I. INTRODUCTION

Although a number of perspectives on drug addiction exist, this chapter focuses on drug addiction as a type of pathology of learning and memory systems, a viewpoint that has become increasingly common since the mid-1990s. Both natural rewards and drugs of abuse appear to use the same systems within the brain to influence and reinforce behavior, and it is well known that these systems are involved in learning and memory, particularly in connecting motivations and memories with behaviors. The next section of the chapter provides an introduction to the major issues of reward and addiction. The following three sections examine drug addiction in a manner based loosely on the stages of memory — namely, acquisition, consolidation, and storage/retrieval. Although we shall see that drug addiction does not mirror these stages perfectly, this model provides a starting point for understanding how learning and memory, reward, and addiction interact at a neurobiological level.
II. REWARD, ADDICTION, AND LEARNING

A. Learning Systems for Reward

The ability of animals to adapt behaviorally in response to external stimuli and to maintain adaptations over a long time is critical for survival. In particular, animals must be able to make adjustments in their nervous systems in response to environmental stimuli that permit adaptive behavioral responses to future encounters with the stimuli. Thus, after discovering food in a particular location, an animal would want to remember that location and seek it out when hungry and do the opposite for locations where danger may exist. A motivational brain circuit provides a neuroanatomical substrate whereby the internal state of the animal (hunger, thirst, etc.) interacts with memory-processing areas and decision-making areas to influence behavior. When an animal becomes hungry, both the desire for food and information regarding how and where food may be acquired are integrated to influence the behavior of the animal. Thus, the neural circuits involved provide mechanisms by which rewards reinforce behavior.

Learning to perform a behavior in order to receive a reward or avoid a negative consequence is termed instrumental or response learning. Such learning is critical to survival and for guiding future behaviors. At the same time an animal is engaged in response learning, it is also learning associations of various stimuli in its environment. This associative (Pavlovian) learning occurs continuously and is a basic mechanism for establishing adaptive responses to environmental stimuli. Therefore, in any response-learning paradigm, it is expected that the animal is engaging in associative learning, and, as we shall see, this associative learning is very much involved in drug addiction and relapse.

Figure 14-1 is a basic diagram of the structures and their connections involved in the motivation/reward/addiction circuit; the reader is referred elsewhere for a detailed description (McFarland and Kalivas, 2003). The ventral tegmental area (VTA) lies in the midbrain and provides the dopaminergic input to most of the forebrain, including the nucleus accumbens (NAc), the prefrontal cortex (PFC), and the basolateral amygdala (BLA). The BLA plays a critical role in modulating emotionally influenced memory consolidation (McGaugh 2002; LaLumiere and McGaugh, 2005). The PFC is involved in executive control and decision-making functions and is known to be involved in working memory (Seamans and Yang, 2004). The NAc, like the BLA and PFC, is important for modulating memories (LaLumiere et al., 2005) but is also critical for integrating information from these other structures and influencing motor/behavioral output. It does so via projections to the VTA and ventral pallidum (VP). The VP, in turn, projects to the medial dorsal thalamus (MD), thus completing the thalamic-cortico-accumbens-pallido loop. This circuitry provides a pathway by which structures involved in decision making, memory, and
motivation are integrated by the NAc and can then directly affect the behaviors of the animal. Addiction, of course, is characterized by detrimental changes in the interaction of decision making, memory, and motivation.

**B. How Drug Addiction and Memory Are Related**

In recent years, addiction has been conceptualized as a disorder of learning and memory (Heyne et al., 2000; Kelley, 2004a). To the extent that consumption of drugs of abuse depends on associative learning mechanisms, drug use mimics normal learning. However, drug addiction extends beyond mere reward processing. For someone addicted to a drug, the motivation for consuming the drug exceeds all other motivations, and the person faces a nearly irresistible urge to seek out and take the drug. Thus, the hallmark of drug addiction is the propensity to relapse, even after long periods of abstinence. People who have consumed a drug of abuse over an extended period and then cease consuming the drug remain for years at a significant risk of relapsing to drug use, perhaps even for the remainder of their lives. This risk is not limited to the effects of the withdrawal symptoms that accompany the early stages of drug abstinence. Rather, relapse appears to be a symptom of changes in the memory and motivation circuitry such that certain stimuli trigger a set of uncontrollable behaviors, with the goal of obtaining and consuming the drug.
Such findings suggest that addiction is a problem of learning and memory. That is, in addicted individuals, the storage of information regarding the reward of the drug has led to maladaptive neural changes that prevent people from retaining control over their behavior and cause them to seek out and consume the drug, even when they know that doing so is against their own best interests. It would also appear that the neural changes involved in drug addiction should map onto the same systems responsible for the processing and storage of natural rewards. And, as we shall see, the systems are similar, but some of the long-term changes induced by the different rewards are different.

