

# Neural Mechanisms of Addiction: The Role of Reward-Related Learning and Memory

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## Key Terms

associative memory, dopamine, plasticity, drug, reward,  
dependence

## Abstract

Addiction is a state of compulsive drug use; despite treatment and other attempts to control drug taking, addiction tends to persist. Clinical and laboratory observations have converged on the hypothesis that addiction represents the pathological usurpation of neural processes that normally serve reward-related learning. The major substrates of persistent compulsive drug use are hypothesized to be molecular and cellular mechanisms that underlie long-term associative memories in several forebrain circuits (involving the ventral and dorsal striatum and prefrontal cortex) that receive input from midbrain dopamine neurons. Here we review progress in identifying candidate mechanisms of addiction.

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## INTRODUCTION

A small number of drugs and chemical agents can come to control human behavior by producing a state called addiction. The core manifestation of this state is compulsive drug use despite serious negative consequences such as medical illness, failures in significant life roles, or the need to engage in criminal activity to obtain drugs. For addicted individuals drugs become valued over all other goals; as a result, the lives of those who are addicted become profoundly narrowed to a focus on obtaining and using drugs. Whereas some regular users cease drug taking on their own, for many, addiction proves a recalcitrant, chronic problem. Despite multiple episodes of treatment, and despite risk of significant life problems, relapses to active drug use are the rule. More effective treatment interventions are much in

need, underscoring the importance of understanding the pathophysiological processes that underlie addiction and its persistence.

A major challenge in studying addiction, or any complex behavioral disorder, is the limitations of animal models. Animal models have proved particularly useful in understanding relevant normal neural processes, such as reward-related learning. Because we know the proximate cause of addiction, the drugs themselves, it has been possible to model some aspects of addiction in animals (Deroche-Gamonet et al. 2004, Vanderschuren & Everitt 2004) more effectively than it has been possible to model most psychiatric disorders. Nonetheless, it is a great challenge to develop laboratory models that reflect the compulsive drug taking behaviors of addicted, free-living human beings. It therefore remains essential to relate findings in animals to clinical observations and to human biology. Early efforts with human brain imaging represent a promising step in this process.

A great deal is known about the initial interactions of addictive drugs with the nervous system. For example, all the proteins that serve as initial molecular targets for addictive drugs have been cloned and characterized (**Table 1**). It has been far more challenging to identify behaviorally relevant mechanisms of drug action that occur downstream of drug binding and the initial effects of this binding on signaling pathways. Much research has focused on how addictive drugs influence neural communication in the short term and how the nervous system adapts to repeated drug exposure in the long term. A substantial body of research on animals and humans suggests that several types of adaptation occur, including homeostatic adaptations (e.g., negative feedback to strong drug stimulation) and synapse specific “Hebbian” adaptations of the type thought to underlie specific long-term associative memory. Here we review the evidence, from multiple levels of analysis, for a central contribution to addiction of the mechanisms underlying long-term associative memory.

**Table 1** Receptors for addictive drugs

Drug	Neurotransmitter mimicked	Drug receptor
Opiates	Endorphins	$\mu$ and $\delta$ opioid (agonist)
Psychostimulants (cocaine, amphetamine)	Dopamine	Dopamine transporter (antagonist-cocaine; reverse transport-amphetamine)
Nicotine	Acetylcholine	$\alpha_2 \beta_4$ nAChR (agonist)
Alcohol	GABA Glutamate	GABA <sub>A</sub> (agonist) NMDA (antagonist)
Marijuana	Anandamide	CB <sub>1</sub> (agonist)

### LONG-TERM CONSEQUENCES OF DRUG-TAKING: TOLERANCE, DEPENDENCE, AND ADDICTION

A variety of natural stimuli with positive survival value, ranging from palatable foods to opportunities for mating, prove rewarding and reinforcing in humans and in animals (see Elements of Reward). A small number of pharmacological agents, notably the psychostimulants (cocaine and amphetamine), the opiates, nicotine, ethyl alcohol, and the cannabinoids, also exhibit potent rewarding properties (Table 1). Humans and animals rapidly learn cues and contexts that predict the availability of these “addictive drugs”; once learned, these cues motivate drug seeking in humans and animal models. In the conditioned place preference model, rats or mice will spend more time in a location in which they have passively received drugs than in an equally accessible location in which they received a saline injection (Domjan 2003). As with natural rewards, drugs are reinforcing; i.e., behaviors aimed at obtaining and taking them tend to increase in frequency with experience. With repeated use both humans and animals will seek and self-administer these drugs in preference to pursuing other goals—even other rewarding goals such as food and sex. Behaviors aimed at obtaining and using drugs exhibit strong motivational pressure; they tend to resist interruption and to proceed to completion even in the face of substantial obstacles.

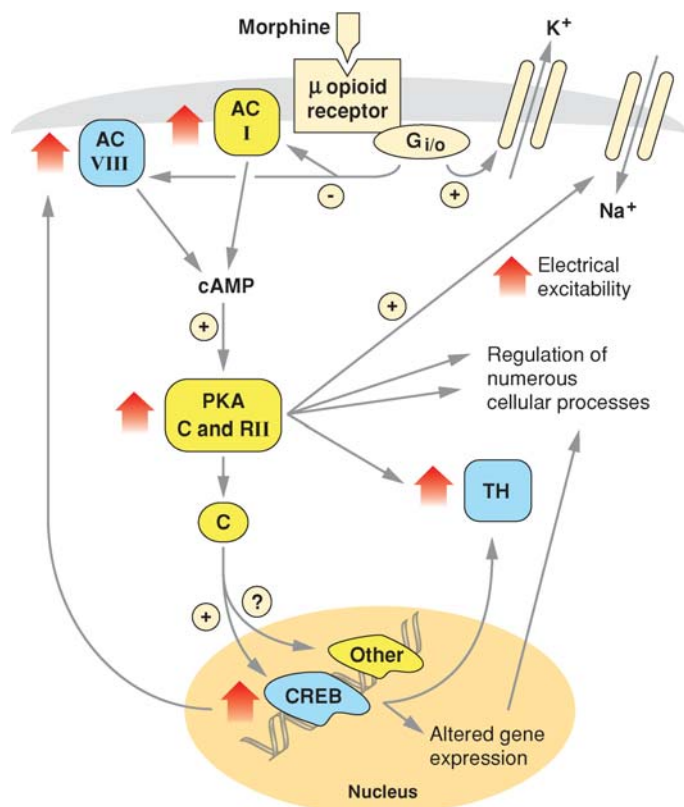
With repeated drug administration, homeostatic adaptations may occur within cells and circuits stimulated by that drug, resulting in tolerance and dependence (Nestler & Aghajanian 1997). The likelihood of tolerance and dependence and their precise manifestations differ markedly among addictive drugs, depending on the expression patterns of each drug’s receptors and the signaling mechanisms engaged by drug stimulation in relevant cells. Cell and

