CHAPTER

61

Addiction

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GENERAL PRINCIPLES

Addiction is characterized by compulsive drug use, despite severe negative consequences

Addiction follows a chronic course, with periods of abstinence followed by relapse. Vulnerability to relapse can persist even after years of abstinence, suggesting that long-lasting and perhaps permanent neurobiological changes underlie addiction. There are tremendous individual differences in vulnerability, reflecting both genetic and environmental influences, and many people experiment with potentially addictive drugs without progressing to compulsive use. Nevertheless, substance abuse accounts for more deaths, illnesses and disabilities than any other preventable health condition. Approximately one in four of all deaths in the United States are attributable to the use of alcohol, nicotine or illicit drugs (Substance Abuse: The Nation's Number One Health Problem, 2001).

Long-term drug exposure produces many physiological and behavioral changes that contribute to addiction. *Tolerance* is the need for increasing doses of a drug to achieve the same effect. *Sensitization* refers to the enhancement of drug responses as a result of repeated drug exposure. For a given drug, it is possible for certain effects to show tolerance and others to show sensitization. *Dependence* is an adapted physiological state of cells or systems that develops to compensate for excessive stimulation by a drug. When drug intake stops, unmasking of this adapted state leads to a *withdrawal syndrome* that may have somatic (physical) components as well as affective and motivational components.

Many forces may drive compulsive drug use

The incentive-sensitization theory of addiction proposes that sensitization occurs in the neural systems that attribute incentive salience to drugs and drug-associated cues (Robinson & Berridge, 2000). Drug 'wanting' sensitizes, even though drug 'liking' typically shows tolerance. Alternatively, addiction has been characterized as a spiraling cycle of hedonic dysregulation driven by many factors but with an important role ascribed to negative affective states that occur during periods of drug abstinence (Koob & Le Moal, 1997). Other theories emphasize the role of learning in addiction, based on the ability of drugs to facilitate some forms of learning and trigger neuroadaptations also seen in learning. Abnormally strong forms of learning are proposed to underlie habitual behaviors associated with addiction (Di Chiara, 1999; Everitt et al., 2001; Hyman & Malenka, 2001). Finally, drugs may produce dysregulation of cortical systems that normally exert inhibitory control over behavior, leading to poor decision making and impulsivity, which in turn drive compulsive pursuit of drugs (Jentsch & Taylor, 1999). These theories are not mutually exclusive. Different factors may contribute at different times to the cycle of addiction (Koob & Volkow, 2010).

NEURONAL CIRCUITRY OF ADDICTION

Natural reinforcers and drugs of abuse increase dopamine transmission

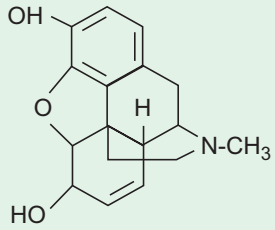
Drugs of abuse—like food, drink and sex—are reinforcing. That is, they 'stamp in' or 'reinforce' learned associations, such that behaviors associated with obtaining the reinforcer tend to be repeated. Different drug classes have different initial targets in brain (Fig. 61-1). However, a common mechanism contributing to the reinforcing actions of most addictive drugs—and those of natural reinforcers—is activation of mesocorticolimbic dopamine neurons (Ch. 14). These neurons originate in the ventral tegmental area (VTA) of the midbrain and project to cortical and limbic target regions (Fig. 61-2). Elevation of dopamine levels in one of these target regions, the nucleus accumbens, is particularly important for reinforcement. The nucleus accumbens serves as an interface between limbic and cortical regions important for motivation, and motor circuits responsible for execution of motivated behaviors. Dopamine neurons in the substantia nigra, which project primarily to dorsal striatum, are also important, particularly in the learning and performance of habitual behaviors associated with addiction. It should be emphasized that drugs of abuse also exert dopamine-independent actions, and these may be of primary importance for the reinforcing effects of some drug classes, e.g., ethanol and opiates (Pierce & Kumaresan, 2006).

The role of dopamine in motivated behavior is an active area of research (Wheeler & Carelli, 2009). Some ideas follow from theories of addiction described above. For example, according to the incentive-sensitization theory of addiction, dopamine signals the incentive salience attributed to drugs and drug-associated cues, causing them to be 'wanted' (Robinson & Berridge, 2000). Another influential theory holds that activation of dopamine neurons is important in learning and predicting the likelihood of reward when an animal is presented with reward-related stimuli (Schultz, 2002). Thus, a normal function of dopamine may be to enable reward-related stimuli to shape behavior, and so promote the learning of adaptive behaviors that enable survival.

While dopamine neurons are activated to a modest degree by natural rewards, drugs of abuse produce a more robust elevation in dopamine levels that in some cases is not subject to normal regulatory mechanisms. For example, dopamine released by natural rewards will be removed from the synapse by the dopamine transporter (DAT). However, cocaine works by blocking this transporter, so cocaine produces larger and more prolonged increases in dopamine levels. Other drugs activate dopamine neurons through indirect mechanisms, as depicted in Figure 61-3. The unregulated release of dopamine initiates compensatory changes in dopamine-receptive neurons that lead to a chain reaction of molecular and cellular adaptations throughout the circuits depicted in Figure 61-2. There is growing evidence that mesolimbic dopamine neurons co-release glutamate, producing fast excitatory effects in postsynaptic target regions such as the nucleus accumbens. This adds another intriguing dimension to signaling in the reward circuit.

A. Opiates

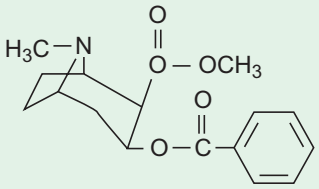
Morphine



Primary target: μ opioid receptor

B. Psychostimulants

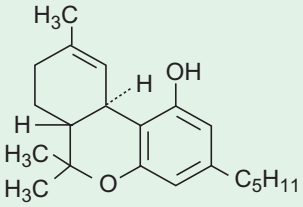
Cocaine



Primary target:
Monoamine transporters

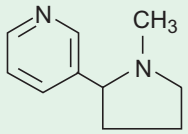
C. Cannabinoids

Δ^9-tetrahydrocannabinol



Primary target:
Cannabinoid CB1 receptor

D. Nicotine



Primary target:
Nicotinic acetylcholine receptor

E. Alcohol

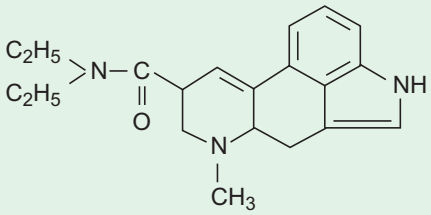
Ethanol

$H_3C - CH_2 - OH$

Primary target:
Ligand gated and voltage gated ion channels

F. Hallucinogens

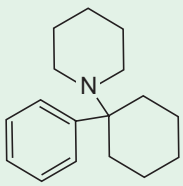
Lysergic acid diethylamine



Primary target:
Serotonin receptors

G. Dissociative Drugs

Phencyclidine



Primary target:
NMDA receptor

FIGURE 61-1 **Major drug classes, structures of prototypical agonists and 'primary targets' implicated in drug class reward.** See Figure 61-5 for structures of amphetamines.

A major challenge is to understand the relationship between drug-induced adaptations and the behavioral changes that characterize addiction. One reason for the difficulty is the sheer number of adaptations that have been described, encompassing signal transduction, gene expression and structural changes. Further complicating the picture, some adaptations reduce drug responsiveness, favoring homeostasis, while others increase drug responsiveness in a

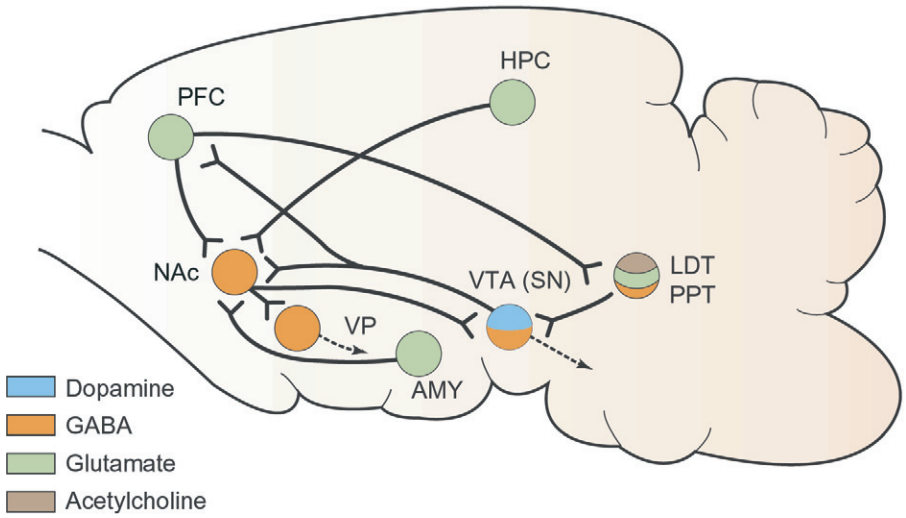


FIGURE 61-2 The mesocorticolimbic dopamine system and associated circuits. The ventral tegmental area (*VTA*) contains both dopamine and GABA neurons that innervate the nucleus accumbens (*NAc*), prefrontal cortex (*PFC*) and other forebrain targets not shown. Nucleus accumbens neurons, which use GABA as their transmitter, receive glutamate inputs from the PFC, amygdala (*AMY*), hippocampus (*HPC*) and thalamus (not shown). These glutamate inputs convey information important for goal-directed behaviors. NAc neurons integrate this information, and then transmit it to brain regions important for execution of these behaviors, including the ventral pallidum (*VP*), VTA and substantia nigra (*SN*), as well as other motor regions (*dashed arrows*). The prefrontal cortex influences this circuitry at many levels by sending descending glutamate projections to many targets, including the NAc, VTA, SN, pedunculopontine tegmental nucleus (*PPT*) and laterodorsal tegmental nucleus (*LDT*). The PPT and LDT send mixed cholinergic, glutamate and GABA projections to the VTA and SN that exert an important regulatory influence on dopamine and GABA cells in the latter regions. Another important regulatory influence on midbrain dopamine neurons arises from lateral habenula (LHb) neurons in the epithalamus (structure not shown); although glutamatergic, LHb cells strongly inhibit dopamine neurons via a GABA intermediate.

feed-forward manner. The molecular and cellular adaptations that underlie addiction are discussed in subsequent sections of this chapter, concluding with a focus on glutamate transmission and plasticity, which are critical for many aspects of addiction.