C. Animal Models of Drug Addiction

One of the critical components in the investigation of behavioral neurobiology is the use of an appropriate animal model for the behavior under study. In addiction research, several models have been developed for investigating the long-term changes induced by repeated drug administration. One major model is drug-induced locomotor sensitization. In rodents, acute administration of many drugs, including psychostimulants and opiates, increases the animal's locomotor activity. Repeated administration of the drug induces neurobiological changes such that later acute administration of the drug produces even greater increases in locomotor activity. This increase in drug-induced locomotion following the final drug administration compared to the first drug administration is called sensitization. Another often-used model is conditioned place preference (CPP). In CPP, animals are administered the drug of abuse before being placed into one chamber of a two-chamber apparatus. They are then given a control injection before being placed into the other chamber. Through repeated pairings, the animals learn to associate one chamber with the drug of abuse. Animals are tested by being given free exploration of the entire apparatus, and animals that have learned the drug–chamber association spend more time in the drug-associated chamber. This model has been particularly useful for investigating the contextual learning that occurs during drug consumption.

The "gold standard" for addiction is self-administration. In this paradigm, animals are trained to perform a response (often, pressing a lever) in order to receive a small administration of the drug. This model is also often used for the study of natural rewards as well. The advantage of this model is that, as with humans who must perform certain actions to obtain and consume the drug of abuse, the animal must perform particular behaviors in order to receive the drug, unlike sensitization and CPP, where experimenters noncontingently administer the drug. Although many findings from noncontingent administration and self-administration have been in agreement, evidence suggests neu-
robiological differences between self-administration of a drug and experimenter administration of the drug (Mark et al., 1999; Stefanski et al., 1999). In addition, this model allows for examination of the most problematic aspect of drug addiction: relapse. After reaching a maintenance level of drug self-administration, animals undergo extinction training, in which further responses do not produce drug administration. After responding has been extinguished, the response behaviors can be “reinstated” by experimenter administration of the drug, by presentation of cues associated with the drug taking, or by administration of a stressor. Each of these reinstatement paradigms models a different aspect of relapse in humans and is addressed later in the chapter.

Clearly, CPP and self-administration are learning-based paradigms. The kinds of learning involved in these tasks (Pavlovian learning in CPP; response learning in self-administration) are also used in normal learning and memory investigations, including the study of aversive learning and memory. Locomotor sensitization, however, does not have any obvious learning component, for the administration of the drug is neither contingent on any behavior nor associated with particular cues. This model would appear to suggest that some neurobiological changes of addiction are due primarily to the pharmacological actions of the drug. However, the fact that sensitization can be affected by manipulating the test versus daily injection environment suggests a role for learning in sensitization (Badiani et al., 1995; Browman et al., 1998).

D. Acquisition, Consolidation, and Retrieval

As noted earlier, this chapter's structure is based on the three basic parts of learning and memory: the acquisition of information from the environment, the consolidation and storage of such information through neuroplasticity mechanisms, and the stimulus-induced retrieval of the information. These have been well studied in the field of learning and memory, and, in fact, the study of drugs of abuse has also examined these issues but through different models. However, it is important to note that studies with drugs of abuse are not easily parsed into these three categories. It is especially difficult to distinguish between acquisition and consolidation because memory consolidation refers to the plasticity (short- and long-term) that occurs immediately after the acquisition to store the acquired information. With drug addiction, each consumption of the drug is a learning event, and, thus, consolidation occurs after each event. However, it is the cumulative consolidation from chronic use of the drug that produces the pathological changes. Therefore, we consider acquisition as the initial reinforcing effects of rewards and drugs of abuse, and the acquisition section addresses those issues. The consolidation section examines the long(er)-term genetic, molecular, and biochemical changes induced by drug reward. In addition, the consolidation section addresses how chronic consumption of the
drug produces neural changes not found with acute consumption and how changes in the neurocircuitry store the information regarding the drug reward. The retrieval section explores how the changes induced by the chronic use of addictive drugs produce the irresistible compulsion to seek out and consume the drug.

III. ACQUISITION

A. Neurobiology of Reward and Reward Learning

How is “reward” represented neurobiologically? As noted, Figure 14-1 provides a basic diagram of the structures involved in the interaction of memories and motivational states and their ability to influence behavior. The NAc is considered to be a crucial point of integration of information by receiving emotional, mnemonic, and cognitive inputs and by projecting to motor output regions (Mogenson et al., 1980; Kelley, 2004b). The basolateral amygdala, which projects to the medial PFC (mPFC) and the NAc (Kelley et al., 1982; Robinson and Beart, 1988; Pitkanen, 2000), is involved in processing emotion and modulating memory consolidation for emotionally influenced learning (McGaugh, 2002, 2004a). The mPFC, while involved in many processes, appears to be critically involved in decision making and impulse control (Kelley, 2004a). The hippocampus mediates short-term declarative memories in humans and spatial and contextual memories in rats (Squire et al., 2004). Together, these three structures send glutamatergic projections to the NAc (Kelley et al., 1982; Christie et al., 1987).