### ELEMENTS OF REWARD

Rewards are experienced as “making things better” and are thus liked, desired (wanted), and pursued (Berridge & Robinson 2003). Thus consumption of rewards (e.g., palatable food, mating, cocaine) produces hedonic consequences (pleasure) that initiate learning processes that consolidate (a) liking the rewarding goal, (b) learning cues that predict its availability and actions that permit its consumption, and (c) assigning value and motivational status to the reward so that the organism can select among numerous behavioral options and determine what level of resources to put toward obtaining a specific goal.

Motivational states such as hunger, sexual arousal, and perhaps early symptoms of drug withdrawal increase the incentive salience of reward-related cues and the reward itself (Kelley & Berridge 2002). The greater the hunger, the greater the likelihood that behavioral sequences aimed at obtaining food will be initiated and carried to conclusion despite distractions and obstacles that may arise.

Positive reinforcement involves an increase over time in the frequency of behaviors that lead to a reward.



**Figure 1**

Opiate actions in the locus coeruleus (LC). Opiates acutely inhibit LC neurons by increasing the conductance of an inwardly rectifying K<sup>+</sup> channel via coupling of μ opiate receptors with G<sub>i/o</sub>. Additional acute inhibitory effects may reflect inhibition of an inward Na<sup>+</sup> current also via G<sub>i/o</sub> caused by inhibition of adenylyl cyclase (AC), reduced levels of cyclic AMP (cAMP), reduced PKA (protein kinase A) activity, and reduced phosphorylation of the responsible channel or pump. Inhibition of the cAMP pathway also decreases phosphorylation of other proteins, thus affecting many other processes in the neuron. For example, reduced PKA activity contributes to reduced phosphorylation of CREB (cAMP response element binding protein), which, in turn, may initiate longer-term changes in LC function. Chronic morphine produces homeostatic adaptations in the LC (*upward bold arrows*) resulting in a marked change in physiology. Chronic morphine increases levels of ACI and ACVIII, PKA catalytic (C) and regulatory type II (RII) subunits, and several phosphoproteins, including CREB and tyrosine hydroxylase (TH), the rate-limiting enzyme in norepinephrine biosynthesis. The intrinsic excitability of LC neurons is increased via enhanced activity of the cAMP pathway and the Na<sup>+</sup>-dependent inward current. These adaptations have been shown to contribute to dependence and withdrawal exhibited by the LC.

circuit specificity can be illustrated by opiate tolerance (the requirement for increased drug dosages to maintain a stable effect): Heroin users develop tolerance to the desired pleasurable effects of the drug, thus driving dosage increases, but do not develop tolerance to the characteristic opiate-induced papillary constriction.

Dependence signifies drug-induced alterations in the physiology of cells and circuits such that, when unmasked by drug cessation, withdrawal symptoms result. As with tolerance, the withdrawal symptoms produced by a drug, if any, depend on the synapses and circuits in which the drug acts and produces adaptations (**Figure 1**) (see Upregulation of the cAMP Pathway: A Biochemical Model of Opiate Dependence). These vary substantially across the different classes of addictive drugs. For example, withdrawal from opiates or ethanol can produce serious physical symptoms including flu-like symptoms and painful abdominal cramps (opiates) or hypertension, tremor, and seizures (alcohol). In contrast, physical withdrawal symptoms do not occur following cessation of cocaine or amphetamine use. Emotional withdrawal symptoms (e.g., anhedonia and dysphoria) and motivational withdrawal symptoms (e.g., drug craving) may occur upon cessation of any of the addictive drugs, but the severity varies markedly among individual users.

Dependence and withdrawal were once considered cardinal symptoms of addiction; it is now recognized that they are neither necessary nor sufficient for a person to be addicted, i.e., to exhibit a strong compulsion to take drugs (O'Brien et al. 1998). Dependence and withdrawal without compulsion are commonly observed in patients who require morphine for cancer pain (Jage 2005) or benzodiazepines for anxiety disorders (O'Brien 2005). Conversely, compulsive use and multiple relapses can be observed in cocaine- or amphetamine-addicted users who have not experienced significant withdrawal symptoms. Whereas avoidance of withdrawal likely contributes to ongoing drug use

(especially with opiates, alcohol, and tobacco), it does not explain, the most frustrating characteristic, from a clinical point of view, of addiction: the persistence of relapse risk long after a person has stopped taking drugs. Once addicted, individuals remain at high risk of relapse even years after they have ceased drug use. As a result, no treatment episode can be considered curative, and for the most seriously addicted individuals, relapses often occur long after any withdrawal symptoms have subsided (McLellan et al. 2000).

