CHAPTER 1

Neurobiology of Substance Use Disorders

Implications for Treatment

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Advances in neuroscience, neuroimaging, pharmacology, and genetics have provided the tools needed to understand neurobiological aspects of the substance-related disorders. While the individual patient, rather than his or her disease, is the appropriate focus of treatment, an understanding of the neurobiology helps clarify the rationale for treatment methods and goals. More importantly, knowledge of brain effects or abnormalities allows for the use of medications that specifically target and reverse known neurochemical problems (Haile & Kosten, 2013). That a substance use disorder (SUD) is indeed a brain disease with neurochemical effects should be conveyed to the patient, in addition to the possibility that certain medications may be helpful.

Chronic substance use eventually results in structural and functional brain abnormalities that, for some, lead to the need to keep taking drugs to avoid a withdrawal syndrome (substance-induced disorder). Another component of SUDs is characterized by intense drug craving and compulsive use that is unique to a particular drug class. As we describe later in this chapter, elements of drug withdrawal and drug craving are mediated by different, yet overlapping, brain circuits. Many abnormalities associated with drug withdrawal resolve within days or weeks after the substance use stops. The abnormalities that mediate craving and compulsion, however, are structural changes that are more wide-ranging, complex, and long-lasting. Structural changes lead to abnormal brain function that may be amplified by environmental effects—for example, stress, social context of initial drug use, and psychological conditioning. Genetics also plays a significant role due to aberrant brain pathways that were abnormal even before the first dose of a particular drug was taken. These pathways predispose an individual to develop an SUD (Russo et al., 2010). Such

abnormalities can produce craving that leads to relapse months or years after the individual has stopped using.

In this chapter we describe, in a simplified way, how drugs affect brain processes that underlie the motivational drive associated with drug use. Basic concepts such as drug tolerance and specific neurobiological processes and mechanisms that relate to withdrawal and intoxication are also addressed. Whereas these processes are highly complex, we try to explain them in terms that can be presented to patients. We also discuss the treatment implications of these concepts. Current models that help describe the development of an SUD are also noted. In the final section we review pharmacological therapy along with mechanism(s) of action in the brain. These actions attempt to offset directly or reverse some of the brain changes associated with a particular disorder. Studies have shown that pharmacotherapy greatly enhances the effectiveness of behavioral therapies. Although researchers do not yet have a comprehensive understanding about how these medications work, it is clear that they often renormalize brain abnormalities that have been induced by either genetic predisposition or chronic administration of high doses of a given substance.

NEUROBIOLOGICAL SUBSTRATES OF DRUG REINFORCEMENT

Many factors, both individual and environmental, influence whether a certain individual who experiments with a drug will continue taking it long enough to develop an SUD. For individuals who do continue, the drug's ability to provide intense feelings of pleasure is a critical reason.

Substances are consumed through many different routes (e.g., snorting, smoking, intravenous injection), and those that penetrate the brain more quickly are more often associated with compulsive use than those that enter the brain slowly (Fowler et al., 2008). In addition to the rapidity with which a drug enters the brain, all drugs associated with SUDs increase the neurotransmitter dopamine (DA) to supraphysiological levels within specific brain reward circuitry (Figure 1.1). The subsequent rise in synaptic DA then binds to unique DA-ergic receptor proteins on the surface of pre- and postsynaptic neurons (Figure 1.2). Another example is the opiate heroin that binds to mu opioid receptors, which are on the surfaces of opiate-sensitive neurons and induce their effects by inhibiting the cyclic adenosine monophosphate (AMP) second messenger system. Inhibition occurs through a G-protein mediated coupling leading to a series of changes in phosphorylation for a wide range of intraneuronal proteins (Nestler, 2012). The ability of heroin to bind to mu opioid receptors imitates the action of endogenous opioids such as beta-endorphin, initiating the same biochemical brain processes that are associated with positive subjective feelings from activities that are normally pleasurable (e.g., eating and sexual activity). Opioids such as oxycodone or methadone are prescribed therapeutically to relieve pain, but when these exogenous opioids activate the reward processes in the absence of significant pain, they can usurp normal brain reward circuitry and motivate repeated use of the drug simply for pleasure.