The NAc is divided into two regions: the core, which surrounds the anterior commissure, and the shell, which surrounds the core primarily on the medial and ventral sides. These two subregions project to different areas, with the core projecting to the ventral and lateral substantia nigra (SN) and to the dorsal VP, whereas the shell projects to the VTA and the ventromedial VP (Zahm and Heimer, 1990; Heimer et al., 1991, 1995). Based on connectivity as well as functional studies, it has been suggested that the core is similar to the dorsal striatum and more directly connected to motor output systems and, thus, is involved in the instrumental behaviors, whereas the shell is more akin to the extended amygdala and involved in emotional processing (Kelley, 2004b). However, it is important to note that studies have found roles for both structures in instrumental learning and that experiments continue to try to dissociate the functions of these subregions (Di Chiara, 2002).

The NAc, along with the hippocampus, the mPFC, and the BLA, receives dopamine (DA) input from the VTA (Fallon and Loughlin, 1995). Most of the DA neurons that innervate the forebrain are located in the midbrain region, specifically in the VTA and the SN (Fallon and Loughlin, 1995). The SN
innervates the dorsal striatum (caudate-putamen), whereas the VTA provides input to the rest of the forebrain, including the ventral striatum (the NAc), the PFC, the amygdala, and the hippocampus. Early theories on drugs of abuse and natural rewards suggested that activation of DA neurons, particularly in the VTA, and release of DA in target structures signaled reward (Ungless, 2004). In fact, plenty of evidence suggests that rewarding or pleasurable stimuli increase DA neuron activation in the VTA and DA release in a variety of structures, especially the NAc (Di Chiara, 2002). However, in recent years it has become increasingly clear that the release of DA does not signal exclusively reward and, in contrast to early theories on DA, does not mediate the pleasurable or hedonic effects of the reward (Di Chiara, 2002). Unpleasant or aversive stimuli increase DA release in a variety of structures, including the NAc, demonstrating a role for DA beyond reward (Inglis and Moghaddam, 1999). But it should be noted that evidence indicates differential responses by DA to aversive versus rewarding stimuli (Di Chiara, 2002; Schultz, 2002). Thus, rather than mediating strictly reward, DA appears to be critical for signaling motivationally relevant stimuli, particularly those that are novel.

Considerable evidence suggests that DA neurons, particularly in the VTA, respond to rewarding stimuli in a phasic manner and, over time, respond to any previously neutral stimuli that are predictive of the reward. However, it appears that the DA responses depend on the predictability of the reward (for review, see Schultz, 2002). Predicted rewards do not cause DA release, whereas unpredicted rewards do; moreover, expected rewards that do not occur lead to a decrease in DA responses. Thus, DA may provide a prediction-error signal. This DA signaling then influences the NAc, presumably by modifying learning regarding the predicted reward and its predictive stimuli.

It is believed that the convergence of DA and glutamate at synapses in the NAc is critical for the integration of information. The glutamatergic signals provide sensory, emotional, and motor information, whereas the DA signals indicate the unpredicted rewards and/or salient events (Kelley, 2004a). Findings support critical roles for both glutamate and DA. Blockade of NMDA or D1 receptors in the NAc core impairs acquisition, but not consolidation, of lever pressing for sugar pellets (Hernandez et al., 2005), suggesting that activation of these neurotransmitters' receptors is important for the online processing of reward stimuli. Despite the lack of a role for those neurotransmitters in consolidation in that study, it is clear that both glutamate and DA are important in the NAc for long-term potentiation (Floresco et al., 2001). Moreover, post-training inhibition of protein kinase A, which is activated by DA receptors, or protein synthesis in the NAc impairs consolidation of instrumental memories (Baldwin et al., 2002; Hernandez et al., 2002), demonstrating that consolidation occurs in the NAc for instrumental learning for natural rewards. Through the coincident signaling of DA and glutamate, memories are formed regarding the circumstances under which the stimuli occur and the actions...
that must be performed in order to obtain the stimuli. However, it is important to note that predicted rewards do not increase DA responses, demonstrating that, under normal conditions, this neural system adapts to the rewards.

**B. Drugs of Abuse and Reinforcement**

Akin to natural reward, addictive drugs encode and reinforce drug-seeking behaviors by regulating DA and glutamate release in the NAc. The acute administration of all drugs of abuse, from alcohol to cocaine to heroin, increases the release of DA in the NAc that is critical for drugs to reinforce behavior. Thus, rhesus monkeys, squirrel monkeys, and rats will self-administer D1 agonists after learning to self-administer cocaine (Self and Stein, 1992; Weed et al., 1993; Grech et al., 1996; Self et al., 1996). Conversely, in rats trained to self-administer cocaine, infusions of the D1 receptor antagonist SCH 23390 into the NAc significantly increase the rate of lever-pressing for cocaine, suggesting that blockade of the D1 receptors in the NAc decreases the reinforcing properties of the cocaine (Maldonado et al., 1993).