Many neuronal circuits are ultimately involved in addiction

These circuits have been studied extensively using animal models of addiction (Koob & Volkow, 2010; Vezina, 2004; Feltenstein & See, 2008; Everitt et al., 2008; Wolf & Ferrario, 2010), which continue to evolve (Ahmed, 2010). Many of the earlier studies, particularly for psychomotor stimulants, focused on behavioral sensitization produced by repeated experimenter-administered injections. Over the course of the injections, behavioral responses gradually intensify or 'sensitize', including responses that provide an index of motivation for drug taking. For example, a previously sensitized rat will later work harder to obtain drugs in a self-administration experiment. Sensitization persists for months after discontinuing drug exposure, reminiscent of the persistence of vulnerability to relapse in recovering addicts. Many recent studies have focused on adaptations produced when animals self-administer psychomotor stimulants or other drugs of abuse. Rats with extensive drug self-administration experience display behaviors reminiscent of addiction including escalation of drug intake, drug taking despite negative consequences, and long-lasting vulnerability to relapse despite long periods of abstinence.

Drug craving in human addicts, and the reinstatement of drug-seeking behavior in animal models of relapse, can be triggered by three types of stimuli: cues associated with prior drug use (such as drug paraphernalia), re-exposure to a low dose of drug and exposure to stress. Animal studies have shown that these stimuli trigger reinstatement of drug seeking through distinct but overlapping neuronal circuits (Feltenstein & See, 2008). For example, the basolateral amygdala is critical for the ability of conditioned cues to maintain and reinstate drug-seeking behavior. Stress-induced reinstatement involves brain corticotropin-releasing factor (CRF) and norepinephrine systems. Cocaine-primed reinstatement requires activation of glutamate projections from the prefrontal cortex to the nucleus accumbens. As drug use becomes habitual, dorsal striatum and orbitofrontal cortex come to play dominant roles (Everitt et al., 2008). For most drugs of abuse (including heroin, cocaine, ethanol, nicotine and marijuana), dependence is associated with adaptations in the HPA axis as well as brain stress systems in the extended amygdala. During withdrawal, these adaptations produce a negative emotional state characterized by dysphoria, anxiety and irritability. This motivates continued drug seeking and relapse (Koob, 2008).

Functional imaging studies in human addicts are yielding results consistent with animal studies. They indicate altered activity in the cortical and limbic neuronal circuits that process information related to motivation and reward, memory and learning, executive function and inhibitory control, interoception, and stress reactivity (Koob & Volkow, 2010). Disruption of these circuits in addicts may be associated

with decreased dopamine transmission (Volkow et al., 2009). Decreased metabolic activity in frontal regions can persist even after prolonged detoxification. This may be indicative of long-lasting cognitive changes that contribute to persistent vulnerability to relapse.

In summary, the transition from controlled to compulsive drug use involves a cascade of events including an increase in motivation to take a drug, driven by enhanced responsiveness of memory and motivational circuits to drugs or drug-associated cues; a decrease in the ability to exert inhibitory control and exercise appropriate judgment, due to alterations in executive function; and a desire to alleviate the negative emotional state that occurs during withdrawal due to functional upregulation of stress systems.

OPIATES

Opiates are drugs derived from opium, including morphine and heroin

Opium, extracted from poppy plants, has been used for recreational and medicinal purposes for thousands of years. Morphine was identified as the active pharmacological ingredient of opium in the early 1800s. Heroin was synthesized from morphine in the late 1800s in an attempt to develop a nonaddicting cough suppressant. Opioid is a more inclusive term that includes opiates, as well as endogenous (naturally occurring) opioid peptides. These include the enkephalins, endorphins, dynorphins and endomorphins (see Ch. 20).

There are three classical opioid receptor types

These are the mu-opioid receptors (MOP-R), kappa-opioid receptors (KOP-R) and delta-opioid receptors (DOP-R); additional diversity may derive from heterodimerization, as described below (Shippenberg et al., 2008). Morphine is relatively selective for the MOP-R. Endorphins and enkephalins bind to MOP-Rs and DOP-Rs. Dynorphin has higher affinity for the KOP-Rs but also binds MOP-Rs and DOP-Rs. Endomorphins have high affinity and selectivity for MOP-Rs. The nociceptin (orphanin FQ/ORL1) receptor (NOP-R), cloned in 1994, is a "nonclassical" opioid receptor that has high structural homology with classical opioid receptors, but very low affinity for conventional opioid ligands. Nociceptin is its endogenous ligand.

MOP-R stimulation produces an intense high, explaining the abuse liability of morphine and heroin, as well as constipation and respiratory depression. KOP-R stimulation does not produce these effects; in fact, KOP-R agonists have dysphoric and aversive effects, and oppose effects of MOP-R stimulation (see below). Prolonged use of morphine or heroin leads to tolerance and dependence, and to craving and withdrawal symptoms when drug use is terminated. Withdrawal symptoms include anxiety, nausea, insomnia, hot and cold flashes, muscle aches, perspiration and diarrhea. Opiate actions in spinal cord, supraspinal sites and brainstem are important for opioid-induced analgesia, autonomic effects, and physical withdrawal symptoms. Opiate effects in both brain reward and brain stress systems are important for reinforcement, the aversive withdrawal state and relapse.

Opioid receptors generally mediate neuronal inhibition

Opioid receptors couple to G_i or G_o, and produce inhibition of Ca^{2+} channels and opening of K^+ channels. They also inhibit adenylyl cyclase. Through this and other downstream signaling pathways, opioid receptors modulate synaptic plasticity and gene expression. Like other G-protein–coupled receptors (GPCRs; see Ch. 21), opioid receptors may interact to form homodimers and heterodimers (DOP-R/MOP-R and DOP-R/KOP-R). This generates receptors with different pharmacology, signaling ability and perhaps trafficking characteristics compared to the cloned receptor subtypes. The significance of this finding is only beginning to be explored, but it may contribute to the pharmacological diversity of opioid receptors, and has exciting implications for drug design (Van Rijn et al., 2010).

Chronic opiate treatment results in complex adaptations in opioid receptor signaling

Many studies have examined mechanisms of tolerance to the analgesic effects of opiates. This is a major clinical problem, as it means that ever-escalating doses are required for the treatment of chronic pain. The classic view was that tolerance reflects a decrease in functional opioid receptors via desensitization and internalization. Desensitization occurs when receptors are uncoupled from G proteins as a result of phosphorylation by G-protein–coupled receptor kinases (GRKs) and arrestin binding (Ch. 21). These events also lead to internalization of opioid receptors by promoting their association with clathrin-coated pits. However, the paradoxical observation that morphine produces tolerance but does not promote efficient receptor internalization has led to a reevaluation of this view and prompted exciting research on opioid receptor regulation (Berger & Whistler, 2010). Although much remains to be learned, one possibility is that lack of internalization promotes tolerance because it is associated with abnormally sustained signaling and resultant adaptations in the target cell and downstream circuits. A key element of this theory is that different agonists direct opioid receptors toward different signaling and trafficking pathways. Understanding the rules governing the function of ligand–receptor complexes may help in the development of opiates that are effective analgesics but have reduced liability to cause tolerance and dependence.

Opiate addiction involves multiple neuronal systems

The neuronal basis of the reinforcing effects of opiates is still an area of active investigation. In the VTA, opiates stimulate MOP-Rs on GABA neurons that synapse on dopamine neurons. This inhibits the GABA neurons, leading to disinhibition of the dopamine neurons and enhanced