A large number of clinical and laboratory observations have converged on the hypothesis that the primary neural substrates of persistent compulsive drug use are not homeostatic adaptations leading to dependence and withdrawal, but rather long-term associative memory processes occurring in several neural circuits that receive input from midbrain dopamine neurons (Wikler & Pescor 1967, Tiffany 1990, O'Brien et al. 1998, Berke & Hyman 2000, Robbins & Everitt 2002, Everitt & Robbins 2005, Hyman 2005). The importance of associative learning mechanisms for human addiction was initially gleaned from the observation that much drug taking, including late relapses, follows exposure to cues previously associated with drug use (Wikler & Pescor 1967, Tiffany 1990, O'Brien et al. 1998). Such drug-associated cues can include external sensory stimuli (e.g., persons, drug paraphernalia, places where drugs were used) and interoceptive stimuli (e.g., bodily feelings—including withdrawal symptoms). In animal models reinstatement of drug self-administration is more strongly motivated by re-exposure to even small doses of the drug, and therefore positive reminders of drug use, than by withdrawal (Stewart & Wise 1992). In humans (O'Brien et al. 1998) and animals (Semenova & Markou 2003), conditioned responses to drug-associated cues, such as arousal, drug craving (humans), or drug seeking (rats), are measurable after signs and symptoms of withdrawal have subsided. In the laboratory, drug-associated cues have been shown to elicit drug urges and sympathetic

## UPREGULATION OF THE cAMP PATHWAY: A BIOCHEMICAL MODEL OF OPIATE DEPENDENCE

Sharma et al. (1975) demonstrated that exposure of cultured neuroblastoma x glioma cells to morphine initially decreased cellular levels of cyclic AMP (cAMP). With continued exposure, however, cAMP levels recovered to normal and, upon addition of an opioid receptor antagonist, cAMP levels increased far above baseline values. These observations were interpreted as tolerance- and dependence-like adaptations at a single cell level and led the authors to hypothesize that upregulation of the cAMP pathway might contribute to opiate tolerance and dependence.

This hypothesis was first tested in the brain a decade later, when a similar upregulation of the cAMP pathway was demonstrated in neurons of the locus coeruleus (LC), the brain's major noradrenergic nucleus (Nestler & Aghajanian 1997). These neurons had previously been shown to develop opiate tolerance and dependence at the cellular level: Opiates acutely decrease the firing rate of LC neurons, the firing rate recovers toward normal with continued opiate exposure, and it increases several fold above normal levels upon the administration of an opioid receptor antagonist. In addition, cAMP had been shown to partly mediate the acute electrophysiological actions of opiates on these neurons. At the biochemical level, it was found that opiates acutely inhibit adenylyl cyclase and cAMP-dependent protein phosphorylation in the LC, this inhibition recovers with chronic opiate administration (tolerance), and these processes increase far above normal in response to an opioid receptor antagonist (dependence and withdrawal). Changes in the cAMP pathway can account for the functional changes observed in LC neurons during the development of tolerance and dependence and during withdrawal (for mechanisms see **Figure 1**).

nervous system activation in addicted human subjects (Childress et al. 1999, Kilts et al. 2001, Bonson et al. 2002). Long-term memories, unlike most homeostatic adaptations, can last for many years or even a lifetime. The importance of associative memory does not exclude a role for long-lived homeostatic adaptations in addiction and its persistence; for example, cocaine has been shown to induce chromatin remodeling (Kumar et al. 2005), a

mechanism that could result in persistent alterations in the expression of multiple genes. Indeed, such an adaptation could play a role in dependence and withdrawal, but also, hypothetically, in the consolidation of drug-related associative memories.

In addition to drug-associated cues, stress may cause reinstatement of drug taking in both animal models and humans (Shaham et al. 2000, Marinelli & Piazza 2002). The mechanism of stress-induced relapse appears to involve activation of brain reward pathways and may thus resemble drug re-exposure rather than withdrawal. The mechanisms by which stress stimulates reward circuits include the release of glucocorticoid stress hormones and several neurotransmitters including corticotropin release hormone and endogenous opioids. Activation of prefrontal cortical circuits may also play a role (Marinelli & Piazza 2002, Lu et al. 2004, Self 2004, Kalivas et al. 2005).

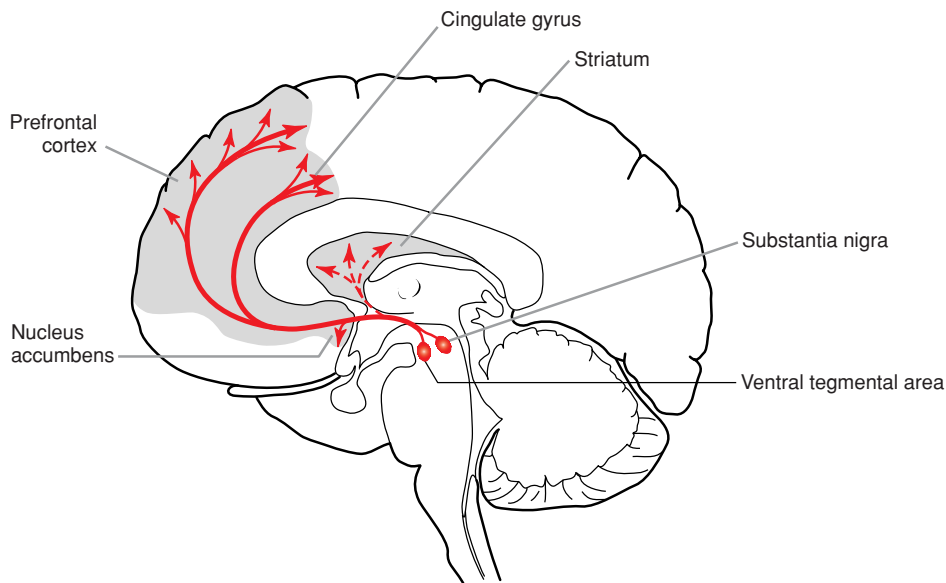
In humans, drug-related cues may produce subjective drug craving as well as drug seeking. The role of subjective drug craving in the initiation of drug seeking remains controversial. Tiffany (1990) has argued that subjective urges may only be experienced strongly if there is an obstacle to obtaining drugs, for example, if drugs are not readily available or if the addicted person is making efforts to limit use. To meet its needs reliably and efficiently, an animal often learns complex action sequences to the point where they become automatic, although still flexible enough to respond to unforeseen obstacles. As complex and flexible as human behavior is, oft-repeated sequences become automatic as well; in addicted individuals, oft-repeated sequences of drug seeking, preparation of drugs for administration, and drug taking take on the appearance of automatic habits (Tiffany 1990, Berke & Hyman 2000). Thus if drugs are readily available, automatic cue-initiated behaviors (more akin to strong habits) may play a more central role than conscious craving (Tiffany 1990, Tiffany & Carter 1998, Everitt & Robbins 2005).