DA receptors are G-protein-coupled receptors that often influence activity in the cAMP-PKA pathway by modulating activity of adenylyl cyclase. In particular, D1 receptors are coupled to Gs proteins, whereas the D2-class receptors are usually coupled to Gi/Go proteins. Intra-NAc infusions of a PKA inhibitor reduce baseline cocaine self-administration and shift the dose–response curve for administering cocaine to the left, suggesting that the inhibitor increases the rewarding effects of the cocaine administration (Self et al., 1998). Conversely, intra-NAc infusions of a PKA activator increase baseline cocaine self-administration and shift the dose–response curve to the right, suggesting that increased levels of PKA reduce the rewarding effects of cocaine. These findings suggest that tonic up-regulation of the cAMP-PKA pathway may underlie tolerance to cocaine, thereby explaining why PKA activators increase cocaine self-administration, whereas PKA inhibitors decrease cocaine self-administration.

In contrast with effects on cocaine self-administration, intra-NAc infusions of the PKA inhibitor have no effect on food-reinforced lever pressing, indicating a specific role for PKA in the NAc for drug self-administration (Self et al., 1998). The lack of influence by PKA regulation on biological reward probably results from the fact that, unlike cocaine, which increases DA release with every administration, repeated exposure to a biological reward reduces the release of DA to presentation of the primary reward, and DA is more effectively released by stimuli associated with reward rather than the reward itself. Thus, DA release comes under control of associative learning engendered by biological rewards, while DA remains under pharmacological control for
drugs of abuse. Therefore, inasmuch as DA is signaling motivational circuitry to learn associations that predict a rewarding stimulus, drugs of abuse continuously engender new associations, while natural rewards will do so only if the reward changes. Indeed, it is the continuous release of DA that may cause the learning associated with drugs of abuse to become pathological.

IV. CONSOLIDATION — LONG-TERM CHANGES FOLLOWING CHRONIC DRUG USE

A. Difficulty in Examining “Consolidation”

In traditional learning and memory paradigms, consolidation refers to the time following a learning event in which the memory for the event is susceptible to external influences on its subsequent retention. During this time, a variety of processes occur in the brain that store the memory in a more-or-less permanent form, but these processes require time following the event. For addiction, however, it is difficult to isolate a specific consolidation period because it is not the one-time use of the drug that leads to the addiction but the chronic consumption of the drug that produces the neural changes underlying addiction. As already discussed, the fact that each drug administration releases DA as if it were the first experience with a reward probably produces the pathological changes in learning that lead to addiction. Therefore, this section examines some of the long-term cellular changes produced by chronic use of drugs of abuse.

B. Changes in Gene and Protein Expression

Given the role of PKA signaling in mediating DA receptor stimulation and the lack of tolerance to drug-induced DA release, it is not surprising that chronic cocaine increases the activity of PKA and the PKA-regulated transcriptional regulator CREB (Terwilliger et al., 1991). Thus, CREB activation in the NAc regulates the motivation to take drugs (Carlezon et al., 1998; Barrot et al., 2002). For example, overexpression of CREB reduces an animal’s sensitivity to the rewarding aspects of the drug, whereas reduced activity of CREB increases the rewarding aspects of the drug (Nestler, 2004). One gene in the NAc regulated by CREB encodes the opioid peptide dynorphin (Nestler, 2004). Dynorphin activates κ opioid receptors, thereby reducing the rewarding effects of drugs of abuse (Shippenberg and Rea, 1997); in fact, κ opioid receptor antagonists reverse the effects of CREB activation (Carlezon et al., 1998). Activation of κ opioid receptors is believed to reduce the rewarding effects of
drugs of abuse by presynaptically inhibiting DA release from the DA neurons that innervate the NAc (Nestler, 2004).

Nestler and colleagues have examined another transcription factor whose induction profile lends itself to the regulation of the long-term changes induced by chronic drug use. Whereas the acute administration of drugs of abuse induces rapid but transient expression of a number of Fos and Jun transcriptional proteins (Graybiel et al., 1990; Nestler, 2004), one member of the Fos family, ΔFosB, accumulates slowly in the NAc over repeated administrations of the drug (Hope et al., 1994; Chen et al., 1995, 1997). Elevated ΔFosB persists for weeks after discontinuing drug administration. Studies with transgenic mice overexpressing ΔFosB indicate that the mice have enhanced sensitivity to cocaine and morphine and show greater motivation to get cocaine (Kelz et al., 1999; Colby et al., 2003; Nestler, 2004). These mice also show enhanced sensitivity to natural rewards (Werme et al., 2002; Nestler, 2004).

Changes in ΔFosB expression regulate other genes and their proteins, and it is assumed that it is through such changes in protein expression that chronic drug use produces its lasting effects. Several targets of ΔFosB, and its downstream target AP-1, have been identified. NAC1 is an AP-1-regulated protein that is up-regulated in the NAc following an acute injection of cocaine as well as following withdrawal from chronic administration of cocaine (Cha et al., 1997). Over-expression of NAC1 in the NAc impairs the development, but not expression, of sensitization (Mackler et al., 2000), whereas NAC1 antisense infusions into the NAc potentiate the motor stimulant effects of cocaine (Kalivas et al., 1999). Another ΔFosB-regulated protein is cyclin-dependent kinase, Cdk5 (Chen et al., 2000), which is involved in neural growth. Chronic cocaine administration increases Cdk5 protein expression (Bibb et al., 2001), and infusions of a Cdk5 inhibitor into the NAc prevents cocaine-induced dendritic growth (Norrholm et al., 2003). Other targets, such as the transcription factor nuclear factor-κB, have also been identified but are still being investigated (Nestler, 2004).

