468e Opioid-Related Disorders

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Opiate analgesics have been abused since at least 300 B.C. Nepenthe (Greek "free from sorrow") helped the hero of the *Odyssey*, but widespread opium smoking in China and the Near East has caused harm for centuries. Since the first chemical isolation of opium and codeine 200 years ago, a wide range of synthetic opioids have been developed, and opioid receptors were cloned in the 1990s. Two of the most important adverse effects of all these agents are the development of opioid use disorder and overdose. The 0.1% annual prevalence of heroin dependence in the United States is only about one-third the rate of prescription opiate use and is substantially lower than the 2% rate of morphine users in Southeast and Southwest Asia. Prescription opiates are primarily used for pain management, but due to ease of availability, adolescents procure and use these drugs with dire consequences. In 2011, for example, 11 million individuals in the United States used nonmedically prescribed pain killers that were linked to over 420,000 emergency department visits and nearly 17,000 overdose deaths. Although these rates are low relative to other abused substances, their disease burden is substantial, with high rates of morbidity and mortality; disease transmission; increased health care, crime, and law enforcement costs; and less tangible costs of family distress and lost productivity.

The terms "dependence" and "addiction" are no longer used to describe substance use disorders. Opioid-related disorders encompass opioid use disorder, opioid intoxication, and opioid withdrawal. The diagnosis of opioid use disorder as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) requires the repeated use of the opiate while producing problems in two or more areas in a 12-month period. The areas include tolerance, withdrawal, use of greater amounts of opiates than intended, craving, and use despite adverse consequences. This new definition of opiate use disorder, reducing the criteria for diagnosis from three problem areas to two, is not expected to change the rates of these disorders because most individuals using these substances meet more than three criteria.

A striking recent aspect of illicit opiate use has been its marked increase as the gateway to illicit drugs in the United States. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opiate dependence are far lower than marijuana. The most commonly used opiates are diverted prescriptions for oxycodone and hydrocodone, followed by heroin and morphine, and—among health professionals—meperidine and fentanyl. Heroin is derived from morphine and acts as a prodrug that more readily penetrates the brain and is converted rapidly to morphine in the body. Two opiate maintenance treatment agents—methadone and buprenorphine—are also misused, but at substantially lower rates, and the partial opiate agonists such as butorphanol, tramadol, and pentazocine are misused even less frequently. Because the chemistry and general pharmacology of these agents are covered in major pharmacology texts, this chapter focuses on the neurobiology and pharmacology relevant to dependence and its treatments. Although the neurobiology of abuse involves all four of the known opiate receptors—mu, kappa, delta, and nociceptin/orphanin—this discussion focuses on the mu receptor, at which most of the clinically used opiates are active.

NEUROBIOLOGY

The neurobiology of opiates and their effects not only include opiate receptors, but also the downstream intracellular messenger systems and ion channels that the receptors regulate. The different functional activities of opiate receptors are summarized in Table 468e-1. Abuse liability of opiates is primarily associated with the mu receptor. All opiate receptors are G protein–linked and coupled to the cyclic adenosine monophosphate (cAMP) second messenger system and to G protein–coupled, inwardly rectifying potassium channels (GIRKs). Opiates activate GIRKs, increasing permeability to potassium ions to cause hyperpolarization, which inhibits the production of action potentials. Thus, opiates inhibit the activity of diverse and widely distributed neuronal types. The major effects of opiates, such as analgesia, sedation, and drug reinforcement are produced through this inhibition of neurons that belong to specific brain pathways.

TABLE 468e-1 ACTIONS OF OPIOID RECEPTORS

Receptor Type	Actions
Mu (μ) (e.g., morphine, buprenorphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa (κ) (e.g., butorphanol)	Dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta (δ) (e.g., etorphine)	Analgesia, euphoria, physical dependence, Hormone changes, appetite suppression, dopamine release
Nociceptin/orphanin (e.g., buprenorphine)	Analgesia, appetite, anxiety, tolerance to opioids, hypotension, decreased GI motility, 5-HT and NE release

Abbreviations: GI, gastrointestinal; 5-HT, serotonin; NE, norepinephrine.

Many opiate actions are related to the specific neuroanatomic locations of mu receptors. Reinforcing and euphoric effects of opiates occur in the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), where opiates increase synaptic levels of dopamine. This increase is due to inhibition of GABAergic neurons that inhibit both the activity of neurons within the VTA and the NAc. The positive subjective effects of opioid drugs also include mu receptor desensitization and internalization, potentially related to stimulation of beta-arrestin signalizing pathways. However, the "high" only occurs when the *rate of change* in dopamine is fast. Large, rapidly administered doses of opiates block γ-aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with "high" in all abused drugs. Therefore, routes of administration that slowly increase opiate blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opiate "high" that follows smoking and intravenous routes. Other acute effects such as analgesia and respiratory depression involve opiate receptors located in other brain areas such as the locus coeruleus (LC).

Opiate tolerance and withdrawal are chronic effects related to the cAMP-protein kinase A (PKA)-cAMP response-element binding protein (CREB) intracellular cascade (Fig. 468e-1). These effects are also reflective of genetic risk factors for developing opiate use disorder, with estimates of up to 50% of the risk for dependence due to polygenic inheritance. Specific functional polymorphisms in the mu opiate receptor gene appear to be associated with this risk for opiate abuse, including one producing a threefold increase in this receptor's affinity for opiates and the endogenous ligand beta endorphin. Epigenetic methylation changes also occur on the DNA of the mu receptor gene of opiate addicts, inhibiting gene transcription. This molecular cascade links acute intoxication and sedation to opiate tolerance and withdrawal mediated by the LC. Noradrenergic neurons in the LC mediate activation of the cortical hemispheres. When large opiate doses saturate and activate all of its mu receptors, action potentials cease. When this direct inhibitory effect is sustained over weeks and months of opiate use, a secondary set of adaptive changes occur that lead to tolerance and withdrawal symptoms (Fig. 468e-1). Withdrawal symptoms reflect, in part, overactivity of norepinephrine (NE) neurons in the LC. This molecular model of NE neuronal activation during withdrawal has had important treatment implications, such as the use of the alpha-2 agonist clonidine to treat opioid withdrawal. Other contributors to withdrawal include deficits within the dopamine reward system.

PHARMACOLOGY

Tolerance and withdrawal commonly occur with chronic daily use, developing as quickly as 6–8 weeks depending on dose concentration