Whatever the relative roles of conscious craving or automatic cue-initiated processes, once activated, drug-seeking is often facilitated by impairment of prefrontal cortical "top-down" control mechanisms that, in a healthy individual, might be expected to inhibit harmful behaviors. In part this may reflect the devaluing of nondrug goals within the prefrontal cortex (PFC) (Montague et al. 2004) and in part may reflect other drug-related effects that might undermine the normal function of the PFC (Paulus et al. 2005), especially the orbitofrontal cortex (OFC) in the control of behavior (Schoenbaum & Roesch 2005).

Before proceeding to a discussion of mechanisms underlying addiction, we must acknowledge that not all individuals are at equivalent risk for experimenting with drugs or for becoming addicted if they do experiment. Indeed, most individuals who sample drugs of abuse do not progress to addiction. Nor does every person who becomes addicted have an equivalent response to treatment. Each of these interindividual differences appears to reflect the interaction of multiple genetic and nongenetic factors (Kendler et al. 2000, 2003; Goldman et al. 2005). Although we recognize the critical importance of defining the genetic, developmental, and environmental factors that account for differences in vulnerability, in the interests of focus, we limit this review to what are presumably shared neurobiological mechanisms that contribute to addiction.

## **ADDICTIVE DRUGS TAP INTO NORMAL MECHANISMS OF REWARD-RELATED LEARNING**

Survival and the continuation of species require that organisms learn the circumstances under which they can obtain food and other resources for bodily needs and find opportunities for mating. Such goals function as rewards (see Elements of Reward). Responses to natural rewards and addictive drugs exhibit many commonalities. These include hedonic



**Figure 2**

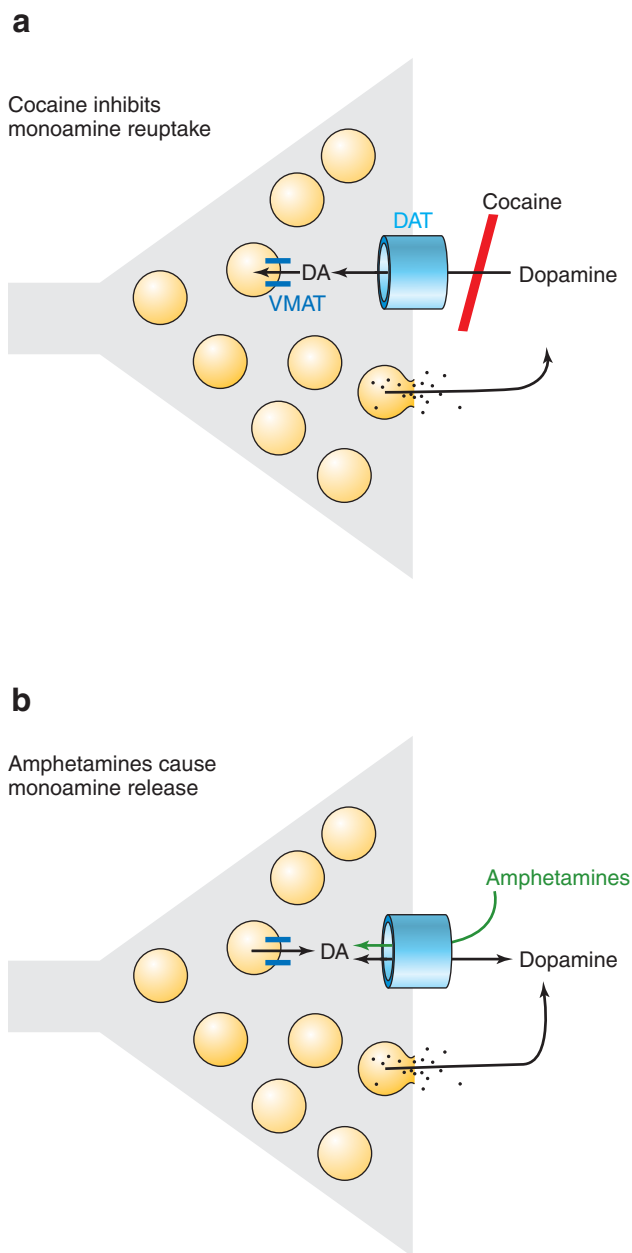
Dopamine projections to the forebrain. Illustrated are projections from the ventral tegmental area to the nucleus accumbens, and prefrontal cerebral cortex, and projections from the substantia nigra to the dorsal striatum (caudate and putamen and related structures).

responses (pleasure), desire or “wanting,” and rapid learning of both predictive cues and efficient behavioral sequences aimed at obtaining the reward. Two major differences between natural rewards and addictive drugs conspire to make addiction remarkably harmful. First, drug rewards tend to become overvalued at the expense of other rewards, contributing to compulsion and to a marked narrowing of life goals to obtaining and using drugs. Secondly, unlike natural rewards, addictive drugs do not serve any beneficial homeostatic or reproductive purpose but instead often prove detrimental to health and functioning. Much work over several decades has begun to paint a picture of how addictive drugs come to masquerade as, and eventually supplant, natural rewards as highly valued goals.

