynthesis of the endogenous opioid, **β**-endorphin. Specifically, the authors report that chronic morphine treatment appears to result in the preferential production of **β**-endorphin 1–27 (which functions as an antagonist at the μ-opioid receptor) relative to **β**-endorphin 1–31 (which functions as an agonist at the μ-receptor). Acute stress also favors the production of **β**-endorphin 1–27 relative to **β**-endorphin 1–31. Chronic treatment with naltrexone (a narcotic antagonist) increases the mRNA for POMC and results in an increase in **β**-endorphin 1–27. The work suggests that the POMC system is quite sensitive to the effects of exogenous opioids as well as to acute stress.

Chronic opioid treatment also produces regionally specific changes in gene expression of a number of second-messenger functions in the brain that are associated with the reinforcing effects of opioids (Beitner-Johnson and Guitart 1992). Taken together, these changes result in decreased dopamine synthesis in the nucleus accumbens and changes in dopamine receptor function.

Structurally, chronic morphine treatment results in a decrease in neurofilament proteins in dopamine neurons in the ventral tegmental area. These effects are regionally specific. The neurofilament proteins form a major component of the cytoskeleton. Consistent with this result, cytoskeletal or cytoskeletal-associated elements of dopamine neurons have been shown to be altered by chronic morphine treatment resulting in selective reduction in the size of ventral tegmental area dopamine neurons (Beitner-Johnson and Guitart 1992).

As described previously, a changed set point also occurs in the locus ceruleus, but in the opposite direction, such that norepinephrine release is increased during withdrawal. Under this changed set-point model, both the positive (drug liking) and negative (drug withdrawal) aspects of drug addiction are accounted for.

It remains to be seen whether specific changes in second-messenger function in locus ceruleus (associated with tolerance and dependence) and the mesolimbic dopamine system persist beyond the period of chronic opioid administration to account for some of the signs and symptoms of protracted withdrawal/abstinence.

In 2000, researchers further specified the changed set-point model in describing additional specific ways that dopamine neurons can become dysfunctional in the face of repeated opioid exposure (Grace 2000). They postulate that the resting level of dopamine released into the nucleus accumbens is the result of two factors: cortical excitatory (glutamate) neurons that drive the dopamine neurons of the ventral tegmental area to release dopamine and autoreceptors (“brakes”) that shut down further release when dopamine concentrations become excessive.

Activation of opioid receptors by heroin and prescription opioids initially bypasses these brakes and leads to a large release of dopamine in the nucleus accumbens. With repeated use and further surges of dopamine in the reward system, the brain responds by increasing the number and strength of the autoreceptors ("brakes") on the dopaminergic neurons of the ventral tegmental area. In the absence of opioid administration, the enhanced autoreceptors lower the resting tone of dopamine in the reward system. This can trigger the dependent addict to take even more opioid to offset this lower resting tone of dopamine. Whenever he or she stops using opioids, a state of relative dopamine deficiency will result, manifesting in opioid withdrawal symptoms such as dysphoria, agitation, body pain, and malaise. This places the individual at high risk for relapse to drug use.

Thus, several mechanisms in the locus ceruleus, ventral tegmental area, and nucleus accumbens pathways are likely operating during addiction and relapse. Additionally, overactive cortical excitatory brain pathways caused by opioid addiction may also contribute to the changed set-point model, in that excitatory cortical projections may produce little activation in the ventral tegmental area during the resting state, leading to additional reductions in dopamine. However, when the addicted individual is exposed to cues that produce craving, the excitatory (glutamate) pathways may get sufficiently active to raise dopamine and stimulate desire for a greater high. This same increase in glutamate activity will raise norepinephrine release from the locus ceruleus to produce a dysphoric state during withdrawal predisposing to relapse and continued addiction.

#### 112.2.3.5 Cognitive Deficits Model

The cognitive deficits model of drug addiction proposes that individuals who develop addictive disorders have abnormalities in the prefrontal cortex, an area important for judgment, planning, and other executive functions. The prefrontal cortex sends inhibitory signals to the dopamine neurons of the ventral tegmental area of the mesolimbic reward system and enables individuals to delay immediate gratification for the sake of longer-term goals. This model proposes that those with addictive disorders have defects in the ability of the prefrontal cortex to inhibit the mesolimbic reward system, and as a result, they have decreased ability to use higher-level judgment or restrain impulses to use drugs.

Supporting this concept, it has been shown that stimulant drugs, such as methamphetamine, can damage a specific brain circuit – the frontostriatal loop – that carries inhibitory (GABA) signals from the prefrontal cortex to the mesolimbic reward system. In contrast, heroin has been shown to damage the prefrontal cortex but not the frontostriatal loop. It may be that individuals predisposed to opioid addiction have some degree of prefrontal damage that is independent of their opioid abuse, either inherited genetically or caused by some other factor or event in their lives (Kosten 1998). Finally, the cognitive deficits model of addiction could explain the clinical finding that heroin addiction tends to be more severe in those with comorbid antisocial personality disorder – a condition that is independently associated with deficits in the prefrontal cortex (Raine et al. 2000).

#### 112.2.3.6 Animal and Human Studies on Brain Changes Associated with Chronic Opioid Analgesic Administration

Chronic opioid exposure is known to produce neuroplastic changes in animals. However, despite theories based on animal models and literature extrapolated from research on heroin addicts, very little direct research has been done evaluating individuals with primary prescription opioid addiction. Additionally, there has been little differentiation in human data between opioid-dependent individuals and nonaddicted users of chronic prescription opioids for pain, two very different clinical populations.

In a recent small cross-sectional study of ten prescription opioid-dependent individuals and 10 age-matched controls, researchers found that the prescription opioid-dependent subjects demonstrated decreased gray matter volume in the bilateral amygdalae (Upadhyay et al. 2010). The amygdala is a key reward-modulating structure that is known to underlie opioid-related addiction, dependence, and tolerance. Morphologic abnormalities in the amygdalae of the prescription opioid-dependent individuals may explain an additional possible deficiency in the neural reward-processing network. The results of this study added to existing animal literature that showed that opioid exposure can have a broad range of effects on the amygdala, including decreased μ-opioid receptor sensitivity (Maher et al. 2005), modulated gamma-aminobutyric acid (GABA) receptor functioning (Zarrindast et al. 2004), and modified glutamate receptor targeting (Glass et al. 2005).

A subsequent pilot study (Younger et al. 2011) was the first longitudinal study to investigate prescription opioid effects on the human brain. In this study, ten nonaddicted opioid-naive individuals with chronic low back pain received structural brain MRIs before and after 1 month of daily morphine analgesic therapy. After 1 month of morphine, the investigators found significant volumetric decreases in the right amygdala and significant volumetric increases in the right hypothalamus, left inferior frontal gyrus, right caudal pons, and right ventral posterior cingulate. These changes persisted on average for 5 months after cessation of opioids. The same scanning procedure was also completed on nine patients with low back pain receiving a blinded placebo substance, and no morphologic changes were found. This study adds to a growing body of evidence that opioid exposure can cause structural and functional derangements in reward- and affect-processing circuitry and suggests that these changes can occur over a short amount of time in humans exposed to prescription opioids. Further research is needed to determine the clinical significance of this as it related to both nonaddicted and addicted individuals.

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