Although considerable work remains in the investigation of the downstream targets of ΔFosB and CREB and how they contribute to addiction, CREB and ΔFosB regulate many genes in opposite directions, consistent with behavioral findings from studies on each protein. It would appear that, during early drug use, increased CREB activity causes compensatory transcriptional events that resist changes induced by the drugs of abuse. However, such compensation increases the amount of the drug taken on subsequent occasions in order to produce the same rewarding effects, perhaps eventually overcoming CREB's effects. Conversely, rather than being involved in compensatory actions, ΔFosB actually mediates the effects of this long-term drug use on gene transcription and protein expression. Presumably, these changes underlie some of the long-term plasticity responsible for addiction (see Fig. 14-2).
C. Long-Term Changes Involved in Drug Addiction

Although the DA system has been a major focus for investigations into chronic drug-induced long-term changes, recent evidence suggests most changes in DA transmission associated with chronic drug use dissipate during abstinence. In contrast, the enduring pathology of addiction appears to be manifested by cellular dysfunctions in glutamatergic transmission in the NAc core. These changes include a decrease in glutamatergic tone, a potentiated increase in glutamate release following an acute cocaine injection, and changes in proteins that regulate postsynaptic glutamate signaling.

As noted, withdrawal from repeated cocaine administration reduces basal glutamate levels in the NAc core of rats (Baker et al., 2003). Basal levels of glutamate are maintained by a cystine–glutamate exchanger (xc-) and only minimally by synaptically released glutamate (Timmerman and Westerink,
1997; Baker et al., 2002). The xc- exchanges one intracellular glutamate for one extracellular cystine molecule. Although repeated cocaine administration does not change basal levels of extracellular cystine, cocaine-treated rats have decreased cystine-glutamate exchange (Baker et al., 2003). Reverse dialyzing cystine into the NAc or giving a systemic injection of N-acetylcysteine, which elevates brain cysteine levels, restores glutamate levels of cocaine-treated rats to normal control levels and prevents the increase in glutamate following an acute injection that mediates cocaine-induced reinstatement of lever pressing. Together, the findings regarding xc- strongly indicate that chronic cocaine administration changes the mPFC-NAc glutamatergic projections in a manner that underlies cocaine-induced relapse.

How do the decreased basal glutamate levels in the NAc affect the propensity to relapse? One mechanism appears to be through reduced tone of presynaptic metabotropic glutamate receptors (mGluR2/3) (Moran et al., 2005). Normally, mGluR2/3 receptors provide inhibitory feedback on presynaptic glutamate release and systemic administration of mGluR2/3 receptor agonists reduces reinstatement for cocaine or heroin seeking (Baptista et al., 2004; Bossert et al., 2004). xc- regulated glutamate in the NAc regulates glutamate release via providing tone on mGluR2/3 (Moran et al., 2005). Thus, reduced tone on mGluR2/3 on PFC afferents, along with changes to glutamatergic neurons themselves, leads to increased glutamate release when mPFC neurons fire. This, in turn, provides greater glutamatergic activation of NAc neurons and initiates drug-seeking behavior.

Evidence also suggests a critical role for Homer proteins in long-term changes induced by chronic cocaine. The Homer family regulates synaptic proteins and has three members (Homer1–3). Homer is known to play a role in learning-induced neural plasticity, and cocaine reduces levels of Homer proteins (Swanson et al., 2001). A role for reduced Homer in addiction is indicated by the fact that reducing Homer produces behavioral sensitization and facilitates cocaine self-administration (Ghasemzadeh et al., 2003; Szumlinski et al., 2004).

ΔFosB appears to have a role in changes in glutamate signaling. ΔFosB overexpression and cocaine induce expression of GluR2, and overexpression of GluR2 in the NAc increases the sensitivity of animals to acute injections of cocaine (Kelz et al., 1999; Peakman et al., 2003). GluR2 is a subunit of the AMPA receptor, and its presence reduces calcium conductance in AMPA receptors (Thomas et al., 2001). Interestingly, these findings would suggest that long-term drug use leads to less glutamate-induced activation of NAc neurons, in contrast to the previous findings. Future work will have to resolve this issue.

Together, these findings indicate that the glutamatergic system, particularly in the connections from the mPFC to the NAc, undergo long-term, if not permanent, changes following chronic use of a drug. It appears that changes
in mPFC neurons and the reduced basal glutamate levels in the NAc lead to increased glutamate release following stimulation of mPFC neurons that subsequently drive NAc-regulated behavior. That these changes persist beyond withdrawal from the drug indicates that they are long-lasting and, as the evidence suggests, underlie the propensity to relapse. Section V provides more evidence suggesting that these long-term changes in the glutamatergic system, rather than the dopaminergic system, are critical for reinstatement in animals.