The mesocorticolimbic (midbrain and cortex) reward system consists of brain circuits activated to a degree by all drugs associated with compulsive use (Figure 1.2).
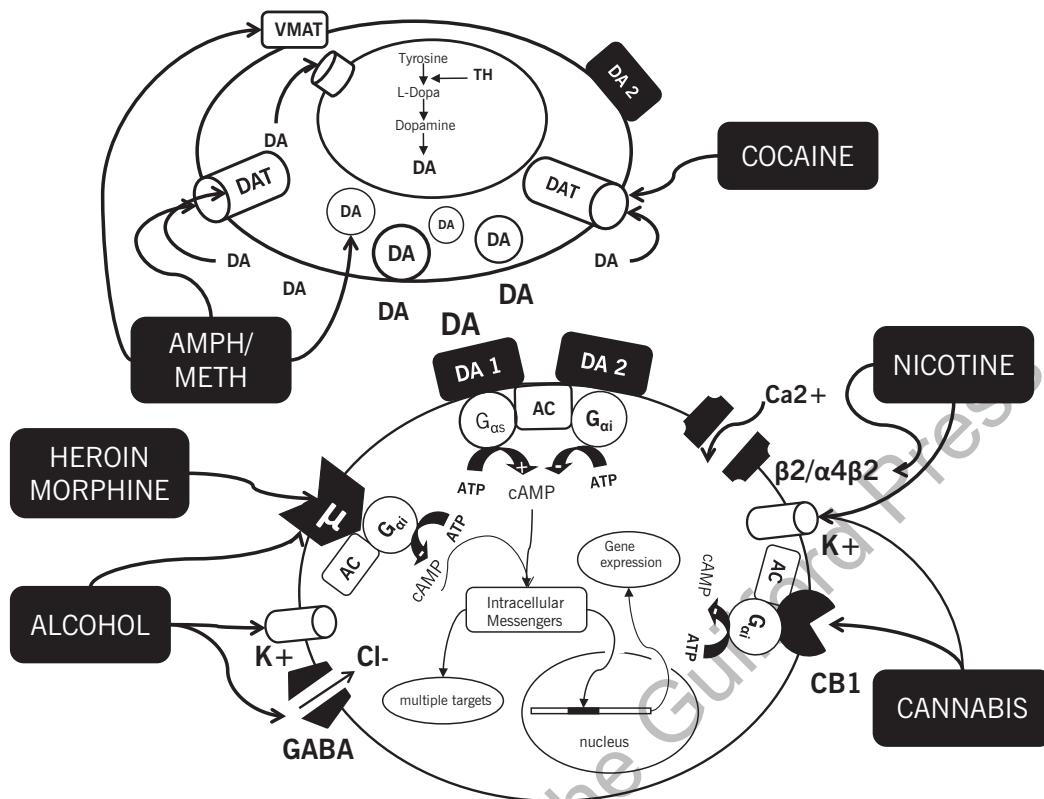
FIGURE 1.1. Hypothetical representation of a dopamine (DA) neuron, its target neuron, receptors, and transduction mechanisms implicated in the actions of various SUDs. Cocaine increases DA levels by blocking reuptake of the neurotransmitter through the dopamine transporter (DAT) back into the presynaptic cell for recycling. Supraphysiological levels of DA then activate their respective DA receptors (DA_1, DA_2). Cocaine-induced enhancement of dopamine activates D_1 receptors. Cyclic AMP levels are then increased via adenylate cyclase (AC) through $G_{\alpha s}$, whereas AC activity is decreased through $G_{\alpha i}$ G proteins. Cyclic AMP can enhance or decrease the action of intracellular messengers that have numerous targets including acting on DNA to initiate or suppress gene expression that alters cell activity. Amphetamine and methamphetamine (AMPH/METH) potently induces mobilization and release of vesicular DA increasing neurotransmitter levels in the synapse. AMPH/METH also prevents the inactivation of DA by altering the DAT and blocking reuptake. These drugs also alter the VMAT preventing normal repackaging of DA into vesicles. Opioids such as morphine and heroin bind to mu receptors on inhibitory GABA neurons in the VTA linked to inhibitory $G_{\alpha i}$ G proteins, subsequently decreasing intracellular cyclic AMP formation. Disinhibition of VTA DA neurons results in increased DA release in the NAc. The exact mechanisms responsible for alcohol's ability to increase DA are unknown; however, evidence suggests GABA, mu receptors, and potassium channels play a role. Nicotine can affect DA levels by at least two mechanisms: (1) increase VTA DA firing by direct activation of $beta_2$ receptors or through (2) receptors on GABA-ergic neurons that lead to disinhibition and increased DA release. Cannabinoids such as THC activate CB_1 receptors on GABA neurons linked to inhibitory $G_{\alpha i}$ G proteins that inhibit AC and cyclic AMP production. The G protein directly couples the CB_1 receptor to presynaptic voltage-dependent Ca^{2+} channels, which are inhibited, whereas inward rectifying K^+ channels are activated. It is hypothesized that inhibition of presynaptic release of GABA in the VTA disinhibits DA neurons, facilitating its release. Evidence also implicates opioid receptors in the ability of cannabinoids to facilitate DA release. TH, tyrosine hydroxylase; DBH, dopamine beta-hydroxylase; DAT, dopamine transporter; DA, dopamine; DA1, dopamine D_1 receptor; DA2, dopamine D_2 receptor; cAMP, cyclic adenosine 3′,5′-monophosphate; $G_{\alpha s}$, stimulatory G protein; $G_{\alpha i}$, inhibitory G protein; VMAT, vesicular monoamine transporter; Ca^{2+}, calcium; K^+, potassium; GABA, gamma-aminobutyric acid; THC, delta-9-tetrahydrocannabinol.
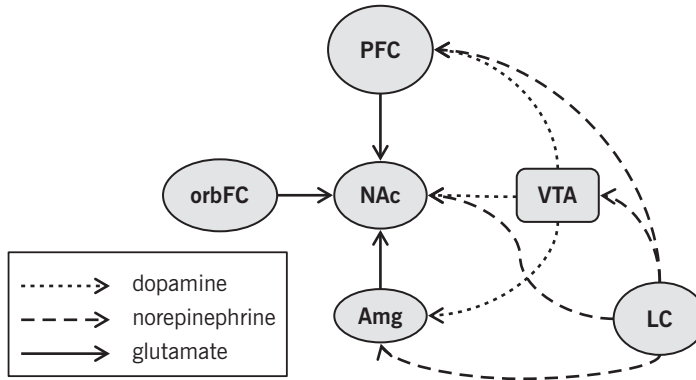
FIGURE 1.2. Representation of neurobiological circuitry that contributes to the reinforcing effects of different substances. Focus is given to neural connections and neurotransmitters DA, NE, and glutamate within mesocorticolimbic circuitry and other important brain structures involved in motor learning and conditioned behavior. Drugs of abuse activate the VTA–NAc pathway, then engage structures involved in learned stimulus–response behavior associated with drug taking. Conditioned reinforcement also involves the Amg, hippocampus (not shown), and NAc. Goal-directed behaviors, self-control, emotional regulation, and working memory involve the PFC and orbFC that send glutamatergic inputs into the NAc. The orbFC has also been linked to drug- and cue-induced "craving" states, along with the Amg and anterior cingulate cortex (not shown). The LC is the primary cell body region that gives rise to NE projections that affect either directly or indirectly most circuits that mediate the various aspects of drug reinforcement and withdrawal. LC NE inputs into the NAc and PFC play an especially important role in stimulant reinforcement, whereas the LC and associated circuits are responsible for withdrawal symptoms from opiates. Conceptually derived from Goldstein and Volkow (2011), Everitt and Robbins (2005), and Koob and Volkow (2010). Amg, amygdala; VTA, ventral tegmental area; NAc, nucleus accumbens; PFC, prefrontal cortex; orbFC, orbitofrontal cortex; LC, locus coeruleus.