### A Central Role for Dopamine

Investigations using diverse methods (including *in vivo* neurochemical measurements, microinjections of agonists or antagonists into specific brain regions, and the placement of lesions) have converged on the conclusion that natural rewards and addictive drugs alike influence behavior as a result of their ability to

increase synaptic dopamine in the nucleus accumbens (NAc), the major component of the ventral striatum (Wise & Bozarth 1987, Koob & Bloom 1988, Di Chiara 1998, Wise 1998) (Figure 2). Whether acting directly or indirectly (Johnson & North 1992, Jones et al. 1998, Tapper et al. 2004, Waldhoer et al. 2004, Justinova et al. 2005), all addictive drugs increase levels of synaptic dopamine within the NAc. The source of dopamine to the NAc (as well as to the amygdala, hippocampus, and PFC) is the ventral tegmental area (VTA) of the midbrain (Figures 2 and 4). The NAc can be subdivided by histology and connective patterns into core and shell regions; it is within the shell region, which is closely connected to other emotion-regulating areas of the brain, that dopamine influences responses to novel rewarding stimuli (Pontieri et al. 1995, Ito et al. 2004). In addition to the NAc, the amygdala and PFC play critical roles in the valuation of rewards and the establishment of reward-associated memories (Everitt et al. 2003, Kalivas et al. 2005). The consolidation of efficient action repertoires aimed at obtaining rewards depends on the dorsal striatum (Graybiel 1998, Packard & Knowlton 2002, Barnes et al. 2005, Vanderschuren et al.



**Figure 3**

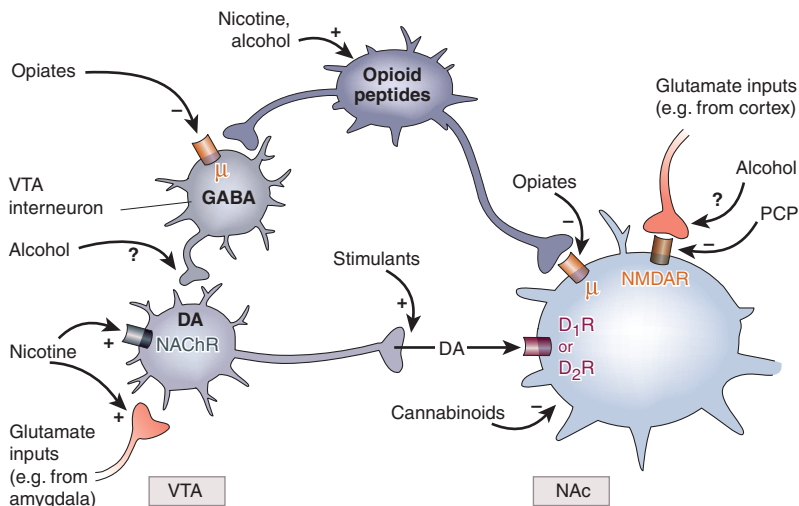
Psychostimulant action. The psychostimulant drugs cocaine and amphetamine increase synaptic dopamine. (*Upper panel*) Cocaine blocks the dopamine reuptake transporter located on the presynaptic membrane, thus acutely increasing synaptic dopamine. (*Right panel*) Amphetamines enter dopamine neurons via their reuptake transporters and interact intracellularly with the vesicular monoamine transporter (VMAT) to release dopamine into the presynaptic terminal. Dopamine (DA) is then “reverse transported” out of the neuron into the synapse.

2005), which receives dopamine from the substantia nigra (SN), a structure contiguous within the midbrain with the VTA.

Despite the enormous research focus on dopamine, we are still not certain precisely what information is encoded by dopamine release in the NAc. Dopamine was initially thought to function as the internal representation of a hedonic state (pleasure), but this has been shown not to be the case, as animals can still exhibit positive hedonic responses in the absence of dopamine. In studies in which dopamine signaling was blocked pharmacologically, by lesioning (Berridge & Robinson 1998), or by genetic inactivation of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine biosynthesis (Cannon & Palmiter 2003, Robinson et al. 2005), animals continue to show hedonic preferences. Because animals that lack dopamine have a defect in the initiation of motor responses and thus cannot approach a goal, they must be placed in close proximity to that goal to test preferences. Mice in which dopamine is blocked or absent exhibit a clear preference (liking) for sweet fluids (containing sucrose or nonnutritive sweeteners) over unsweetened alternatives when placed in proximity to these substances.

Dopamine has also been shown to not be required for hedonic responses to opiates or for learning cues predictive of opiate administration (Hnasko et al. 2005). Dopamine antagonists and lesions of VTA dopamine neurons, for example, do not abolish intravenous heroin self-administration. Moreover, animals will self-administer opiates directly into the NAc, where  $\mu$  opioid receptors expressed on NAc neurons appear to bypass dopamine inputs from the VTA (Pettit et al. 1984, Bardo 1998). Cannabinoids, ethanol, and nicotine are also thought to produce reward partly via nondopaminergic mechanisms. Further, mice in which TH has been genetically inactivated not only continue to show hedonic responses to food rewards (liking), but can also still learn relevant cues. Animals without dopamine cannot, however, use





**Figure 4**

Actions of opiates, nicotine, alcohol, and phencyclidine (PCP) in reward circuits. Ventral tegmental area (VTA) dopamine neurons (*bottom left*) project to the nucleus accumbens (NAc) (*bottom right*). Different interneurons, schematically diagrammed above, interact with VTA neurons and NAc neurons. The rewarding properties of opiates are mediated by  $\mu$  opiate receptors found in two locations in brain reward circuits. VTA dopamine neurons are tonically inhibited by GABAergic interneurons that express  $\mu$  opiate receptors. Opiates acutely inhibit these interneurons thus disinhibiting the dopamine projection neurons, which then release dopamine in the NAc and other terminal fields. In addition, there are  $\mu$  opiate receptors expressed by NAc and dorsal striatal neurons. Opiates can stimulate these receptors directly and produce reward in a dopamine-independent manner. Nicotine, acting on nicotinic acetylcholine receptors (NACHRs) in the VTA, cause dopamine release. Ethyl alcohol, acting on GABA<sub>A</sub> receptors in the VTA, can also cause dopamine release. Phencyclidine (PCP), which blocks the NMDA glutamate receptor channel and cannabinoids acting via CB1 cannabinoid receptors in the VTA (*not shown*), also produce dopamine release. Cannabinoids, alcohol, and PCP can also act directly on the NAc. PCP, phencyclidine (“angel dust”).