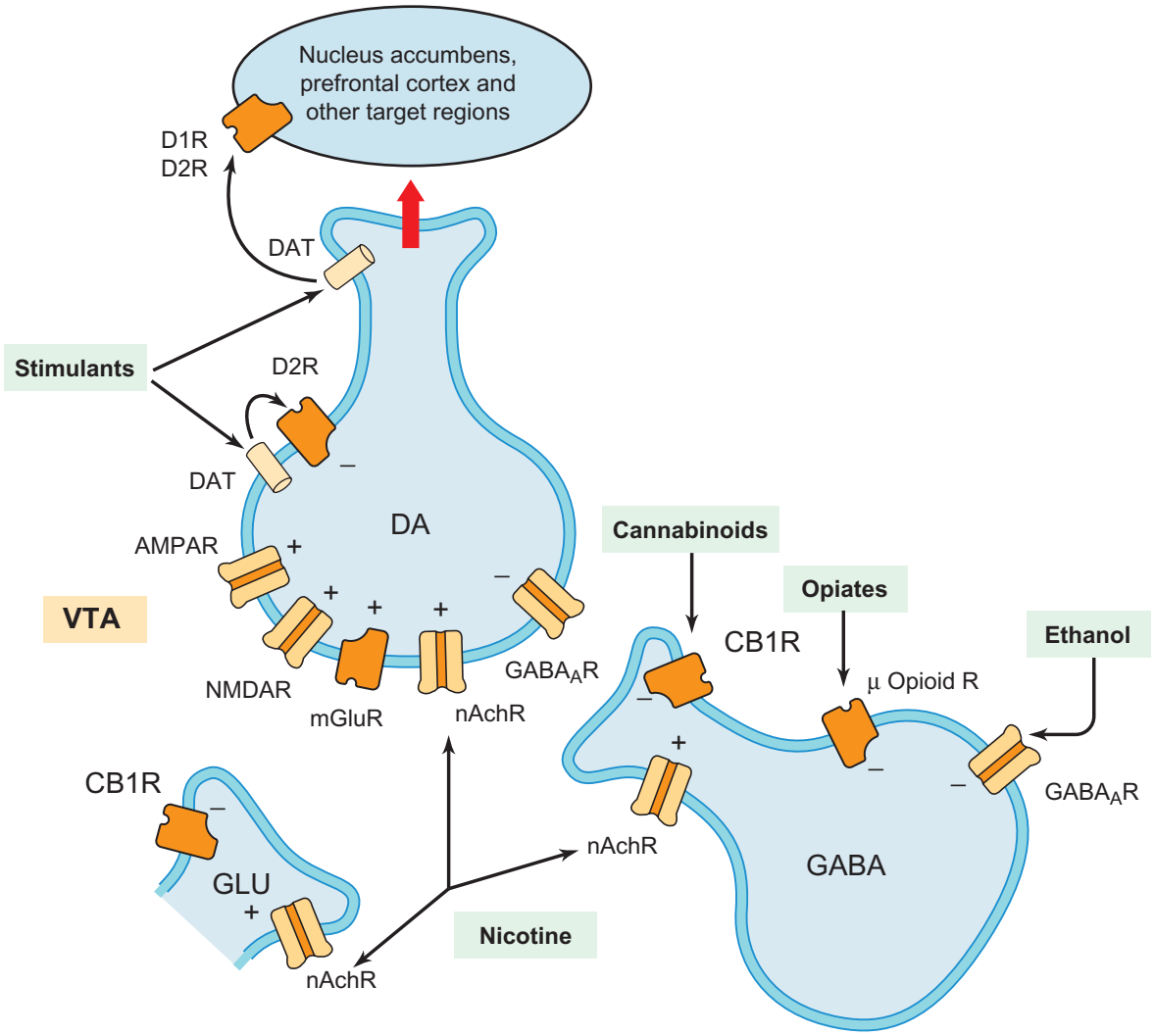


FIGURE 61-3 All reinforcing drugs increase dopamine transmission in the mesocorticolimbic dopamine system, but they use different mechanisms. Psychomotor stimulants interact with the dopamine transporter (*DAT*) to elevate extracellular dopamine levels. Opiates, ethanol and cannabinoids are believed to decrease GABA transmission in the ventral tegmental area (*VTA*), thereby disinhibiting dopamine neurons. However, other mechanisms may also be involved in the effects of these drugs. For example, ethanol can directly excite dopamine neurons via voltage-gated ion channels. Nicotine excites dopamine cells directly and by altering the balance between inhibitory and excitatory inputs to the dopamine neurons. Dopamine-independent mechanisms also contribute significantly to the reinforcing effects of drugs of abuse.

dopamine release in the nucleus accumbens and other target areas (Fig. 61-3). However, opiates also exert dopamine-independent effects in the nucleus accumbens by activating MOP-Rs on nucleus accumbens neurons themselves. Endogenous cannabinoid systems are also important in mediating the rewarding effects of opiates, and vice versa, and in relapse (De Vries & Shippenberg, 2002; Maldonado et al., 2006). Chronic opiate use produces adaptations in brain stress systems in the extended amygdala involving enhanced norepinephrine and CRF signaling. These adaptations are important for producing the aversive effects of the opiate withdrawal syndrome, for stress-induced relapse, and for the increased anxiety that occurs during prolonged abstinence and contributes to relapse vulnerability (Koob & Volkow, 2010).

Upregulation of the cyclic AMP (cAMP) second-messenger pathway is a well-established molecular adaptation

It occurs in many brain regions after chronic administration of opiates and other drugs of abuse. The locus coeruleus (LC) has been a useful model system for studying upregulation of the cAMP pathway (Nestler, 2004). Located in the brain stem, the LC is the largest cluster of norepinephrine-containing neurons in the brain and normally participates in regulation of autonomic function, attentional states and stress responses. Acutely, opiates suppress the activity of LC neurons via G_i-coupled receptors that inhibit adenylyl cyclase activity (Chs. 19 and 21). Chronic opiate administration leads to compensatory upregulation of specific subtypes of adenylyl cyclase

and specific subunits of protein kinase A. The transcription factor cyclic AMP response element–binding protein (CREB) plays a critical role in this adaptive response. Upregulation of the cAMP pathway increases the excitability of LC neurons, enabling them to fire at normal rates despite the continued presence of opiates. When opiates are withdrawn, upregulation of the cAMP pathway is no longer opposed by inhibitory effects of opiates, leading to a dramatic rebound activation of LC neurons that contributes to somatic withdrawal symptoms. Of course, upregulation of the cAMP pathway is only one of many cellular mechanisms contributing to adaptive changes in the LC and other regions after chronic opiate administration.

The nucleus accumbens is another brain region in which the cAMP pathway is upregulated by chronic administration of opiates, as well as some other drugs of abuse. This leads to increased transcription of CREB-regulated proteins, including dynorphin, the endogenous ligand for the KOP-R. Dynorphin acts in the accumbens to reduce dopamine and glutamate transmission. In the presence of opiates, this effect of dynorphin may serve as a homeostatic adaptation that diminishes drug responsiveness by reducing activation of the dopaminergic system. However, once opiates are no longer present, decreased dopamine release may contribute to anhedonia and dysphoria during the early phase of opiate withdrawal (De Vries & Shippenberg, 2002).

There are two main treatments for the opiate withdrawal syndrome

One is replacement therapy with methadone or other MOP-R agonists that have a longer half-life than heroin or morphine, and produce mild stimulation rather than euphoria. They also produce cross-tolerance to heroin, lessening heroin's effect if patients relapse. Withdrawal is also treated with the α_2 agonist clonidine, which decreases the activity of norepinephrine neurons, thereby reducing opiate withdrawal symptoms.

Endogenous opioid systems are an integral part of the reward circuitry

As such, they contribute to adaptations that underlie addiction to many classes of drugs (Shippenberg et al., 2008). For example, interactions of endorphins and enkephalins with MOP-Rs and DOP-Rs contribute to the reinforcing effects of cocaine and ethanol. Dynorphin is upregulated by other drugs of abuse (e.g., cocaine, ethanol, nicotine) as well as by stress (Koob, 2008). Activation of KOP-Rs produces behavioral and neurochemical alterations that oppose those of various drugs of abuse and, in rodent models, mimic those produced by stress. KOP-R ligands are being evaluated as treatments for cocaine addiction. Naltrexone, a nonspecific opioid receptor antagonist, is approved in the United States for the treatment of individuals with alcohol dependence. It appears to block some of the reinforcing properties of alcohol, and reduces rates of relapse to alcohol drinking in some individuals (see Translational Box: A Novel, Unexpected Treatment for Alcoholism).

PSYCHOMOTOR STIMULANTS

This drug class includes cocaine and amphetamine derivatives

Low-to-moderate doses lead to increased activity, talkativeness and feelings of euphoria and general well-being, along with decreases in fatigue and in food intake. Repetitive motor activity (stereotyped behavior) is produced by higher doses, and very high doses can produce convulsions, hyperthermia, coma and death. Stimulants have some therapeutic uses. For example, amphetamine is used to treat narcolepsy, and methylphenidate (Ritalin) is used in the treatment of children with attention deficit hyperactivity disorder (ADHD). Available evidence indicates that childhood stimulant treatment for ADHD does not increase the risk of substance abuse in adulthood (Volkow & Swanson, 2008).

Transporters for dopamine (DAT), serotonin (SERT) and norepinephrine (NET) are the initial targets for psychomotor stimulants

By interacting with these transporters (Chs. 12 and 13), psychomotor stimulants increase extracellular levels of monoamine neurotransmitters. Cocaine is a monoamine uptake inhibitor. The reinforcing effects of cocaine correlate best with its binding potency at the DAT. Amphetamine and other important stimulants are shown in Figure 61-4. These drugs interact with DAT, SERT and NET with varying relative affinities. Some, like methylphenidate, appear to block uptake in a manner similar to cocaine, while others, including amphetamine itself, are transported substrates. Through the latter mechanism they promote monoamine efflux by reverse transport via a process known as exchange diffusion (Sulzer et al., 2005). The amphetamines are also lipophilic weak bases and likely transported substrates of the vesicular monoamine transporter (VMAT), which transports monoamines into synaptic vesicles. Once inside the vesicles, amphetamines collapse the vesicular pH gradient that is required for vesicular dopamine sequestration (Chs. 5, 12). This promotes redistribution of dopamine from vesicles to the cytosol, making more dopamine available for reverse transport (Sulzer et al., 2005). In addition, amphetamine elevates cytosolic monoamine levels by inhibiting monoamine oxidase and stimulating tyrosine hydroxylase. Recent studies suggest that amphetamine and cocaine can also cause DAT internalization, an additional mechanism for reducing DAT function.

In experimental animals, repeated exposure to high doses of some psychomotor stimulants produces long-term decreases in markers for the integrity of dopamine and serotonin nerve terminals. In rats, high-dose amphetamine preferentially damages dopamine terminals, methamphetamine damages serotonin and dopamine terminals, and 3,4-methylenedioxymethamphetamine (MDMA) preferentially damages serotonin neurons. MDMA is the major constituent of the street drug Ecstasy. Many recent studies have focused on methamphetamine toxicity because of its escalating abuse. It is now appreciated that methamphetamine produces damage to cell bodies in the cortex and other regions, indicating that

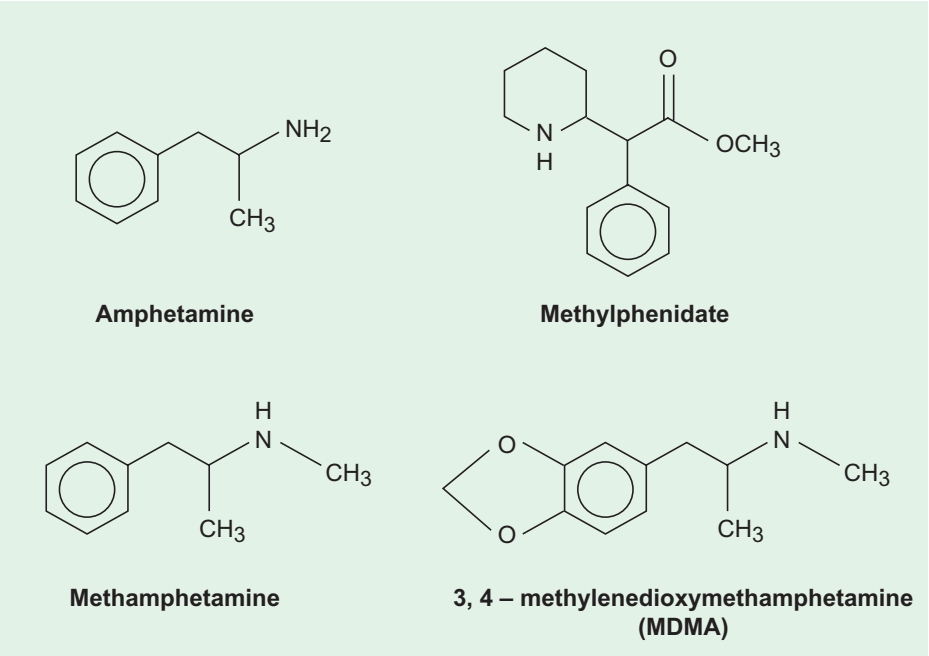


FIGURE 61-4 **Amphetamine and other important stimulants.**

toxicity is not limited to dopamine and serotonin terminals. Animal studies show that neurotoxic effects of methamphetamine involve a neurodegenerative process mediated by oxidative stress, excitotoxicity and metabolic compromise due to mitochondrial dysfunction. Interestingly, stress not only promotes substance abuse but also increases vulnerability to the neurotoxic effects of stimulants (Yamamoto et al., 2010).