This system generates signals in a part of the brain called the ventral tegmental area (VTA) that result in DA release in another brain structure into which VTA neurons project, the nucleus accumbens (NAc). This release of DA into the NAc is associated with positive subjective drug effects (Volkow et al., 2010). Other areas of the brain create a lasting record or memory that associates these good feelings with the circumstances and environment in which they occur (hippocampus). These memories, called "conditioned associations," have a neurocircuitry that often leads to the craving for drugs (amygdala, Amg). For example, when an individual with a SUD reencounters persons, places, or things (orbitofrontal cortex, orbFC) associated with drug use they may trigger the individual to make poor decisions and seek out more drugs in spite of many obstacles and detriment to themselves (prefrontal cortex, PFC) (Goldstein & Volkow, 2011).

Other substances activate this same brain circuitry but via different mechanisms and by stimulating or inhibiting different neurons within these circuits (Figure 1.1, Table 1.1). For example, opioids and cannabinoids can directly inhibit NAc activity, while stimulants such as cocaine and amphetamine (AMPH)-type substances such

TABLE 1.1. Drug Targets and Mechanism of Action

Drug	Target	Primary mechanism of action
Cocaine	DAT/NET/SERT	Binds to presynaptic monoamine transporters and blocks their reuptake, thereby increasing synaptic levels.
Amphetamine/ methamphetamine	NET/DAT, VMAT2, MAO	Induces NE and DA presynaptic release, reverses transporters.
Nicotine	nAChR agonist	Increases firing of VTA DA neurons through nicotinic $beta_2$ receptors; disinhibits DA neurons via $alpha_4$ $beta_2$ receptors on VTA GABA-ergic neurons.
Opioids (morphine, heroin)	Mu receptor agonist	Increases DA release by disinhibition of inhibitory GABA-ergic neurons through mu receptors.
Cannabis	CB_1 receptors	Increases DA by disinhibition of VTA DA neurons through CB_1 receptors on GABA-ergic neurons.
Alcohol	Undefined	Increases DA either by direct action or possibly by disinhibition via GABA-ergic receptors.

Note. VTA, ventral tegmental area; DAT, dopamine transporter; NET, norepinephrine transporter; SERT, serotonin transporter; VMAT2, vesicular monoamine transporter; MAO, monamine oxidase; nAChR, nicotinic acetylcholine receptor.

as methamphetamine (METH) act indirectly by binding to various DA transporters and either inhibiting the reuptake of DA back into the VTA neurons for recycling (cocaine) or actively pumping DA out of the VTA neuron (AMPH, METH; Figure 1.2). Although cocaine, AMPH, and METH bind DA transporter (DAT) sites all over the brain, the DAT sites in the VTA terminals that synapse with neurons in the NAc play a significant role in the positive subjective effects of these drugs. Since stimulation of the DA D_2 receptors inhibits the cyclic AMP cascade, this increase in DA in the synapse leads to relative inhibition of NAc neurons. The mechanism is more complex than this, however, since stimulation of D_1 receptors has the opposite effect on cyclic AMP (e.g., increases), and both D_1 and D_2 receptors are present on NAc neurons. D_2 receptors are also located on presynaptic neurons, where they serve as autoreceptors that, when stimulated, decrease release of presynaptic DA. The presumption is that D_2 receptor effects predominate perhaps simply due to more D_2 receptors or to a higher affinity of the D_2 than the D_1 receptors for DA. Activation of the cyclic AMP system results in myriad effects, including phosphorylation of intracellular proteins, receptors, receptor channels, sites on DNA that induce the expression of multiple genes, some related to synaptic plasticity that is long-lasting (Paulzen, Veselinovic, & Gründer, 2014). Other substances may be even more indirect in their stimulation of DA. For example, nicotine and benzodiazepines stimulate ion channels for calcium/sodium and chloride, respectively (Sulzer, 2011). The Ca^{2+}/sodium channel is a nicotinic receptor that normally binds acetylcholine, while the chloride channel is associated with gamma-aminobutyric acid (GABA) receptors. Activation of these ion channels can lead to depolarization of VTA neurons and release of DA from NAc neuron terminals either directly (nicotine) or indirectly (GABA). Entry of Ca^{2+} into the VTA neuron is required to facilitate the fusion of synaptic vesicles—that