information about rewards to motivate goal-directed behaviors (Robinson et al. 2005); i.e., they cannot act on their preferences. Overall, however, the conclusions to be drawn from lesions or from dopamine-deficient TH knockout mice are not entirely clear. The knockout mice, for example, likely have developmental compensations to the lack of dopamine, require intermittent L-dopa (which transiently restores dopamine) in order to survive, and require behavioral activation by caffeine to exhibit learning. It appears dopamine is not needed for hedonic responses. The lesion and knockout mice suggest that, under certain circumstances, dopamine is not required for reward-related learning. At the same time,

there is strong evidence (e.g., in intact non-human primates) to suggest that, under normal circumstances (e.g., in the absence of lesions), dopamine plays a central role in reward-related learning (Schultz et al. 1997, Schultz 2006). Finally, dopamine appears to be required for motivated behaviors aimed at obtaining rewards. Based on such considerations, Berridge & Robinson (1998) have proposed that dopamine transmission in the NAc mediates the assignment of “incentive salience” to rewards and reward-related cues, such that these cues can subsequently trigger a state of “wanting” for the goal object as distinct from “liking.” An animal can still like something in the absence of dopamine

transmission; however, the animal cannot use this information to motivate the behaviors necessary to obtain it. In this view, dopamine release in the NAc binds the hedonic properties of a goal to motivation (wanting) and thus plays a critical role in the formation of reward-related associations that regulate behavior.

Other views of dopamine action have been developed from reinforcement-learning models. Such models begin from the assumption that an animal will act to maximize future rewards (Sutton & Barto 1998, Montague et al. 2004). According to this theory, the brain estimates and holds in memory the value of possible actions based on the amount of reward each action has yielded in the past. The animal uses these stored values to predict, for any possible action, the likely resulting rewards or punishments. The actual reward gained from an action is then compared with the prediction; the difference constitutes a “reward prediction error.” Dopamine has been hypothesized to encode such a reward prediction error and would thus act to shape future behavior to maximize reward. A reinforcement-learning model of dopamine action is consistent with a role for dopamine in assigning incentive salience (Montague et al. 2004) but is also consistent with broader roles for dopamine in reward-related learning.

Schultz and colleagues have examined the applicability of reinforcement-learning models to the primate brain and behavior (Schultz et al. 1993, 1997; Hollerman & Schultz 1998; Schultz 1998, 2006). They recorded from VTA dopamine neurons in alert monkeys as they underwent classical conditioning. Monkeys were trained to expect a set amount of sweet juice at a fixed time after a sensory cue. In awake monkeys, dopamine neurons exhibit a relatively consistent basal (tonic) pattern of firing; superimposed on this basal pattern are brief phasic bursts of spike activity, the timing of which is determined by the prior experience of the monkey with rewards. Specifically, an unexpected reward—in these experiments, delivery of juice—produces a

transient (phasic) increase in firing. As the monkey learns that a signal reliably predicts a reward of a certain magnitude after a certain time interval, there is no increase in the firing of dopamine neurons when the juice is made available. The reward is “just as expected”; thus there is no prediction error. As the monkeys learn the cues that predict reward, dopamine neurons fire at the earliest reliable predictor. (The earliest predictor is, by definition, unexpected.) If a cue normally predicts reward, but the reward is withheld, there is a suppression of the tonic firing of dopamine neurons at the time the reward would have been expected. In the language of reinforcement-learning models, tonic activity signals that things are “as expected,” phasic bursts signal a positive reward–prediction error (“better than expected”), and pauses in firing signal a negative prediction error (“worse than expected”) (Montague et al. 1996, 2004).

Recent partial support for this model comes from recordings from single midbrain dopamine neurons. Bayer & Glimcher (2005) found that the average firing rate of dopamine neurons could encode a reward prediction error of the kind required by reinforcement-learning models if the outcome was better than expected (positive reward–prediction errors). When the outcome was worse than expected (negative reward–prediction errors), the firing rate was always 0 Hz in their experiments and therefore had limited informational content. They hypothesize that another system must encode quantitative information about negative reward–prediction errors.

Computational models based on reinforcement-learning models and the physiologic findings to date have generated hypotheses to explain the advantage of addictive drugs over natural rewards (Montague et al. 2004, Redish 2004). Because addictive drugs reliably increase synaptic dopamine as a result of their direct pharmacologic actions, whenever such drugs are taken the brain will receive a signal that the drug reward was “better

than predicted.” Even if the subjective effects of the drug fall far short of the expectation created by drug-related cues, the pharmacologically induced release of dopamine will produce what the brain interprets as a positive prediction-error signal. Such signals would create a marked advantage for drugs over all other rewarding stimuli and would thus shape behavior toward increased drug use and relative devaluation of other goals. In short, these models predict repetitive pathological overlearning on drug-related cues and drug experiences, pathological because dopamine is released whatever the actual experience (Montague et al. 2004). If these models are right, dopamine-releasing pharmacologic agents act as Trojan horses that dominate the normal associative learning mechanisms that shape reward-related behavior (Hyman 2005).