The important and controversial questions are whether similar neurotoxic changes occur in the human brain at the lower doses used by humans; whether these doses produce functional impairment (detected in behavioral or brain imaging studies); whether functional changes are attributable to neurotoxicity versus other mechanisms (e.g., plasticity); and whether any observed changes are reversible. The answers depend on the stimulant in question and the amount and duration of drug use. However it is clear that both methamphetamine and MDMA can produce cognitive deficits, for example, impairment in tasks that test memory function or behavioral control. Some deficits may recover with abstinence while others may persist (Fernández-Serrano et al., 2010).

Cocaine and amphetamines initiate neuronal adaptations by repeatedly elevating monoamine levels but ultimately affect glutamate and other transmitter systems

Effects of cocaine and amphetamine on dopamine transmission are most closely linked to reinforcement. These drugs interact with the DAT on dopamine nerve terminals to increase extracellular dopamine levels in dopamine-innervated brain regions. When this occurs repeatedly, the resulting overstimulation of postsynaptic dopamine receptors leads to a complex cascade of downstream changes that involves many brain regions and transmitter systems. Dopamine neurons themselves also undergo complex changes in their regulation during repeated psychomotor stimulant exposure and withdrawal (Wolf, 1998; Kauer & Malenka, 2007; Thomas et al., 2008). While psychomotor stimulants are "on board," elevation of dopamine levels in the VTA activates D2-class dopamine autoreceptors on the dopamine neurons, inhibiting dopamine cell firing. After discontinuing repeated psychomotor stimulant exposure, the activity and excitability of dopamine neurons are increased due to changes in regulatory mechanisms in the VTA, including autoreceptor subsensitivity and the development of long-term potentiation (LTP) at excitatory synapses onto dopamine neurons. Interestingly, this LTP persists when cocaine has been self-administered, whereas it is transient when cocaine is injected by the experimenter.

Increased dopamine cell firing is one event that enables subsequent, and often very persistent, adaptations in the dopamine-innervated limbic and cortical regions that regulate motivated behavior. Although these adaptations involve many neurotransmitter systems, the role of glutamate transmission has received considerable attention in recent years (Wolf & Ferrario, 2010; Wolf, 1998; Kauer & Malenka, 2007; Thomas et al., 2008; Kalivas, 2009; Olive, 2009). This is due, in part, to glutamate's central role in plasticity and the recognition that addiction is a form of plasticity, a topic considered in the last section of this chapter. However, the focus on glutamate also reflects its critical role in controlling addiction-related circuitry (Fig. 61-2). For example, at the cellular level, dopamine and glutamate inputs converge on postsynaptic neurons in the nucleus accumbens and dorsal striatum, with dopamine playing a neuromodulatory role and glutamate driving synaptic transmission. Ultimately, drug-seeking behavior in psychomotor stimulant–experienced rats requires glutamate transmission to these striatal regions.

Dopamine receptor transmission involves multiple signaling cascades and is altered in psychomotor stimulant addiction

Dopamine receptors can be divided into two major families, based on pharmacology and signal transduction mechanisms: the D1-like receptors (D1 and D5) and the D2-like receptors (D2, D3 and D4) (Ch. 14). This section will focus on D1 and D2 receptors. D1 receptors are positively coupled to adenylyl cyclase, while D2 receptors are negatively coupled to adenylyl cyclase. In addition, both receptors influence other signaling mechanisms. Both serve as postsynaptic receptors in the nucleus accumbens, dorsal striatum, amygdala, prefrontal cortex and other dopamine-innervated regions. D2 receptors also serve as presynaptic autoreceptors. Both D1 and D2 receptors mediate psychomotor stimulant actions and undergo neuroadaptations in rodent models of psychomotor stimulant addiction (Anderson & Pierce, 2005). Humans addicted to stimulants show reduced D2 receptor levels, and there is also evidence that D2 receptor levels contribute to individual differences in vulnerability to addiction (Volkow et al., 2009).

Initially, studies of psychomotor stimulant-induced neuroadaptations focused on D1 receptor signaling through the cAMP-dependent protein kinase (PKA) pathway. Through this pathway, D1 receptors can exert both rapid and long-lasting actions on the excitability of postsynaptic neurons. The rapid actions reflect PKA phosphorylation of targets that include N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors, Na^+ channels and Ca^{2+} channels. Longer-lasting actions reflect PKA regulation of transcription factors such as CREB (Ch. 27). More recent studies have demonstrated that PKA is only part of the picture. Psychomotor stimulants also regulate other signaling cascades, including mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase (ERK) and the phosphoinositide-3-kinase pathway (McGinty et al., 2008). More work is needed to unravel the interplay in postsynaptic neurons between signaling pathways activated by dopamine, glutamate and other inputs. For example, CREB activity is regulated by ERK, PKA and calcium/calmodulin-dependent protein kinases. Complex cross-talk between many signaling pathways is ultimately required for recruitment of mechanisms that enable synaptic and structural plasticity (Fig. 61-5).

CANNABINOIDS (MARIJUANA)

Marijuana and hashish are derivatives of the cannabis sativa plant

Although cannabinoids have been used for centuries for recreational and therapeutic purposes, dramatic advances in cannabinoid neurobiology have occurred since 1990 (Maldonado et al., 2006; Freund et al., 2003; Budney & Hughes, 2006; Ligresti et al., 2009; Lovinger, 2008). This is attributable to the cloning of cannabinoid receptors and the discovery of endogenous cannabinoids, termed endocannabinoids.

Marijuana's major effect in humans is a mildly euphoric and relaxing 'high', although higher doses can cause anxiety, paranoia and panic. Other effects include increased appetite, distorted perceptions, impaired coordination, difficulty in thinking and problem solving, and problems with learning and memory. The psychoactive component of cannabis is Δ^9-tetrahydrocannabinol (THC). Research over the past decade has shown that long-term marijuana abuse can lead to dependence and has identified a cannabis withdrawal syndrome (characterized by irritability, anxiety, decreased appetite, restlessness and sleep difficulties) that contributes to relapse. However, cannabinoids also have therapeutic potential, which has led to their legalization for medical purposes in some localities. Preparations of THC alone, synthetic THC analogs, and THC together with cannabidiol (CBD) are used for the treatment of nausea and emesis produced by cancer chemotherapy and for appetite induction in AIDS patients. Cannabinoid agonists and antagonists also have potential utility for a number of other conditions including metabolic disorders, pain and inflammation, gastrointestinal and hepatic disorders, neurological and neurodegenerative disorders, psychiatric disorders (anxiety, depression and post-traumatic stress disorder) and even for drug and alcohol addiction (see below).

Cannabinoid effects in the CNS are mediated by the CB1 receptor

This G_i/G_o-protein-coupled receptor was cloned in 1990. The CB2 receptor was cloned three years later; its role in the CNS is still unclear. The CB1 receptor is by far the most abundant GPCR in the mammalian brain. It is highly expressed in the hippocampus, neocortex, basal ganglia, cerebellum, limbic regions and brain stem. Accordingly, cannabinoids modulate a wide variety of functions, including learning, memory, motivation, motor activity and pain processing. Most CB1 receptors are found on presynaptic nerve terminals. When activated, they inhibit the release of glutamate, GABA and other neurotransmitters through mechanisms that involve inhibiting Ca^{2+} currents and altering K^+ channel gating. CB1 receptor–mediated presynaptic inhibition plays an important role in synaptic plasticity (see below). CB1 receptors are also coupled to inhibition of adenylyl cyclase and activation of the MAPK/ERK pathway, as well as other protein kinase signaling cascades that regulate gene expression (see Part 3, Intracellular Signaling). Like other GPCRs, CB1 receptors undergo agonist-induced desensitization involving G-protein uncoupling in response to phosphorylation by GRKs and receptor internalization.

Cannabinoids share with other drugs of abuse the ability to increase the firing rate of VTA dopamine neurons and increase dopamine release in the nucleus accumbens. One mechanism involves stimulation of presynaptic CB1 receptors on GABA nerve terminals in the VTA, leading to decreased GABA release and disinhibition of dopamine neurons (Fig. 61-3). This is probably important for the reinforcing effects of cannabinoids. However, cannabinoid actions in other brain regions are likely to contribute importantly to their behavioral effects, including effects on GABAergic and glutamatergic synaptic transmission in the nucleus accumbens and striatum. Endogenous opioid systems play a role in cannabinoid effects on dopamine release and, more generally, in the reinforcing