contain packaged neurotransmitter—in the VTA with the cell membrane that leads to release of DA from these vesicles. Similarly, the primary active constituent in cannabis, delta-9-tetrahydrocannabinol (THC), inhibits the inhibitory action of GABA on VTA neurons (through CB_1 receptors), thereby increasing synaptic DA levels at terminal sites within the NAc. For some substances, however, such as alcohol, we do not yet have a clear idea of the biochemical mechanisms that mediate reinforcement. Evidence does suggest that alcohol acts, in part, through mu opioid receptors such as heroin, or GABA receptors such as the sedative/hypnotic drugs (benzodiazepines). The active ingredient in the inhalant toluene increases neurotransmission directly by stimulating VTA neurons leading to DA release in NAc terminals. Inhalant use disorders are associated with profound neurotoxicity (Sulzer, 2011).

The ability of a substance to activate brain reward circuitry potently and produce positive subjective effects is one reason that individuals continue to use a given substance, particularly in the early stages. However, the continued desire and compulsion to use drugs builds over time and extends beyond simple pleasure seeking. This increased compulsion is related to enhanced incentive to procure and take drugs despite recurrent interpersonal problems or having to give up important social or occupational roles. Drug use in situations that may be physically harmful or continued use knowing a physical or psychological problem is directly related to the particular drug consumed are also criteria related to SUDs. Chronic drug consumption eventually leads to synaptic plasticity, which is responsible for tolerance and withdrawal upon cessation of drug use. The intensity of tolerance and withdrawal varies greatly across different drug classes but undoubtedly contributes to continued use. Although it may seem an almost insurmountable objective, reversal or normalization of altered neurotransmission, usually with behavioral treatments and/or pharmacotherapies, is essential to produce a positive clinical outcome.

DRUG TOLERANCE AND WITHDRAWAL

From a clinical standpoint, withdrawal can be one of the most powerful factors driving dependence or addictive behaviors. This seems particularly true for opioids, alcohol, benzodiazepines, nicotine, and, to a lesser extent, stimulants such as cocaine and METH. For hallucinogens or inhalants, however, withdrawal symptoms seem to have more limited importance. Treatment of the patient's withdrawal symptoms is based on understanding how withdrawal is related to aberrant brain chemistry and neuroadaptations in response to chronic repeated high doses of these drugs (Everitt & Robbins, 2005; Goldstein & Volkow, 2011; Kalivas & O'Brien, 2008; Koob & Volkow, 2010; Robison & Nestler, 2011).

Consistent with the concept of drug-induced neuroadaptations, repeated exposure to escalating dosages of most drugs alters brain physiology. Two clinically important consequences of these neuroadaptive effects include drug tolerance (the need to take higher and higher dosages of drugs to achieve the same effect) and withdrawal (a syndrome that occurs once drug use is decreased or discontinued). The neurobiological substrates responsible for tolerance and withdrawal symptoms overlap, since withdrawal symptoms occur only in patients who have developed tolerance.

Tolerance occurs because the brain cells that have receptors or transporters on them gradually become less responsive to the stimulation by the exogenous substances. For example, more heroin or morphine is needed to inhibit cyclic AMP and downstream second messenger systems within the VTA–NAc circuit, as well as to stimulate VTA neurons to release the same amount of DA in NAc terminals. Therefore, more opioid is needed to produce pleasurable subjective effects compared to that produced in previous drug-taking episodes. The mechanisms responsible for this reduced response are related to altered intracellular cyclic AMP–protein kinase A and cyclic AMP response element-binding protein (CREB) that lead to subsequent changes in gene expression of various proteins (Figure 1.2). Altered gene expression results in long-term structural changes not only in genes responsible for neuron integrity (brain-derived neurotrophic factor [BDNF], glia-derived neurotrophic factor [GDNF]) and sensitivity but also changes in amount of receptors and transporters. Indeed, chronic cocaine-induced inhibition of the DAT is associated with decreased DA D_2/D_3 receptors, whereas the DAT, norepinephrine transporter (NET), and serotonin transporter (SERT) are increased presumably to compensate for cocaine's effects (Table 1.2). These alterations, along with changes in other proteins and neurotransmitters associated with tolerance, may be considered an attempt by the brain to attain relative homeostasis in response to drug-induced disruption of normal neurotransmission. Tolerance to alcohol may be due to a more complex series of yet to be determined

TABLE 1.2. Neuroimaging Studies That Reveal Neurobiological Abnormalities Associated with Chronic Substance Use

	Cocaine	AMPH/METH	Nicotine	Opioids	Cannabis	Alcohol
Baseline DA	↓	↓	—	—	—	↓
DA release	↓	↓	—	↓	↓	↓
D_2/D_3	↓	↓	↓	↓	NC	↓
DAT	↑	↓	↓	↓	↓	↓
NET	↑	—	—	—	—	—
SERT	↑	↓	—	NC	—	NC
VMAT2	↓	↓	—	—	—	—
Glutamate	↑	↓	NC	↓	↓	↑
GABA	↓	—	↓	—	—	NC↓
GABA-alpha$_5$R	—	—	—	—	—	↓
Mu receptor	↑	—	—	NC	—	↑