D. Structural Changes

In addition to changes in protein expression and function, the storage of memories is also believed to be mediated by structural changes in neurons, particularly in neuronal connectivity (Moser et al., 1994). Addiction research has focused on changes in morphology of dendrites and dendritic spines, for these regions of the neuron receive the vast majority of synaptic inputs and appear to be important for experience-induced changes (Kasai et al., 2003). The dendritic spines are of special interest because, in the NAc, excitatory, glutamatergic inputs make contact at the head of the spine and dopaminergic axons synapse on the shaft of the spines. This "triad" of the NAc medium spiny neuron, the glutamatergic input, and the DA input is believed to be critically involved in the plasticity induced by drugs of addiction in the NAc.

Long-term use of cocaine, amphetamine, nicotine, or morphine has been shown to change the dendritic morphology in the NAc. Cocaine and amphetamine, whether self-administered or administered by the experimenter, increase spine density and dendritic branching in the NAc (Robinson and Kolb, 1997, 1999a; Robinson et al., 2001; Li et al., 2003; Norrholm et al., 2003; Crombag et al., 2005; Ferrario et al., 2005). These studies have also found increases in spine density and dendritic branching in the mPFC pyramidal neurons. As already noted, both regions appear to be critically involved in the long-term behavioral changes induced by chronic drug use. Nicotine appears to have morphological effects similar to those of cocaine and amphetamine (Brown and Kolb, 2001), but morphine decreases dendritic branching and spine density in the NAc and the mPFC (Robinson and Kolb, 1999b; Robinson et al., 2002). Researchers have also found a reduction in DA neuron size in the VTA following chronic morphine treatment and withdrawal (Sklair-Tavron et al., 1996; Spiga et al., 2003).

These morphological adaptations persist for over three months (Kolb et al., 2003). Although there is some evidence for differences between self-administered and experimenter-administered drugs on dendritic morphology (Robinson et al., 2002), most studies find similar effects, suggesting that any
learning associated with self-administration is unnecessary/unrelated to structural changes. That is, these changes are due to the unconditional effects of the drugs themselves and may be unrelated to learning during drug taking.

V. RETRIEVAL

A. Different Kinds of Retrieval/Reinstatement for Drugs of Addiction

The most insidious problem and, in fact, the hallmark of addiction is the propensity to relapse. For example, approximately 90-95% of cocaine addicts relapse within six months of undergoing treatment for their addiction. Relapse can be evoked in three distinct ways that can be experimentally modeled. First, addicts may relapse if they consume a small amount of the drug. Second, addicts may relapse if they encounter stimuli that they associate with their drug taking. And third, addicts may relapse following a particularly stressful event. Each of these types of relapse has been examined in rats with the self-administration/reinstatement model of addiction. When the animal’s lever pressing has been extinguished, the animal undergoes a reinstatement session in which it receives a priming injection of the drug, a cue that was previously paired with the drug training is presented, or a foot shock is administered to the rat. However, lever presses during reinstatement do not themselves produce any drug infusions. These three types of reinstatement (drug priming-induced, cue-induced, and stress-induced) are used as models of the three categories of relapse in humans. From a learning-and-memory perspective, these three reinstatement methods are types of retrieval of the original memory, which lead to the inability of the rat to resist seeking out the drug of abuse.

B. Circuitry Underlying Reinstatement of Drug Seeking

Studies have examined the circuitry involved in reinstatement and identified the critical neural pathways involved. Using GABA receptor agonists to inactivate structures, McFarland and Kalivas (2001) found that the dorsal PFC, the VTA, the NAc core, and the VP (but not the ventral PFC, the NA shell, the SN, the central nucleus of the amygdala, the BLA, or the mediodorsal thalamus) are necessary for cocaine-induced reinstatement. Moreover, of the four structures involved in cocaine-induced reinstatement, only the VP is necessary for reinstatement of food-seeking behavior, suggesting that the dorsal PFC, the VTA, and the NAc core are specific to reinstatement of drug seeking but not to reinstatement of natural reward seeking. Because cocaine increases DA
release, cocaine-induced reinstatement must depend on activation of DA receptors within the brain. However, despite the critical role of DA receptors in the NAc core during acquisition of lever pressing for cocaine, these receptors do not appear to be important for reinstatement, because blockade of DA receptors in the core or the VP does not prevent cocaine-induced reinstatement (McFarland and Kalivas, 2001). However, blockade of DA receptors in the dorsal PFC prevents such reinstatement, suggesting that changes in the PFC and the PFC projection to the core are the critical ones involved in relapse. Supporting this, microdialysis experiments demonstrate that cocaine-induced reinstatement is associated with a rise in glutamate levels in the NAc but not with a rise in DA levels (McFarland et al., 2003).