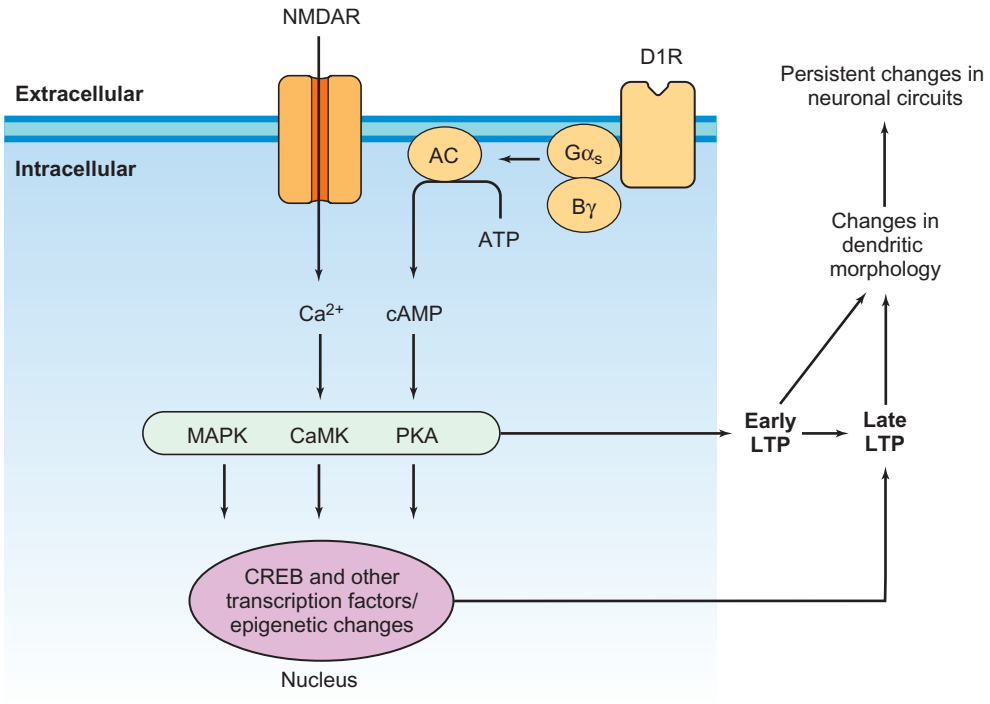


FIGURE 61-5 **Convergent effects of D1 receptor and glutamate receptor signaling influence neuronal excitability by regulating ion channels and receptors in the membrane (see text) and influence gene expression by activating transcription factors such as CREB, as well as via related epigenetic mechanisms.** D1 receptors signal via PKA as well as other cascades, including ERK and the phosphoinositide-3-kinase pathway. Some effects are mediated indirectly by DARPP-32, a potent inhibitor of protein phosphatase-1 that is involved in many aspects of addiction (see Ch. 24). There is considerable cross-talk between D1 receptors and other receptors located in dopamine-receptive neurons—for example, NMDA, AMPA, mGluR, D2 dopamine, serotonin, adenosine, opiate and $GABA_A$ receptors. The NMDA receptor plays an important role in activating Ca^{2+}-dependent signaling pathways. Convergent activation of cAMP and Ca^{2+} signaling pathways is necessary for some responses, e.g., CREB activation. The same signaling cascades are critical for activity-dependent forms of plasticity such as LTP. During the early phase of LTP, which requires activation of several protein kinases, synaptic strength is increased by mechanisms that include the synaptic insertion of additional AMPA receptors. This is followed by a later, more persistent component of LTP that requires protein synthesis. Presumably this is related to the spine enlargement and formation of new spines that is coordinated with AMPA receptor synaptic insertion during LTP. Remodeling of spines, as well as presynaptic terminals, is thought to underlie persistent changes in the activity of neuronal circuits. The ability of drugs of abuse to influence the same signaling pathways that mediate synaptic and structural plasticity helps to explain their ability to produce the persistent behavioral changes that constitute addiction.

effects of cannabinoids, as opioid antagonists block cannabinoid self-administration in animals.

Endocannabinoids are endogenous ligands for the CB1 receptor

The best established endocannabinoids are anandamide (*N*-arachidonoyl ethanolamide) and 2-AG (2-arachidonyl glycerol). Pathways involved in the formation and inactivation of anandamide and 2-AG are shown in Figure 61-6. Some steps in their formation are Ca^{2+}-dependent. This explains the ability of neuronal depolarization, which increases postsynaptic intracellular Ca^{2+} levels, to stimulate endocannabinoid formation and release. Some neurotransmitter receptors (e.g., group I metabotropic glutamate receptors) stimulate endocannabinoid formation by modulating postsynaptic Ca^{2+} levels or signaling pathways (e.g., phospholipase C) that regulate endocannabinoid formation.

Endocannabinoids are derived from lipids, making them different from classical and peptide transmitters in several important respects. The latter are stored in vesicles after their synthesis and released by exocytosis in response to action potential invasion of the nerve terminal. In contrast, endocannabinoids are produced 'on demand' when neuronal activity or occupation of membrane receptors leads to cleavage of membrane lipid precursors. Endocannabinoid release is poorly understood, but it is not vesicular. It could involve simple diffusion through the plasma membrane, although facilitation of endocannabinoid release by a membrane transporter is also possible. Furthermore, their hydrophobic nature raises questions about how they cross the extracellular space.

Endocannabinoids serve as retrograde messengers that regulate synaptic plasticity

After they are synthesized and released by postsynaptic neurons, endocannabinoids act on presynaptic CB1 receptors on neighboring nerve terminals to decrease transmitter release. This retrograde signaling is essential for

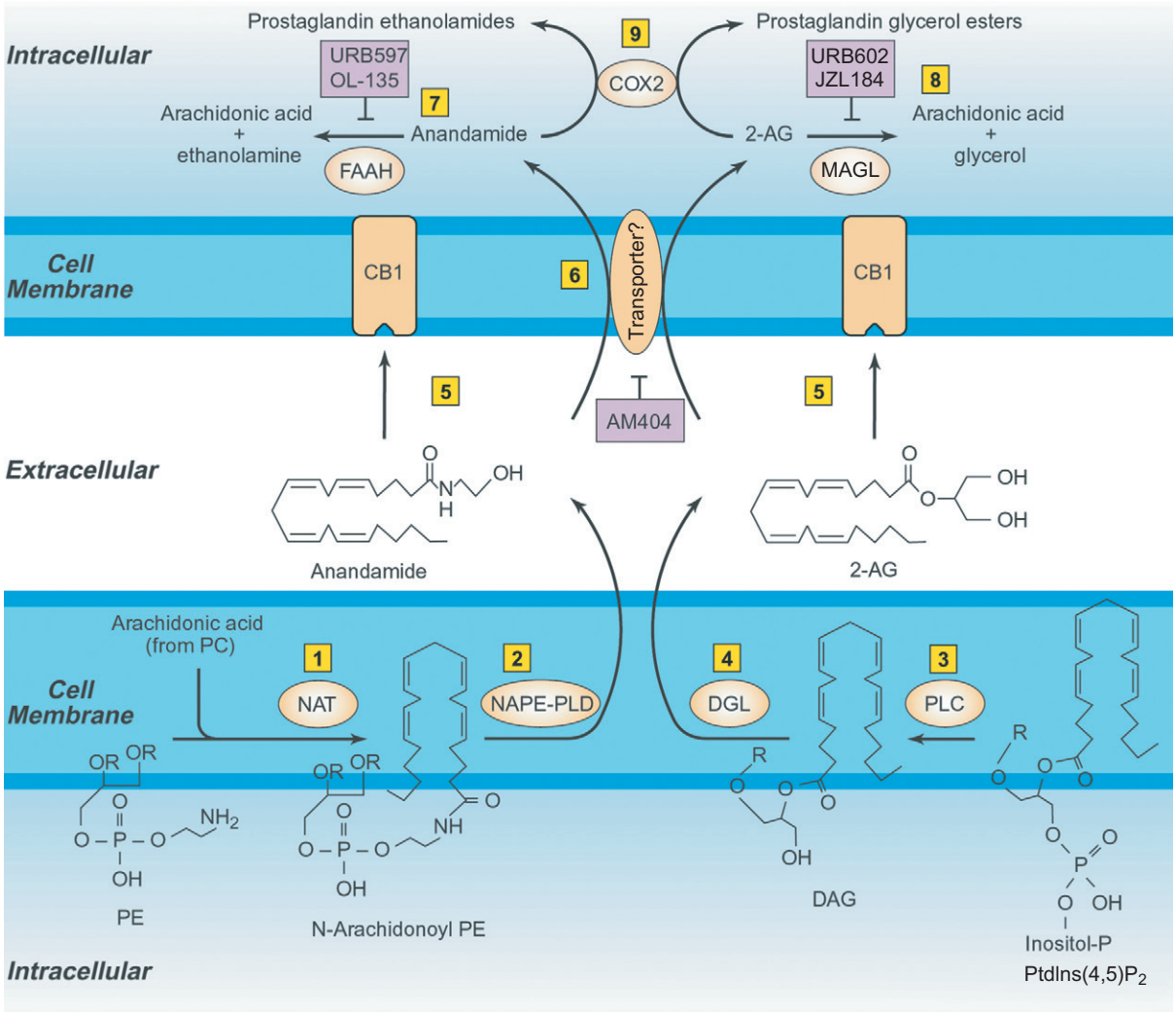


FIGURE 61-6 **Formation and inactivation of the endocannabinoids anandamide and 2-AG. (1)** *N*-arachidonoyl phosphatidylethanolamine (*N*-arachidonoyl PE), required for synthesis of anandamide, may be formed by *N*-acyl transferase (*NAT*), which transfers an arachidonate moiety, derived from the sn-1 position of phospholipids such as phosphatidylcholine (*PC*), to the primary amino group of PE. **(2)** Anandamide is generated from the hydrolysis of *N*-arachidonoyl PE, catalyzed by *N*-acylphosphatidylethanolamine-hydrolyzing phospholipase D (*NAPE-PLD*). **(3)** Phospholipase C (*PLC*) catalyzes the hydrolysis of phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P_2) to diacylglycerol (*DAG*) and inositol (1,4,5)-triphosphate. **(4)** DAG lipase (*DGL*) catalyzes the formation of 2-AG from DAG. An alternative pathway for 2-AG formation involves the formation of a 2-arachidonoyl-lysophospholipid such as lyso-PI (catalyzed by phospholipase A1) followed by its hydrolysis to 2-AG (catalyzed by lyso-PLC). **(5)** Anandamide and 2-AG are agonists at the CB1 receptor. **(6)** Anandamide and 2-AG may be removed from the extracellular space by carrier-mediated transport. AM404 blocks endocannabinoid uptake. **(7)** Anandamide is hydrolyzed by a membrane-bound fatty acid amidohydrolase (*FAAH*), which is inhibited by URB597 and OL-135. **(8)** 2-AG is hydrolyzed by monoacylglycerol lipase (*MAGL*). MAGL is inhibited by URB602 and JZL184. **(9)** Anandamide and 2-AG are converted to prostaglandin ethanolamides and glycerol esters, respectively, by cyclooxygenase-2 (COX-2). Abbreviations: *AA*, arachidonic acid; *R*, fatty acid group.

depolarization-induced suppression of excitatory and inhibitory transmission (DSE and DSI, respectively). These forms of short-term synaptic depression are initiated by postsynaptic Ca^{2+} increases (leading to endocannabinoid formation) and expressed by CB1 receptor–mediated decreases in transmitter release. Retrograde endocannabinoid signaling also mediates some forms of long-term depression (LTD) that are initiated postsynaptically but expressed presynaptically, although in this case an additional mechanism besides CB1 receptor activation is apparently necessary to account for the long-lasting nature of presynaptic inhibition. Marijuana may alter normal endocannabinoid-mediated synaptic effects and synaptic plasticity. For example, chronic THC exposure leads to loss of endocannabinoid-mediated LTD in the nucleus accumbens, which may be important for tolerance and addiction. Effects on synaptic plasticity could also contribute to the disruption of memory and information processing associated with marijuana use.