Note. Data from Albrecht et al. (2013); Buchert et al. (2004); Chang and Haning (2006); Cosgrove et al. 2009, 2010; Ding et al. (2010); Ernst and Chang (2008); Fehr et al. (2008); Gorelick et al. (2005); Heinz et al. (1998, 2005); Hietala et al. (1994); Hou et al. (2011); Jacobsen et al. (2000); Leroy et al. (2012); Licata and Renshaw (2010); Lingford-Hughes et al. (2012); Malison et al. (1998); Martinez et al. (2005, 2007, 2009, 2012); Moszczynska et al. (2004); Narendran et al. (2012); Reneman et al. (2002); Rominger et al. (2012); Sevy et al. (2008); Shi et al. (2008); Urban et al. (2012); Volkow et al. (1990, 1993, 1997, 2001, 2002); Wang et al. (1997, 2012); Yang et al. (2009). DA, dopamine; DAT, dopamine transporter; NET, norepinephrine transporter; SERT, serotonin transporter; VMAT2, vasicular monoamine transporter; ↑, increase; ↓, decrease; NC, no change.

neurobiological changes at neuronal and molecular levels. Evidence suggests tolerance to alcohol involves GABA, opioid, DA and other neurochemical systems, including excitatory amino acid neurotransmitters such as glutamate and its multiplicity of receptor subtypes (Sulzer, 2011). Tolerance to cannabinoids/THC probably has a similar mechanism to that of opioids, since the cannabinoid CB1 receptor is also coupled to inhibitory G-proteins that decrease cyclic AMP levels and is associated with low D_2/D_3 receptor numbers. In contrast to cocaine, however, yet common to most other substances, chronic cannabinoid use is associated with decreased DAT levels (Table 1.2). Neurobiological mechanisms that relate tolerance following chronic hallucinogen administration such as lysergic acid diethylamide (LSD) are complex and presently unknown but probably involve changes in serotonergic 5-HT$_2$ receptors linked to the phosphoinositol phosphate (PIP) second messenger system.

TABLE 1.3. Medications Assessed and Indicated for SUDs

Addiction	Medication	Mechanism	Action
Cocaine	Disulfiram	Dopamine beta-hydroxylase	↓NE
	Doxazosin	Alpha$_1$ receptors	↓NE
	Lofexidine	Alpha$_2$ receptors	↓NE
	Modafinil	DAT, alpha receptors	↑DA, glutamate, orexin, ↓ GABA
	Topiramate	Na$^+$,Ca^{2+}, GABA	↓ glutamate
	Gabapentin	Na$^+$,Ca^{2+}, GABA	↓ glutamate
	N-Acetylcysteine	Cystine–glutamate exchanger	↑ glutamate
	Methylphenidate	DAT	↑ DA
Amphetamine/ methamphetamine/ MDMA	Bupropion	DAT, NET	↑DA, NE
	Naltrexone	Mu opioid receptors	↓ mu receptor activation
	Rivastigmine	Acetylcholinesterase	↑ acetylcholine
	Perindopril	ACE	↑ DA
	Modafinil	DAT, alpha receptors	↑ DA, glutamate, orexin, ↓ GABA
	Varenicline	Alpha$_4$ beta$_2$ receptors	↑ cholinergic effects
Nicotine	Nicotine[a]	Nicotinic cholinergic receptor	↑ DA
	Varenicline[a]	Alpha$_4$ beta$_2$ receptors	↑ cholinergic effects
	Bupropion[a]	DAT, NET	↑ DA, NE
	N-Acetylcysteine	Cystine–glutamate exchanger	↑ glutamate
	D-Cycloserine	NMDA	↑ glutamate function
Opioids (morphine, heroin)	Methadone[a]	Mu opioid receptors	↑ mu receptor activation
	Buprenorphine[a]	Mu, delta, kappa opioid receptors	↑↓ opioid receptor activation
	Naltrexone[a]	Mu opioid receptors	↓ mu receptor activation
Cannabis	Dronabinol	CB receptors	↑ CB receptor stimulation
Alcohol	Disulfiram[a]	Aldehyde dehydrogenase	↑ acetaldehyde
	Naltrexone[a]	Mu opioid receptors	↓ mu receptor activation
	Acamprosate[a]	NMDA receptors	glutamate/GABA modulation
	Topiramate	Na$^+$,Ca^{2+}, GABA	↓ glutamate

[a]FDA indication for SUD.

Opioids provide an outstanding example to illustrate how neuroadaptations associated with tolerance relate to withdrawal symptoms. Opioid withdrawal symptoms stem from changes in another important brain system, involving NE-ergic cell bodies located at the base of the brain—the locus coeruleus (LC; Figure 1.1). Neurons in the LC produce NE and widely distribute it to other parts of the brain, including the PFC, NAc, VTA, brainstem, and various subcortical regions, where it stimulates wakefulness, breathing, blood pressure, and general alertness, among other functions. When opioid molecules bind to mu receptors on neurons in the LC, they suppress NE release, resulting in drowsiness, slowed respiration, and low blood pressure—familiar depressant effects associated with opioid intoxication. Upon repeated exposure to opioids, however, LC neurons adapt to counter these depressant effects by increasing NE neurotransmission. Logically, when opioids are present, their suppressive impact is offset by increased NE, and the patient feels more or less normal, aside from the euphoric effects of the drug. When opioids are not present to suppress increased NE neurotransmission, withdrawal symptoms such as tremors, anxiety, muscle cramps, and diarrhea are triggered. Other brain areas within mesolimbocortical circuitry, in addition to the LC, also contribute to the production of opiate withdrawal symptoms. For example, patients may not be inclined to eat, since opioid-induced tolerance results in reduced VTA–NAc DA neurotransmission that is essential to the motivational and pleasurable characteristics associated with natural rewards such as food. At least in the case of opioids, and possibly other substances, neuroadaptive changes due to chronic drug consumption results in compensatory changes that in the absence of the drug also produce psychological (craving) withdrawal symptoms that contribute to continued drug use. Indeed, decreased baseline DA levels, compromised DA neurotransmission, and altered D_2/D_3 numbers within the NAc are associated with chronic substance use across many drug classes. As Table 1.3 illustrates, numerous medications have been tested as possible treatments for various SUDs. Many of the medications increase DA neurotransmission aimed at reversing abnormally low neurotransmitter levels.