The primate experiments on which such models of dopamine action are, in part, based have not been extended to addictive drugs. Addictive drugs raise important questions about the dopamine signal on which current reinforcement-learning models are based. Natural rewards and the stimuli that predict them produce brief bursts and pauses in the firing of dopamine neurons, but addictive drugs such as amphetamine may elevate synaptic dopamine levels for hours and thus would disrupt all normal patterns of dopamine release, both tonic and phasic, with an exaggerated and prolonged dopamine signal (Knutson et al. 2004). The mechanisms by which such prolonged elevations of dopamine levels affect reward-related behavior remain to be understood. Extension of investigations of dopamine action to humans will rely on such technologies as positron emission tomography and functional magnetic resonance imaging. These technologies are already being used to study reward-related behaviors in humans but lack the temporal precision of the invasive electrophysiological recordings that can be performed in nonhuman primates; thus for the time being human and primate research serve complementary purposes.

## Dopamine Action in the Prefrontal Cortex and Dorsal Striatum

The PFC underlies working memory, which is the ability to hold information “on line” so that it can be integrated with other information, updated, and used to guide behavior. Thus it has been hypothesized that the PFC is an important contributor to the representation of goals, assignment of value to them, and the ability to select actions based on the resulting valuations (Miller & Cohen 2001, Matsumoto et al. 2003, Roesch & Olson 2004, Rolls 2004, Kringelbach 2005). The maintenance of goal representations within the PFC is critical for the cognitive control that permits goal-directed behaviors to proceed to a successful conclusion (Miller & Cohen 2001, Rolls 2004). For example, successfully obtaining food (or drugs) may demand that an extended sequence of actions be carried out and that distractions be resisted and obstacles overcome. Thus the PFC not only has a positive role in guiding an organism successfully to a goal, but must also suppress maladaptive responses. Within the PFC, the OFC is networked with the amygdala, dorsal striatum, NAc, hypothalamus, insula, and medial prefrontal cortex and is thus in a position to integrate emotional and motivational information with object representations held in working memory (Schoenbaum & Roesch 2005). For example, the predicted value of a potentially rewarding object appears to be represented within the OFC together with the amygdala (Gottfried et al. 2003, Kringelbach 2005).

Similar to the NAc, the PFC receives dopamine innervation from the VTA. In line with its posited role in reinforcement learning, phasic dopamine release has been hypothesized to gate the updating of information in the PFC such that appropriate new goals can be encoded and selected (Cohen et al. 2002, Montague et al. 2004). As in the NAc, addictive drugs would be expected to produce a distorted and excessive dopamine signal in the OFC and other regions of the PFC because of their ability to elevate dopamine by

their direct pharmacologic action. This distorted dopamine signal has been hypothesized to produce overlearning of drug-related cues, thus leading to the valuation of drugs above other goals (Montague et al. 2004). In this context, long-term potentiation (LTP), a leading synaptic model for memory storage, at hippocampal-prefrontal cortical synapses appears to be enhanced by D1 dopamine receptor (D1DR) activation (Gurden et al. 2000).

In addition to distorting valuations of goals and thus narrowing the focus of behavior, drug taking has been hypothesized to impair the top-down control over behavior by producing pathological adaptations in the PFC (Kalivas et al. 2005). Much of the evidence for defects in activation of the PFC in humans comes from neuroimaging studies (Volkow et al. 1993, Volkow & Fowler 2000, Goldstein & Volkow 2002, Kaufman et al. 2003, Paulus et al. 2005). In general, impairments in executive function and thus increased impulsivity have been correlated with the diminished ability to recruit the PFC in regular drug users. Together, pathological overvaluation of drug-related cues and impairment of some aspects of top-down control could make significant contributions to loss of control over drug use, a core characteristic of addiction.

Whereas NAc dopamine plays a critical role in the establishment of drug-seeking behaviors, in rats, at least, the dorsal striatum progressively takes on a central role as drug seeking becomes well established (Everitt et al. 2001, Everitt & Robbins 2005, Vanderschuren et al. 2005). In rats the NAc shell is required for the initial acquisition of cocaine self-administration, but the acquisition of cocaine seeking in response to cocaine-associated cues depends on the NAc core, a region with connectivity and organization similar to the dorsal striatum (Ito et al. 2004). Once the ability of cocaine-associated cues to maintain drug seeking becomes fully consolidated, there is a further shift in its neural substrate: It is no longer the NAc but the dorsal striatum that is required. Blockade of dopamine receptors or AMPA/kainate

receptors in the NAc did not interfere with the ability of conditioned stimuli to maintain drug seeking, but infusions of antagonists to either neurotransmitter into the dorsal striatum successfully blocked drug seeking in response to cocaine-associated cues (Vanderschuren et al. 2005). These data are consistent with the hypothesis that, as cue-activated drug seeking and drug taking become well established, there is a progressive shift from motivated seeking of goals, behavioral responses dependent on the NAc, to stimulus-response habits, which are dependent on the dorsal striatum. Such a shift would help explain cue activated-automatized or habit-like drug seeking in addicted humans and the recalcitrance of drug-seeking habits to treatment interventions, in line with the overall resistance of well-ingrained habits to disruption (Tiffany 1990, Berke & Hyman 2000, Everitt & Robbins 2005, Vanderschuren et al. 2005).

## REWARD-RELATED LEARNING

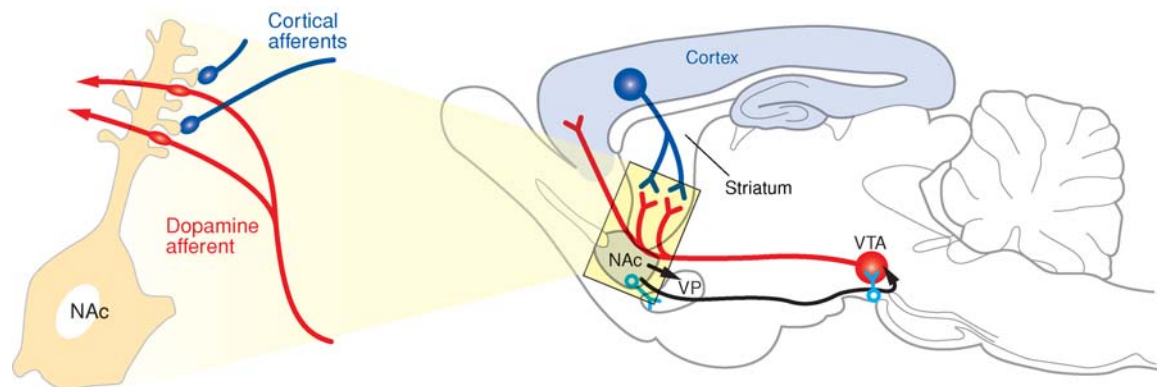
Stimulus-reward and stimulus-action learning processes associate specific cues and contexts, with particular responses such as wanting a reward, taking action to gain that reward, or consummation/consumption. Learning the predictive significance of a specific cue and connecting that information with appropriate responses require the storage of specific patterns of information in the brain. This stored information must provide internal representations of the reward-related stimulus, its valuation, and a series of action sequences so that the cue can trigger an efficient and successful behavioral response. The same must be true for aversive cues that signal danger.