There are many similarities between endogenous opioid and cannabinoid systems

Both CB1 and MOP-Rs are G_i/G_o-coupled receptors that share some signaling mechanisms and cellular effects, such as presynaptic inhibition. Both opioids and cannabinoids produce analgesic and rewarding effects. Finally, both systems are integral components of the reward circuitry and thus participate in responses to other drug classes. For example, in animals, blockade of endocannabinoid transmission attenuates reinstatement of cocaine- and heroin-seeking behavior and decreases motivation for alcohol consumption. It is likely that the mechanism involves CB1 receptor-mediated modulation of synaptic transmission and synaptic plasticity in reward-related brain regions such as the VTA, nucleus accumbens, dorsal striatum and amygdala. Drugs targeting endocannabinoid transmission may be useful in treating some aspects of addiction.

NICOTINE

Nicotine is responsible for the highly addictive properties of tobacco products

Addiction occurs in ~30% of those who experiment with tobacco products, and more than 80% of those who attempt to quit smoking will relapse within a year. Withdrawal from nicotine produces a syndrome characterized by nicotine craving as well as dysphoria, anxiety, irritability, restlessness and increased appetite. It is treated with nicotine replacement therapies, such as nicotine gum and patches; through treatment with the nicotinic partial agonist varenicline; and/or with bupropion, a drug that is classified as an antidepressant but has multiple and complex effects in brain. Nicotine addiction has been reviewed at cellular and systems levels (Picciotto & Corrigall, 2002; Fagen et al., 2003; Changeux, 2010).

Nicotine is an agonist at the nicotinic acetylcholine receptor (nAChR)

Activation of this receptor depolarizes target cells (see Ch. 13). nAChRs are composed of five subunits surrounding a central ion-channel pore. Twelve different nicotinic receptor subunits are expressed in the nervous system (α2–α10 and β2–β4). Of these, a subset is expressed in the VTA (α3–α7 and β2–β4). It is thought that α7 receptors form homomeric receptors; α3, α4 and α6 form heteromeric channels with β2 or β4; and α5 and β3 can associate with other α/β pairs. Studies in knockout mice implicate several subunits in the ability of nicotine to modulate dopamine neurons (α4, α6, α7, β2, β3) but suggest that β2-containing receptors play a critical role in reinforcement, as β2-subunit knockout mice do not self-administer nicotine. Emerging evidence suggests that a cluster of genes encompassing the α5 subunit is associated with smoking behavior in human subjects and that this subunit is involved in nicotine withdrawal in mice.

nAChRs exist in three basic conformational states: closed, open and desensitized. There are both short- and longer-lasting desensitized states. The extent to which desensitization occurs depends on the subunit composition of the nAChR, as well as the concentration and duration of agonist exposure. For example, prolonged exposure to low agonist concentrations, such as occurs during smoking, can induce receptor desensitization. Cycles of receptor activation and desensitization contribute to smoking behavior. For example, the first cigarette of the day may be perceived as the most pleasurable because high-affinity nAChRs are still available for activation. These include the β2-containing receptors on dopamine and GABA cells of the VTA, which are readily desensitized during smoking (see below). With long-term nicotine exposure, the number of nAChRs is upregulated, potentially because nicotine acts as a chaperone that stabilizes assembly of nAChRs. The functional significance remains uncertain, but this could represent an early step in sensitization of nicotine-induced behaviors.

The ventral tegmental area (VTA) is a critical site for nicotine action

Intra-VTA nicotine is sufficient to produce behavioral effects, whereas injections outside the VTA are not effective. Activation of dopamine transmission by nicotine is important for its reinforcing effects in drug-experienced animals. For example, nicotine self-administration is reduced by blocking dopamine transmission in the nucleus accumbens. Complicating the picture, however, is evidence implicating dopamine activation in aversive effects of intra-VTA nicotine in naïve animals. Brain regions connected to the VTA also play important roles in nicotine's actions, notably the pedunculopontine tegmental nucleus and the adjacent laterodorsal tegmental nucleus (see Fig. 61-2). These regions send cholinergic (as well as glutamate and GABA) projections to the VTA that are important regulators of dopamine cell activity. Thus, the acetylcholine system, along with endogenous opioid and cannabinoid systems, can be considered part of the natural reward circuitry. In this context, it is not surprising that nAChR transmission is implicated in the reinforcing effects of other drug classes, including psychomotor stimulants and ethanol.

Within the VTA, nicotine exerts its effects via nAChRs located on dopamine neurons, GABA neurons and glutamate nerve terminals. Dopamine and GABA neurons of the VTA express β2-containing receptors, which include α4 as well as other subunits. α7-containing receptors are expressed by glutamate nerve terminals in the VTA, and by a subset of dopamine and GABA neurons. Differential desensitization of nAChRs is important for nicotine's action in the VTA. While β2 receptors on the dopamine cells and GABA terminals desensitize readily in response to a smoker's nicotine levels, the α7 receptors on glutamate terminals desensitize to a lesser extent and continue to promote glutamate release, which now excites the dopamine cells even more effectively due to the decrease in inhibitory GABA synaptic inputs. This enables sustained activation of dopamine transmission. Furthermore, by enhancing glutamate release, presynaptic α7 receptors in the VTA can produce LTP at excitatory synapses onto dopamine neurons. This further enhances the excitability of dopamine

neurons. nAChRs also influence synaptic plasticity in other regions, including the prefrontal cortex, hippocampus, amygdala and striatum, and circuits involving these regions contribute to nicotine addiction. Finally, endocannabinoid and endogenous opioid transmission in the reward circuitry have been demonstrated to play important roles in nicotine's behavioral effects and represent potential targets for therapeutic intervention.

ETHANOL, SEDATIVES AND ANXIOLYTICS

Alcoholism is a chronic relapsing disorder

The risk of alcoholism depends on a complex interaction between genetic factors and environmental factors including stress. Chronic alcohol use influences this interaction, for example, by triggering epigenetic changes and upregulating stress responses. Historically, ethanol's actions were attributed to nonspecific disruption of the lipid bilayer of neurons. It is now recognized that ethanol has specific molecular targets, and that effects of long-term ethanol exposure are due to neuroadaptations as well as neurotoxicity (Siggins et al., 2005; Spanagel, 2009; Heilig et al., 2010).

The symptoms of mild ethanol intoxication vary among individuals, ranging from stimulation to sleepiness. At higher doses, sedating effects increase. Intoxicating doses impair memory, judgment, reaction time and self-control. Consuming large amounts of alcohol in a short period of time can result in severe respiratory depression and death (acute alcohol poisoning). After repeated exposure, tolerance can be substantial. Alcoholics may attain very high blood alcohol levels without appearing grossly sedated. Heavy use inevitably leads to physical dependence. The severity of the ethanol withdrawal syndrome depends on the degree of dependence and the number of prior withdrawal episodes. Symptoms can include tachycardia, sweating, tremor, hypertension, anxiety and agitation, and can progress to include delirium tremens (confusion and perceptual changes) as well as seizures and other life-threatening complications. The severity of these symptoms is one factor that contributes to the resumption of alcohol consumption early in withdrawal. However, the major problem in the treatment of alcohol dependence in humans is continued vulnerability to relapse even after prolonged withdrawal periods. This vulnerability is linked to the neuroadaptations described below.

Ethanol interacts directly with ligand-gated and voltage-gated ion channels

Ethanol interacts with a wide range of ion channels, including $GABA_A$, NMDA, glycine, nACh and 5-HT3 receptors, as well as L-type Ca^{2+} channels and G protein-activated inwardly rectifying K^+ channels (GIRKs). This is important both for acute effects and long-term adaptations. Most attention has focused on ethanol's ability to act as a negative allosteric modulator of NMDA receptors and to enhance GABA transmission through both presynaptic and postsynaptic mechanisms. During long-term ethanol exposure, compensatory changes occur that alter ethanol's effects. For example, NMDA receptors are upregulated, while $GABA_A$ receptors are functionally downregulated due to changes in receptor subunit composition. This results in increased neuronal excitability during acute withdrawal, when ethanol is no longer present to decrease NMDA receptor function and enhance GABA transmission. The increase in glutamate tone may contribute to withdrawal-related seizures and neurotoxicity. Different mechanisms may come into play during protracted ethanol withdrawal.

Multiple neuronal systems contribute to the reinforcing effects of ethanol

Like other drugs of abuse, acute ethanol increases the firing rate of VTA dopamine neurons (Fig. 61-3). The mechanism underlying this effect is still not completely defined. Many studies implicate disinhibition of dopamine neurons as a result of altered MOP-R and GABA transmission in the VTA, but ethanol also directly excites dopamine neurons by affecting voltage-gated ion channels. This activation of VTA dopamine neurons contributes to the acquisition of ethanol reinforcement in the early stages of addiction, but other transmitter systems are also important and may play more persistent roles. In addition to modulating dopamine transmission, endogenous opioids contribute to ethanol addiction through non-dopaminergic actions. Endocannabinoid transmission also plays a role in excessive ethanol consumption and craving, as does glutamate transmission via ionotropic receptors and particularly via metabotropic glutamate receptor (mGluR) 5. The nucleus accumbens is one important locus for these effects. In animal models, antagonists of opioid, endocannabinoid and mGluR5 receptors, injected into the nucleus accumbens or given systemically, can decrease ethanol consumption and reinforcement; decreasing glutamate transmission by stimulating inhibitory presynaptic mGluR2/3 receptors is also effective.