PROGRESSION TO SUBSTANCE USE DISORDER

As we have seen, the initial pleasure from drugs is derived through the brain's natural reward system and promotes continued use. This may be viewed as the beginning stage in the development of an SUD. Limited or occasional use may then transition to active daily, even compulsive drug administration. Subsequently, repeated exposure to these drugs may result in a transition to compulsive and unremitting chronic drug taking characterized by intense craving, tolerance, and a withdrawal syndrome upon cessation of drug use. Often physical and/or psychological withdrawal occurs upon stopping drug intake and further contributes to relapse risk. In the case of opiates, use is essential to avert the unpleasant symptoms associated with withdrawal syndrome, whereas withdrawal symptoms from other drugs may be minimal and contribute little to relapse after discontinuation. Emerging evidence indicates that neuroplastic changes occur at each stage in the development of SUDs. These changes recruit and strengthen connections between specific brain areas, while reducing the influence of

other areas. As noted earlier, long-lasting neuroadaptive brain changes may underlie compulsive drug-seeking behavior and are related to adverse consequences (societal, occupational, and physical) that are the hallmarks of SUDs (Everitt, 2014). Importantly, research indicates that the development of an SUD is also greatly influenced by an interaction between an individual's genetic makeup and environmental factors (stress in particular). Several models have been generated to help explain how occasional drug use produces changes in the brain that may lead to compulsive use. In reality, this process probably involves many different factors that have yet to be recognized or explained.

THE "CHANGED SET POINT" MODEL

The "changed set point" model of substance use has several variants based on altered neurobiology of DA neurons in the VTA and NA neurons in the LC during early phases of withdrawal and abstinence. The basic premise is that drug use alters a biological or physiological setting or baseline. One variant, by Koob and LeMoal (2001), is based on the idea that neurons of the mesolimbic reward pathways are naturally "set" to release enough DA in the NAc to produce a normal level of pleasure. Koob and LeMoal suggest that drug consumption leads to a vicious cycle that involves changing this set point to the degree that the release of DA is reduced when normally pleasurable activities occur and drugs are not present. Similarly, a change in set point occurs in the LC, but in the opposite direction, such that NE release is increased during withdrawal in particular, as described earlier. This model accounts for both the positive (drug-liking) and negative aspects (drug withdrawal syndrome) associated with SUDs.

   A specific way that the DA neurons can become dysfunctional relates to an alteration in their baseline ("resting") levels of electrical activity and DA release (Grace, 2000). In this second variant of the changed set point model, baseline DA levels are regulated by two factors that influence the amount of basal DA release in the NAc: cortical excitatory (glutamate) neurons that drive the VTA DA neurons to release DA, and autoreceptors ("brakes") that shut down further release when DA concentrations become excessive. Activation of different receptor subtypes by various substances, such as mu opiate receptors by heroin, initially bypasses these brakes, and this leads to the release of high levels of DA in the NAc. However, with repeated chronic drug use, the brain responds to augmented DA by increasing the number and strength of the brakes on DA-ergic VTA neurons. Eventually, inhibitory autoreceptor control leads to decreased basal DA that is insufficient for normal neurotransmission. When this occurs, the individual will increase the total amount of drug consumed, such as heroin, in order to counteract reduced resting DA levels. When the individual stops taking a sufficient amount of drug to maintain a certain level of DA, deficient DA neurotransmission may result. This DA deficiency produces dysphoria (pain, agitation, malaise) coupled with other withdrawal symptoms that can lead to a cycle of chronic relapse to drug use.

   A third variation of the set point change theory emphasizes drug-induced sensitization. "Sensitization" in this context relates to altered sensitivity to drug-associated

environmental cues (incentive salience) that leads to drug "wanting" (pathological incentive motivation). This theory also states that craving for drugs may have greater influence in perpetuating use than reinforcement (drug "liking") or withdrawal (Berridge, Robinson, & Aldridge, 2009). In fact, incentive sensitization theory posits that the pleasurable aspects of drugs decrease as a full-blown SUD is established and drugs are "liked" less. The way the theory explains this is that only brain circuits that mediate the motivational aspect of incentive salience (drug "wanting") are sensitized, not circuits that mediate "liking" (drug-associated euphoria). The interactions between the mechanisms that mediate incentive salience and those responsible for learning or conditioning are essential to this theory. During periods of abstinence, when the drug is not available, memory of drug use and desire (wanting) or craving for the drug can be a major factor leading to drug-seeking behavior and subsequent relapse. Craving may represent increased activity of cortical (orbFC/PFC) excitatory (glutamate) projections, which can regulate DA in the NAc. NE-ergic neurons from the LC that project to and influence neurons in the VTA, NAc, and PFC may also play a role. Glutamate activity may increase, thereby increasing DA neurotransmission in the NAc and generating drug wanting or craving. In addition to glutamatergic input from the PFC (Figure 1.1), NE regulates VTA and NAc DA neurotransmission. Although drug withdrawal is not emphasized by this theory, NE projections from the LC also play an important role in withdrawal symptoms, particularly with opiates such as heroin. Consistent with the proposed circuitry, medications that show promise as pharmacotherapy for SUDs block or normalize glutamate and attenuate NE neurotransmission. Furthermore, as we discuss in the next section, studies also consistently show that individuals with SUDs have compromised PFC/orbFC activity responsible for normal impulse control, executive functioning, and memory processes. Accordingly, medications that increase PFC/orbFC function and memory also show promise as treatments.