Conditioned cue-induced reinstatement appears to depend on the same structures involved in cocaine-induced reinstatement, including the NAc core (but not the shell) (Fuchs et al., 2004) and the dorsal PFC (McLaughlin and See, 2003). However, in addition, the BLA is selectively involved in conditioned cue-induced reinstatement (Kantak et al., 2002; McLaughlin and See, 2003).

Foot-shock-induced reinstatement appears to require activity in circuitry similar to that with cocaine-induced reinstatement requires (i.e. dorsal PFC, NAc core, and VP) but, in addition, also depends on the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the NAc shell (McFarland et al., 2004). It appears that foot-shock stress activates limbic circuitry. The central nucleus of the amygdala, which is part of this circuitry, projects to the VTA, and this projection is believed to mediate activation of the DA neurons projecting to the PFC and initiating reinstatement.

### C. Connection to Other Systems

One of the most interesting neurobiological problems in the field of drug addiction is how a particular set of behaviors and not others is triggered during relapse. In this chapter, we have presented findings regarding how drugs of abuse are rewarding, how they induce long-term changes, and how, through these long-term changes, reinstatement or relapse to drug seeking and drug taking can be triggered. Based on such findings, it might seem that the basic structure of addiction has been identified — i.e., dysfunction in the prefrontal cortex–nucleus accumbens system allows particular triggers to reinstate drug seeking. However, while the primary infrastructure has been identified, these findings do not address the major issue of how this infrastructure selects drug-related behaviors over more adaptive behaviors. The systems involved in drug addiction did not evolve to subserve the consumption of drugs of abuse and serve to integrate motivational states with memories to control behaviors (see earlier discussion). Although it is clear that dysfunction in decision making
and impulse control is important, we do not know how the desire to consume drugs overrides other desires and motivations in drug addicts. It seems logical to assume that the competition between other desires and the desire for drugs must occur in the mPFC. Based on that assumption, there must then be subsets or networks of neurons within the mPFC that maintain "memories" of the repeated drug use, suggesting that there must also be networks of neurons maintaining memories for other motivations.

How does the desire to seek drugs trigger specific drug-seeking behaviors? Although we often refer to the accumbens-pallidal output as simply "behavioral" or "motor," the effects of drug primes, cue primes, or stress do not trigger general changes in behavior. Instead, they trigger very specific behaviors to seek out and consume drugs of abuse. In the self-administration model, animals given a drug prime do not engage in random behaviors or even random lever pressing. Rather, they selectively press the lever that had been paired with the drug during initial training and ignore the lever that had been paired with nothing. Therefore, the output of the accumbens and VP is not just to increase behaviors but to activate a specific set of behaviors. This implies that, just as in the mPFC, there are specific neuronal networks that are selectively changed by repeated drug use and selectively triggered during reinstatement/relapse. Such neuronal networks could then connect with downstream structures and trigger specific drug-seeking behaviors. These networks must be "bound" to each other, because drug effects on the mPFC networks during reinstatement lead to activation of drug-related neuronal networks in the NAc and the VP. However, due to the difficulty in examining such issues in both learning and memory and addiction, research has not provided any answers as to how this information remains bound and how activation in the mPFC leads to a specific set of behaviors.

D. Reconsolidation

In considering the development of treatments for addiction, the largest problem is the enduring nature of addiction. Relapse remains a significant risk for most individuals for a long time, if not permanently, indicating that the changes induced by the chronic use of drugs of abuse are virtually unalterable. A recently revived idea in the field of learning and memory is that, upon retrieval, memories undergo a kind of reconsolidation in which the retrieval of the memory induces lability in the memory trace again, rendering it susceptible to external influences again (Nader et al., 2000; Debiec et al., 2002). Such findings have produced great interest on the part of researchers because they raise the possibility of eliminating old, troublesome memories, and addiction memories would appear to be excellent candidates for such elimination (Centonze et al., 2005). In fact, recent work has investigated the susceptibility
of “addiction” memories to reconsolidation. Lee et al. (2005) trained rats to self-administer cocaine, infusions of which were paired with a light cue. After the training was completed, rats underwent a single cue exposure session, prior to which they received intra-BLA infusions of Zif268 antisense oligonucleotides. Subsequent testing demonstrated that rats receiving this treatment had impaired memory for the cue–drug association. Infusions of the antisense oligonucleotides alone (with no cue exposure) had no effect, indicating that cue exposure reactivated the memory and rendered it labile again. Using a CPP model, Miller and Marshall (2005) found that pre- or posttest infusions of a MEK inhibitor into the NAc core impaired memory when tested on a subsequent retrieval test. Infusions of the inhibitor alone (with no retrieval test) had no effect on subsequent retrieval tests. Together, these findings indicate the ability to interfere with drug memories through manipulations after retrieval of the memory.