Once dependence develops, ethanol's anxiolytic effects become a critical factor that maintains continued ethanol consumption because they provide relief from the negative emotional state associated with alcohol withdrawal. This negative/anxiogenic state is due to alcohol-induced neuroadaptations in stress systems in the extended amygdala. These neuroadaptations lead to an upregulated response to stressors that is important for maintaining excessive alcohol consumption and vulnerability to stress-induced relapse. CRF plays a particularly important role in these neuroadaptations, although other neuropeptides (including substance P and its neurokinin 1 receptor) and GABA are also important. CRF and neurokinin 1 receptor antagonists decrease alcohol consumption and stress-induced relapse in dependent animals.

Pharmacotherapies for alcoholism are improving

Disulfiram has been used for many years to help prevent relapse, but compliance is often low. Disulfiram inhibits aldehyde dehydrogenase, an enzyme involved in alcohol metabolism, resulting in the buildup of acetaldehyde when

alcohol is consumed. This produces unpleasant effects such as tachycardia, nausea and anxiety. Benzodiazepines are used to treat withdrawal hyperexcitability (see next section). More recently, naltrexone and acamprosate have been approved for use in alcohol-dependent individuals (see Translational Box: A Novel, Unexpected Treatment for Alcoholism). The opioid antagonist naltrexone is used to decrease alcohol consumption and craving, based on the role of opioid receptors in the reinforcing effects of ethanol (above). The target of acamprosate is less well defined, but this drug is believed to reduce craving by opposing the hyperglutamatergic state associated with alcohol withdrawal. However, effect sizes for both drugs are small, perhaps because of heterogeneity of response among patients. A clinical trial is underway to determine if patients motivated by reinforcing effects of ethanol will respond to naltrexone, while those seeking to relieve withdrawal symptoms will respond to acamprosate. Looking towards the future, both animal studies and clinical trials have shown promising results with additional drugs targeting glutamate, GABA, neurokinin 1, 5-HT3 and nACh receptor transmission, and there is optimism regarding the potential for using genetic and other markers to define appropriate patient populations for particular treatments.

Barbiturates and benzodiazepines are used to treat anxiety

Sedatives such as the barbiturates were commonly used until the introduction of benzodiazepines in the early 1960s. Both of these drug classes have abuse liability, although less than stimulants and opiates. There is cross-tolerance and cross-dependence among ethanol, barbiturates and benzodiazepines, as all are positive allosteric modulators of $GABA_A$ receptors and produce decreased GABA transmission after chronic treatment.

HALLUCINOGENS AND DISSOCIATIVE DRUGS

Hallucinogens produce an altered state of consciousness

Users may experience perceptual distortions and sometimes hallucinations, mood changes (ranging from elation to depression or paranoia) and intense arousal. High doses can elicit a 'mystical–religious' experience, accounting for the important role of naturally occurring hallucinogens, such as mescaline (the psychoactive component of peyote), in religion and philosophy in early cultures. Hallucinogen use tends to be episodic and limited, not chronic or compulsive, so these drugs are not associated with drug dependence or addiction. Nevertheless, there can be serious adverse consequences, including accidents due to impaired judgment and 'bad trips' characterized by severe anxiety. Psychotic reactions have been reported in a small proportion of users. In addition, flashbacks that resemble the original experience occur in a small proportion of former users. This is termed hallucinogen persisting perception disorder.

Two categories of hallucinogens can be defined based on chemical structure: the tryptamines, which include lysergic acid diethylamide (LSD), and the phenethylamines, which include mescaline and MDMA. MDMA is discussed in the section on Psychomotor Stimulants above. This section will focus on LSD, the most potent hallucinogenic drug (Nichols, 2004). Based on structural similarity between tryptamines and serotonin, interactions between LSD and serotonin systems have been suspected since the 1950s. The hallucinogenic properties of LSD are now attributed mainly to its partial agonist effects at $5\text{-}HT2_A$ receptors. However, LSD's mechanism still remains puzzling, because its high *in vivo* potency is not predicted from its receptor affinity or intrinsic activity at known signaling pathways. A possible explanation is related to the realization that different agonists can activate different signaling pathways through the same receptor (agonist-directed signaling). Perhaps LSD produces a unique pattern of activation of 5-HT2 receptor–signaling pathways. It is also possible that other monoamine receptors contribute to LSD's actions. At the neuronal systems level, frontal cortex and thalamus are important sites of LSD action. Modulation of glutamate transmission in these regions probably underlies distortions in perceptual and cognitive function. Effects of LSD on neurons of the locus ceruleus, an important region for gating of sensory inputs, may contribute to enhancement of sensory experiences after taking LSD.

Phencyclidine (PCP) is a dissociative drug

PCP and ketamine were developed in the 1950s as general anesthetics for surgery. They were discontinued because patients sometimes became delusional during recovery from anesthesia. PCP became a drug of abuse in the 1970s. It is classified as a dissociative drug because it distorts perception and produces feelings of dissociation from reality. Its effects can be powerfully euphoric as well as dysphoric. Notably, PCP mimics both negative symptoms (e.g., apathy and social withdrawal) and positive symptoms (e.g., delusions, paranoia and hallucinations) of schizophrenia. Tolerance and withdrawal have not been well studied in humans. Long-term users of PCP report problems with memory, thinking and mood. PCP overdose is associated with dangerous physical complications.

PCP is a noncompetitive antagonist of NMDA-type glutamate receptors. It binds to a site within the open NMDA receptor ion channel (Ch. 17). Because PCP mimics schizophrenic symptoms, the discovery that it blocks glutamate transmission was a major impetus for the development of glutamate-based theories of schizophrenia (see Ch. 58). Although PCP is a weak dopamine-uptake inhibitor, its reinforcing effects in rat self-administration models reflect NMDA receptor blockade, not an increase in dopamine transmission. However, PCP can activate dopamine neurons indirectly, by blocking NMDA receptors that influence dopamine neurons. Similarly, other transmitter systems are influenced by PCP via pathways 'downstream' of NMDA receptor blockade. Thus, the pharmacology of PCP action in animal models of addiction is complex. Very high doses of PCP and other noncompetitive NMDA receptor antagonists produce neurodegeneration in animal models.

ADDICTION AND NEURONAL PLASTICITY SHARE COMMON CELLULAR MECHANISMS

Drugs of abuse "rewire" neuronal circuits by influencing synaptic plasticity

Results described above indicate that addiction is associated with long-lasting changes in the activity of particular neuronal circuits. It is now accepted that this "rewiring" involves the same mechanisms that enable learning and memory, that is, activity-dependent forms of plasticity (e.g., LTP, LTD or homeostatic plasticity) that alter the strength of glutamate synapses. The first clues came from studies showing that glutamate transmission was required for the development of behavioral sensitization and associated cellular changes in the mesolimbic DA system (Wolf, 1998). Indirect support came from studies showing that drugs of abuse and learning activate common signal transduction pathways (Hyman & Malenka, 2001). For example, the MAPK/ERK pathway, critical for learning and memory, is increasingly implicated in plasticity related to addiction (Thomas et al., 2008). Learning and drugs of abuse also have in common the ability to regulate spine structure, as discussed below. Most recently, there has been an explosion of research demonstrating that drugs of abuse influence synaptic strength and subsequent synaptic plasticity in brain regions important for addiction (Wolf & Ferrario, 2010; Kauer & Malenka, 2007; Thomas et al., 2008). Some drugs may influence LTP or LTD directly by altering excitatory transmission (e.g., cannabinoids or nicotine), while psychomotor stimulants probably do so indirectly through their effects on protein kinases and other signaling molecules involved in synaptic plasticity. The type and direction of plasticity depends on the drug, the circumstances of drug exposure and the brain region.

One of the first examples of drug-induced synaptic plasticity was the demonstration that cocaine and some other drugs of abuse elicit LTP at excitatory synapses onto dopamine neurons of the VTA (Kauer & Malenka, 2007; Thomas et al., 2008). This increases the excitability of the dopamine neurons, which is likely to be a key event for triggering downstream adaptations in nucleus accumbens and other forebrain regions. Other examples of drug-induced synaptic plasticity have since been described that are linked to longer-term changes in drug-exposed rats. For example, a switch to a higher conductance AMPA receptor subtype in the nucleus accumbens mediates enhanced cocaine craving after long periods of withdrawal (Wolf & Ferrario, 2010). Beyond LTP and LTD, there is increasing interest in the idea that drugs may elicit plasticity via synaptic scaling (a form of homeostatic plasticity in which synapses adjust AMPA receptor levels and other parameters to compensate for prolonged changes in activity) or by affecting the intrinsic excitability of neurons (due to alterations in voltage-gated ion channels) (Wolf & Ferrario, 2010). Some cellular and behavioral examples of drug-induced plasticity may be related to long-lasting increases in brain derived neurotrophic factor (BDNF), an important regulator of synaptic plasticity in the nervous system (Thomas et al., 2008). Other transmitters also modulate reward-related plasticity, including the orexin peptides (Harris & Aston-Jones, 2006).

Drugs of abuse have profound effects on transcription factors and gene expression

These effects are clearly important for long-lasting changes in brain function. They go hand-in-hand with drug-induced synaptic plasticity, since protein synthesis is required for aspects of LTP and associated spine remodeling (see Ch. 56). Two transcription factors strongly implicated in addiction are CREB and ΔFosB (Nestler, 2004). CREB is important for learning and memory and is activated by phosphorylation. Addictive drugs influence many of the signal transduction pathways that regulate its phosphorylation state (see Ch. 27). ΔFosB isoforms are highly stable products of the *fosB* gene that accumulate in nucleus accumbens and other regions during chronic drug treatment, enabling novel patterns of gene expression. Changes in gene expression initiated by these transcription factors contribute to 'sensitizing' adaptations that promote drug-taking as well as 'compensatory' adaptations that oppose drug-taking (e.g., dynorphin upregulation; see Opiates above). CREB and ΔFosB levels return to normal following weeks or months of drug withdrawal, so changes downstream of or independent of these factors must be responsible for longer-lasting plasticity.