The Cognitive Deficits Model

The cognitive deficits model proposes that individuals who develop SUDs have abnormalities within the PFC. The PFC is important for regulation of judgment, planning, impulse control, and other executive functions. To help us overcome some of our impulses for immediate gratification in favor of more important or ultimately more rewarding long-term goals, the PFC sends inhibitory signals to the mesolimbic reward system.

The cognitive deficits model proposes that PFC signaling to the mesolimbic reward system is compromised in individuals with substance use disorders, as a result, they have reduced ability to use judgment to restrain their impulses and are predisposed to compulsive drug-taking behaviors (Goldstein & Volkow, 2011). Consistent with this model, PFC deficits are common among individuals with a history of chronic drug use. Indeed, the longer individuals have been using, the greater the amount of damage and the worse their executive functioning. Furthermore, drug-associated deficits do not fully reverse upon stopping drug use. More specifically, chronic alcohol abusers have abnormally low levels of the inhibitory neurotransmitter GABA, the neurochemical in which glutamatergic neurons from the PFC regulate DA release within

the VTA and NAc (Table 1.2). Interestingly, individuals with heroin use disorder may have PFC damage that is independent of their opioid use, which they may have inherited genetically or that is caused by some other factor or event in their lives. Pre-existing PFC damage may predispose individuals because they lack impulse control; this, coupled with further drug-induced PFC damage from chronic repeated drug use, increases the severity of these problems (Goldstein & Volkow, 2011).

THE IMPORTANT ROLE OF STRESS

The notion that patients with SUDs are more vulnerable to stress than the general population is a clinical truism. Numerous preclinical studies have documented that physical stressors (e.g., foot-shock or restraint stress) and psychological stressors can cause animals to reinstate drug seeking and self-administration (Epstein, Preston, Stewart, & Shaham, 2006). Furthermore, stressors can trigger drug craving in humans with SUDs (Sinha, 2013). One potential explanation for these observations is that drugs including opiates and stimulants increase levels of cortisol, a hormone that plays a primary role in responses to stress. Cortisol in turn increases the sensitivity of the mesolimbic reward system (Koob & Zorrilla, 2010). By these mechanisms, in certain individuals stress may contribute both to the drug craving and the compulsion for continued drug use.

PHARMACOLOGICAL INTERVENTIONS AND TREATMENT IMPLICATIONS

Opioid Use Disorder

We next illustrate how long-term pharmacotherapies for opioid use disorder such as methadone, naltrexone, and buprenorphine can counteract or reverse the abnormalities underlying this disease (Table 1.3). These agents are particularly informative because they have agonist, antagonist, and partial agonist activity respectively. We do not review short-term treatments for relieving the withdrawal syndrome associated with abruptly stopping drug use, but we do refer readers elsewhere for detailed neurobiological explanations for various abstinence initiation approaches (Kosten & Haile, 2015; Kosten & O'Connor, 2003).

Methadone is a long-acting opioid medication with effects that last for days. Methadone can be associated with a use disorder, but because of its sustained stimulation of the mu receptors, it alleviates craving and compulsive drug seeking and use. In addition, methadone therapy tends to normalize many aspects of the hormonal disruptions linked to chronic opioid consumption (Kling et al., 2000; Schluger, Borg, Ho, & Kreek, 2001). For example, it moderates the exaggerated cortisol stress response (discussed earlier) that increases the danger of relapse in stressful situations.

Naltrexone is used to help patients avoid relapse after they have been detoxified from opioids. Its main therapeutic action is to occupy mu opioid receptors in the brain with a 100-fold higher affinity than agonists such as methadone or heroin, so that opioids taken exogenously cannot activate the receptor and in turn stimulate the

brain's reward system. An individual who is adequately dosed with naltrexone does not experience the euphoric effects of opioids and is therefore less motivated to use them. An interesting neurobiological effect is that naltrexone appears to increase the number of available mu opiate receptors, which may help to renormalize the imbalance between the receptors and G (guanine nucleotide-binding) protein coupling to cyclic AMP (Kosten, 1990). Naltrexone is also sometimes used to detoxify patients rapidly from opioids. In this situation, while naltrexone blocks mu receptor activation, another drug, clonidine, suppresses opioid-induced excessive NE output that contributes to withdrawal symptoms (Kosten, 1990). Clonidine prevents withdrawal symptoms by activating alpha$_2$-adrenergic autoreceptors responsible for preventing release of NE. These receptors are co-localized with mu opiate receptors on LC neurons, and both receptor types inhibit cyclic AMP synthesis through similar inhibitory G proteins (Mazei-Robison & Nestler, 2012). Interestingly, unique to naltrexone's pharmacology, very low doses have been shown to produce agonist-like effects such as analgesia (Younger & Mackey, 2009). Preclinical studies also show that low-dose naltrexone blocks opioid-induced NE overproduction during withdrawal (Van Bockstaele, Qian, Sterling, & Page, 2008). Consistent with this, low-dose naltrexone in combination with an opioid medication during detoxification reduces withdrawal symptoms and craving (Mannelli et al., 2009).