Such results would appear to be very exciting, but at the moment they should be put into the context of a larger debate within the learning and memory field on reconsolidation (McGaugh, 2004b). Evidence suggests that reconsolidation is not merely a recapitulation of consolidation (Debiec and Ledoux, 2004; von Hertzen and Giese, 2005). The processes involved in consolidation and reconsolidation are qualitatively different, and thus the term reconsolidation is actually inappropriate. Moreover, a number of groups have found significant caveats to the reconsolidation hypothesis, including the following problems. (1) Reconsolidation does not occur for some learning tasks (Cammarota et al., 2004); (2) reconsolidation effects are (sometimes) temporary (Judge and Quartermain, 1982; Lattal and Abel, 2004); and (3) the time span between original learning and the retrieval test can affect whether reconsolidation occurs (Milekic and Alberini, 2002). Because these problems have yet to be solved in traditional learning and memory experiments and because addiction–reconsolidation experiments have not yet systematically addressed these issues, it is difficult to know whether such investigations hold promise for addiction treatment. In particular, if older memories are less susceptible to reconsolidation (Milekic and Alberini, 2002), addiction may not be amenable to such treatment, for there is typically a significant interval between the beginning of addiction and the seeking of treatment.

VI. CONCLUSIONS

A. Addiction as Disorder of Memory

This chapter has focused on addiction in terms of its relationship with learning and memory. We have presented some of the important findings regarding drug reward and addiction as part of the stages of memory. If addiction is a
kind of pathological memory, then it is reasonable to ask where, within these stages, this pathology exists. Certainly, rewarding stimuli and the learning that accompanies such stimuli are not pathological and do not normally induce memories or behaviors considered to be pathological. In addition, many of the initial effects of drugs of abuse are quite similar to those of natural rewards. Therefore, it seems unlikely that the pathology exists from the first consumption of the drug. It is also unlikely that the problem of addiction lies in retrieval processes, for evidence indicates significant changes in neural processing even in the absence of retrieval.

Instead, the genesis of addiction can be conceptualized as pathological memory consolidation. The evidence presented in this chapter suggests that it is not the consolidation of the first experience with a drug that is pathological but, rather, the continued use over a period of time. Although the neurobiological responses to natural rewards and drugs of abuse are similar, these responses diverge when the rewards/drugs are repeatedly administered or encountered. Clearly, the brain has evolved to have adaptive processes that prevent a natural reward from taking exclusive control of the motivational processes. However, the mechanisms for preventing that are circumvented by the consumption of drugs that induce repeated activation of mesocorticolimbic DA release beyond what would occur naturally. Thus, a neural system, highly sensitive to motivational stimuli in order to promote survival, is not prepared for the effects of repeated pharmacological activation. Figure 14-2 presents schematic diagrams illustrating the processes underlying normal reward learning and drug–reward learning.

Through repeated drug use, the memories for these motivational stimuli, the behavioral patterns used to satisfy the desires, and the previously neutral stimuli that become associated with the drugs become superconsolidated. When the associated stimuli, such as the sight of the drug or the context in which the drug was consumed, trigger these superconsolidated memories, the desire to take the drug become all-encompassing, and the individual engages in the behaviors that he/she knows will lead to consumption of the drug, regardless of the person’s best interest. This idea of a superconsolidated memory has recently become part of the understanding for the development of post-traumatic stress disorder (PTSD) (Schelling, 2002; Schelling et al., 2003, 2004). PTSD develops following a traumatic incident or series of traumatic incidents that appear to be “seared” into their memories. Patients with PTSD usually suffer intrusive memories, and these memories can be triggered by particular stimuli, especially those that remind them of stimuli present during the initial traumatic incidents. Unfortunately, due to the lack of a good animal model for PTSD, it is difficult to assess the neurobiological similarities between PTSD and drug addiction. However, it is interesting that there is a high degree of comorbidity between addiction and PTSD, suggesting overlapping neurobiological vulnerabilities.
B. Summary

Learning about natural rewards and learning about drugs of abuse utilize initially the same pathways in the brain. However, repeated use of drugs produces changes in the brain not normally found with repeated natural rewards, which is most likely due to the ability of drugs to go directly to the brain and have their pharmacological effects. In doing so, the drugs alter the functioning of a number of structures in the brain, of which the NAc and the PFC are particularly prominent due to their apparent roles in addiction. These alterations include changes in gene and protein expression, morphological changes in the neurons, and changes in glutamatergic signaling. In many ways, the process of drug addiction mimics the stages of memory, from acquisition to consolidation and finally retrieval. But in drug addiction, the changes induced by the drugs are detrimental to people in terms of their ability to resist future consumption of the drug. In particular, the pathology of drug addiction appears to arise from the repeated use of a drug that induces a kind of superconsolidation of the memories for the drug. Whether such superconsolidation can be reversed is unknown, but treatments based on counteracting some of the long-term dysfunctional changes are being developed (Kalivas and Volkow, 2005). Nevertheless, because addiction is conceived as pathological learning, the fields of learning and memory and addiction will become more intertwined and will continue to inform one another on the basic functioning of motivational learning.

REFERENCES