Exciting recent findings show that drugs of abuse can influence gene expression through epigenetic mechanisms that alter chromatin structure on specific gene promoters (Renthal & Nestler, 2008). Chromatin (DNA wrapped around histone proteins) is usually highly condensed, limiting access of transcriptional activators to genes. Post-translational modification of histones, or DNA itself, can alter chromatin structure, which in turn increases or decreases the availability of particular genes for transcription. Drugs of abuse have been shown to elicit epigenetic changes by regulating the acetylation, phosphorylation and methylation of histones. Conversely, pharmacological and genetic manipulation of histone modifying enzymes can influence behavioral sensitivity to drugs of abuse. One way that drugs of abuse (and other stimuli) can produce epigenetic changes is by stimulating signaling pathways that activate transcription factors. For example, both phosphorylated CREB and ΔFosB can recruit histone-modifying enzymes to the promoters of specific genes. Epigenetic changes can be transient or very long lasting. It remains to be determined whether they mediate long-lasting changes important for addiction. However, even stable epigenetic changes are chemically reversible. Thus, pharmacological manipulation of epigenetic changes is a possible route for reversing drug-induced neuroadaptations.

Persistent adaptations may involve changes in the structure of dendrites and dendritic spines

Dendritic spines are the postsynaptic contact sites for most excitatory synapses in the brain. Structural changes in dendrites and spines were originally described after

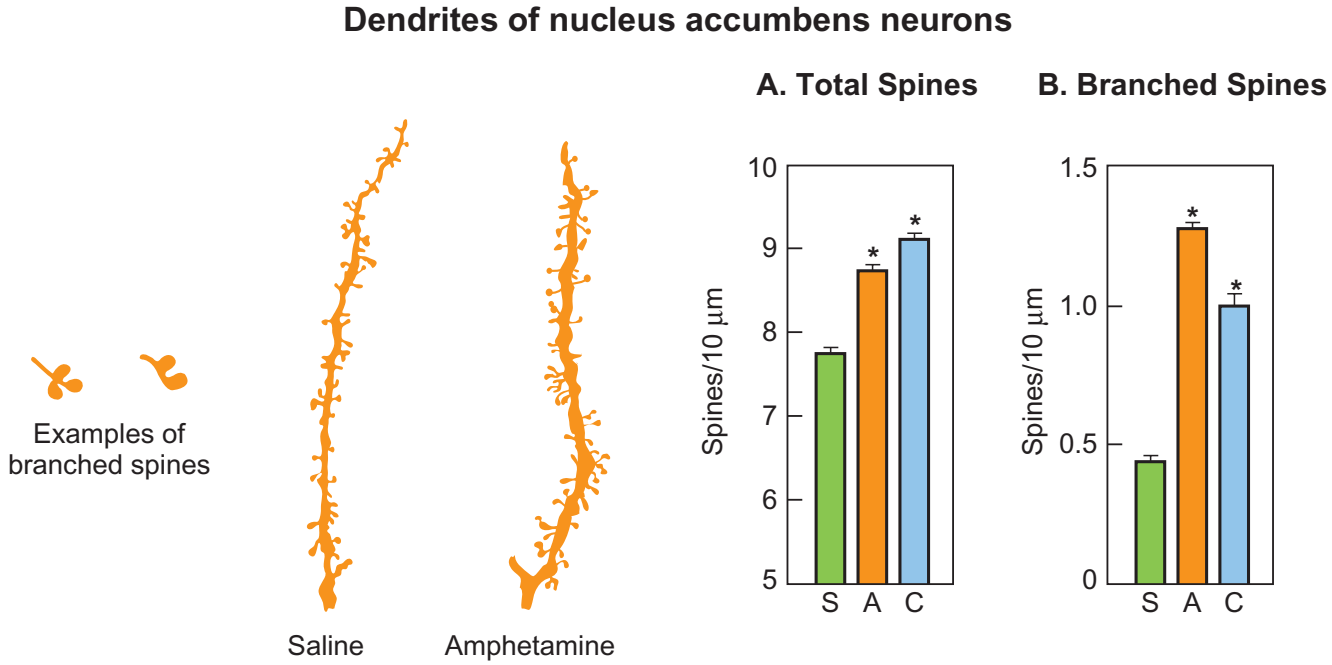


FIGURE 61-7 **Repeated exposure to amphetamine or cocaine increases spine density and the number of branched spines in medium spiny neurons, the major cell type of the nucleus accumbens. Left: camera lucida drawings of representative dendritic segments.** Rats received 20 injections of saline (*S*), amphetamine (*A*) or cocaine (*C*) over 4 weeks and were then left undisturbed for about 1 month prior to analysis. Adapted from Robinson, T. E. & Kolb B., *Eur. J. Neurosci.* 11; 1598–1604, 1999.

experience-dependent forms of plasticity, such as exposure to an enriched environment, and in association with LTP or LTD. They are mediated by complex signaling pathways that ultimately affect actin polymerization and thus spine morphology. There is overlap between these pathways and those that regulate AMPA receptor trafficking, consistent with coordinated changes in spine dynamics and AMPA receptor levels during synaptic plasticity. For example, LTP Is associated with spine enlargement and formation of new spines, along with increased insertion of AMPA receptors into spine synapses, whereas LTD is associated with spine retraction and AMPA receptor removal.

It is now appreciated that structural plasticity in the reward circuitry is produced by most drugs of abuse (Robinson & Kolb, 2004; Russo et al., 2010). For example, both cocaine and amphetamine increase spine density and dendritic branching in the nucleus accumbens and prefrontal cortex (Fig. 61-7). These structural changes, which are among the most long-lasting adaptations reported in response to repeated drug exposure, should be envisioned as occurring in concert with the drug-induced changes in synaptic plasticity and gene expression discussed above. Thus, drug-induced changes in synaptic activity and signaling pathway activation probably trigger coordinated and interdependent changes in gene expression, synaptic glutamate receptor levels, and spine structure (Fig. 61-5). ΔFosB, which partly mediates cocaine-induced increases in spine density in the nucleus accumbens, is an example of a potential bridge between these processes.

An important challenge is to understand the relationship between neuronal plasticity in particular pathways and specific behavioral alterations that underlie addiction. For example, plasticity in specific pathways presumably explains how drug-associated cues acquire a heightened ability to control behavior in drug addicts or why brain stress systems "misfire" during withdrawal. If we identify the pathways that are rewired, and understand the pharmacology of systems that regulate these pathways or accomplish the rewiring, perhaps pharmacological treatments can be devised to reduce craving and relapse.

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A NOVEL, UNEXPECTED TREATMENT FOR ALCOHOLISM

Charles P. O'Brien

An excellent example of a totally new approach to treatment originating in an animal model is that of the discovery of the efficacy of naltrexone and other opioid antagonists for the treatment of alcoholism. During the 1970s, self-administration of ethanol by rats and monkeys either by oral or intravenous route became available. This enabled researchers to experimentally manipulate factors that influenced self-administration and to test the influence of other drugs on this phenomenon. A breakthrough occurred in 1979 when Altshuler (Altshuler et al., 1980) first reported his findings in a small group of Rhesus monkeys that were selected for their willingness to self-administer intravenous alcohol. Prior to the alcohol session, the monkeys received either saline or one of three graded doses of naltrexone. The animals showed a clear dose-response effect, with naltrexone producing a suppression of alcohol self-administration. Subsequently the finding was replicated in rats and in vervet monkeys with oral self-administration of alcohol.

Opioid antagonists were originally developed for the treatment of heroin addiction, and there was absolutely no idea when they were first synthesized that they might be used to treat alcoholism. But the results from animal models were consistent and clear. Beginning in 1983, a group of researchers who studied both animal models and conducted treatment studies in humans obtained an IND to administer naltrexone to patients with alcoholism. At this time, the medication was not yet approved for heroin addiction. The first non-blinded studies utilized a dose of 50 mg, the same dose chosen for heroin addiction, and some but not all alcoholics reported loss of pleasure from alcohol. Later, a placebo controlled, double-blind trial in chronic alcoholics receiving intensive psychotherapy at the Philadelphia VA Medical Center was conducted (Volpicelli et al., 1990; Volpicelli et al., 1992). Half of the patients received naltrexone and half received placebo. The results were consistent with the findings in the animal models: the patients randomized to naltrexone reported less alcohol craving, less reward from alcohol if they did drink, and a significantly lower relapse to heavy drinking. This study was completely based on animal models and had no pharmaceutical company funding.

The findings from the first study were predictable from the results in animal models but they were not accepted in the clinical community, possibly because they raised the issue of a similarity between alcoholism and heroin addiction. Indeed, the main hypothesis was that alcohol could activate endogenous opioid transmission, thus producing reward via some of the same pathways as heroin. Subsequent animal studies using microdialysis in the reward system (nucleus accumbens) showed that alcohol increases dopamine, which is blocked by pretreatment with naltrexone. In the 1980s, however, the linkage between opioids and alcohol was not generally accepted and thus only the Penn group conducted naltrexone studies in alcoholics. The pharmaceutical company that owned the drug for the treatment of heroin addiction did not wish to pursue the alcohol indication.

Beginning about 1990, the University of Connecticut Alcohol Center in collaboration with Yale attempted to replicate the Penn study and reported almost identical findings (O'Malley et al., 1992). Through a series of lucky coincidences, the data were eventually presented to the FDA and, after review, the treatment of alcoholism was added to the official indications for naltrexone. Thus a completely new treatment approach was developed from animal models and translated into a practical clinical intervention with no pharmaceutical support for the pivotal clinical trials. The value of the animal model in this situation is that it permitted the discovery of a novel mechanism of alcohol reward with important clinical implications. Since this discovery in animals and the subsequent early clinical trials, other opioid receptor antagonists have been found useful in alcoholism, and an extended release depot version of naltrexone has been marketed that only requires one injection per month for treatment efficacy. The depot version is now FDA approved for both alcoholism and opioid addiction.

Since only a subset of alcoholics respond to naltrexone, a pharmacogenetic mechanism was hypothesized. An allele of the μ opioid receptor gene has been identified as a marker for increased euphoria from alcohol that is blockable by naltrexone and a strong clinical response to naltrexone in alcoholism treatment trials (Oslin et al., 2003; Anton et al., 2006). A mouse model with a "knocked-in" human μ opioid gene also shows an enhanced dopamine response to alcohol (Ramchandani et al., 2011). This treatment may become the first medication in psychiatry to be guided by genotype.

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