Buprenorphine's action on the mu opioid receptors elicits two different therapeutic responses within neural circuits affected by chronic opioid consumption that are dose-dependent like naltrexone. At low doses, buprenorphine has agonist effects, but at high doses, it behaves like naltrexone, blocking the receptors so strongly that it can precipitate withdrawal in individuals who take high doses of opiates (e.g., those maintained on more than 40 mg of methadone daily). Because of its unique mechanism of action, chronic treatment with buprenorphine also prevents changes in the sensitivity of the mu receptor that likely play a role in relapse (Virk, Arttamangkul, Birdsong, & Williams, 2009). Several clinical trials have shown that buprenorphine is as effective as methadone when used at sufficient doses (Stotts, Dodrill, & Kosten, 2009). Buprenorphine has a safety advantage over methadone, since high doses precipitate withdrawal rather than the suppression of consciousness and respiration seen in overdoses of methadone and heroin. Thus, buprenorphine has less overdose potential than methadone, since it blocks other opioids and even itself as the dosage increases. Finally, buprenorphine can be given three times per week, simplifying observed ingestion during the early weeks of treatment (Kosten & Fiellin, 2004).

Stimulant Use Disorder

Next we review potential medications for stimulant use disorders and how they may exert therapeutic actions on neural circuitry adversely affected by chronic drug use. Because there are presently no U.S. Food and Drug Administration (FDA)-approved medications for stimulant use disorder, development is of the utmost importance. Fortunately, recent studies assessing medications specifically targeting NE show promise. For example, prazosin and doxazosin are alpha$_1$-adrenergic receptor antagonists, and currently both medications are indicated for the treatment of hypertension. Prazosin also has shown some benefit in treating symptoms associated with posttraumatic

stress disorder (PTSD; Cukor, Spitalnick, Difede, Rizzo, & Rothbaum, 2009) likely because these individuals display increased NE release and receptor sensitivity linked to disruption in sleep and vivid nightmares. Several clinical trials have shown that prazosin significantly improves these symptoms (Raskind et al., 2007; Taylor, Freeman, & Cates, 2008). By extension, prazosin's ability to improve PTSD symptoms suggests that it may attenuate stress associated with relapse to drug use (Kosten, Rounsaville, & Kleber, 1988).

Evidence continues to indicate that alpha$_1$-adrenergic receptors are particularly crucial in mediating the behavioral effects produced by stimulants. NE in the PFC can activate alpha$_1$-adrenergic receptors that then enhance DA effects of stimulants in the NAc. This NE enhancement is blocked by prazosin directly infused into the PFC or administered peripherally (Blanc et al., 1994; Darracq, Blanc, Glowinski, & Tassin, 1998; Drouin et al., 2002). Prazosin also blocks drug-induced reinstatement of cocaine-seeking behavior in an animal model of relapse (Zhang & Kosten, 2005).

Prazosin's short half-life of 2–3 hours in humans may limit its use as a treatment for cocaine use disorder. In contrast, doxazosin has a much longer half-life (22 hours). Similar to the effects seen in animal studies with prazosin, doxazosin blocks the behavioral effects of cocaine in rodents (Haile, Hao, O'Malley, Newton, & Kosten, 2012). Moreover, Newton and colleagues (2012) showed that doxazosin (4 mg/day for 9 days) decreased cocaine's (20 and 40 mg) positive subjective effects, including "desire" for cocaine in non-treatment-seeking individuals with cocaine use disorder. Consistent with these results, a pilot outpatient clinical trial indicated that doxazosin (8 mg daily) significantly reduced cocaine use compared to placebo (Shorter, Lindsay, & Kosten, 2013). Prazosin and doxazosin have also shown potential in treating alcohol use disorder (Verplaetse, Rasmussen, Froehlich, & Czachowski, 2012). Although preliminary, these studies suggest that the alpha$_1$ receptor may be a viable therapeutic target for various SUDs. Large outpatient clinical trials are needed to extend and confirm these promising preliminary findings.

SUMMARY

SUDs are most appropriately understood as chronic, relapsing medical conditions. The neurobiology of these disorders is becoming well understood, but much remains unknown about the genomic mechanisms that predispose individuals to developing long-term drug use. The mesolimbic reward system involving many different inter-relating neurotransmitter systems is central to clinical consequences of chronic drug use, including tolerance and withdrawal. Other brain areas, neurochemicals, and peripheral hormones such as cortisol also are relevant to continued drug use. Pharmacological interventions are highly effective for opiates, and we have illustrated three different approaches using an agonist, an antagonist, or a partial agonist. We also discussed promising medications for AMPH-like and cocaine use disorders for which we have no pharmacotherapies. Given the complex biological, psychological, and social aspects of these diseases, they must be accompanied by appropriate psychosocial treatments. Clinician awareness of the neurobiological basis that underlies the action of these drugs, and information sharing with patients can provide insight

into patient behaviors and problems, and clarify the rationale for treatment methods and goals.

ACKNOWLEDGMENT

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