As discussed above, phasic dopamine release in the NAc, PFC, amygdala, and dorsal striatum appears to mark the motivational significance and value of particular experiences, cues, or action responses. The firing of VTA dopamine neurons does not, however, encode specific information about specific experiences, cues, or actions. The dopamine

innervation of the brain consists of a relatively small number of cell bodies in the midbrain that project widely throughout the neuraxis with single cells innervating multiple targets (Foote & Morrison 1987) (**Figure 2**). Dopamine neurons within the VTA project throughout the limbic forebrain and PFC, whereas dopamine neurons within the SN project to the dorsal striatum. This diffusely projecting architecture cannot support the processing and storage of detailed information; it does, however, appear to be ideal for coordinating responses across the NAc, amygdala, hippocampus, and PFC (terminal fields of VTA dopamine neurons) and the dorsal striatum (terminal fields of SN dopamine neurons) to salient stimuli, including rewards. As a result dopamine release could shape valuations of goals and reward-related behavior by interacting with circuits that encode precise information about a stimulus and what it predicts (e.g., that a certain alley, a certain ritual, or a certain odor—but not a closely related odor—predicts drug delivery with a high probability). Such information-rich data

concerning reward-related experiences, predictive cues, and action sequences are likely stored using mechanisms similar to those underlying all other forms of associative long-term memory (Di Chiara 1998, Berke & Hyman 2000, Hyman & Malenka 2001, Everitt & Wolf 2002, Robbins & Everitt 2002, Chao & Nestler 2004, Hyman 2005), namely by complex and bidirectional activity-dependent changes in the patterns and strength of excitatory synapses that utilize the neurotransmitter glutamate and perhaps similar changes at inhibitory synapses that utilize the neurotransmitter GABA.

The associative interactions between dopaminergic afferents and glutamatergic circuits in such functionally diverse structures as the NAc, PFC, amygdala, and dorsal striatum may bring together information about the motivational state of the organism with specific sensory information (whether interoceptive or in the environment) and stored motor responses (**Figure 5**) (McFarland et al. 2003, Kalivas 2004). These considerations suggest the core features of addiction result



**Figure 5**

Dopamine-glutamate interactions in the striatum. The major neuronal cell type in both the nucleus accumbens (NAc) and dorsal striatum is the medium spiny neuron, which is, as implied by its name, characterized by dendritic spines. As shown, glutamatergic afferents from the cerebral cortex and dopaminergic afferents from the ventral tegmental area (VTA) or substantia nigra (SN) interact at spines in the NAc (colored box) and dorsal striatum permitting integration of information-rich sensorimotor data from the cortex with information about the motivational state of the organism from the midbrain. As shown in the inset (left panel), the glutamatergic afferents synapse on the heads of spines and dopaminergic afferents provide synapses “en passant” on the necks of spines, providing an arena for interaction.

from usurpation of the normal mechanisms of reward-related learning and memory. The persistence of addiction, including the risk of relapse long after any withdrawal symptoms have subsided, would result from the persistence of stored associations, distributed in multiple terminal fields of dopamine innervation. These associations are presumably stored as alterations in synaptic weights and, ultimately, for the very long term, by physical remodeling of synaptic connections (Berke & Hyman 2000, Hyman & Malenka 2001).

### Sensitization

Whereas some behavioral responses of addictive drugs exhibit tolerance, other responses increase with repeated dosing, a phenomenon called sensitization (Kalivas & Stewart 1991). This phenomenon is best characterized for the psychostimulants cocaine and amphetamine (Dougherty & Ellinwood 1981) but can also be observed with opiates (Vezina et al. 1987) and other drugs. Sensitization is most strongly elicited if drug dosing is intermittent (e.g., once daily), whereas tolerance predominates with constant dosing (Dougherty & Ellinwood 1981). In rats, for example, repeated daily injections of cocaine or amphetamine produce a progressive increase in locomotor activity in response to a fixed dose of the drug. Sensitization can exhibit context dependence and therefore associativity. If, for example, a rat is taken from its home cage to a novel “test” cage for intermittent amphetamine injections, the sensitized locomotor response to a challenge dose is much greater if the challenge is given in the test cage than in the home cage or in a different environment (e.g., Badiani et al. 1995, Hinson & Poulos 1981). In some paradigms, the expression of a sensitized response can be limited entirely to the drug-associated environment (Anagnostaras & Robinson 1996, Tirelli & Terry 1998). Sensitization can also be long-lived; locomotor sensitization has been observed for over a year in rats following

the termination of amphetamine administration (Paulson et al. 1991).

Given its context dependence and persistence, sensitization has been proposed as a central neural mechanism underlying addiction (Robinson & Berridge 1993, 2003; Kalivas 2004; Vezina 2004). Robinson & Berridge (1993, 2003) have put forward an incentive-sensitization theory of addiction, which holds that, just as repeated drug administration sensitizes locomotor responses, it can also sensitize neural circuits that assign incentive salience (but not hedonic value or liking) to drugs and drug-related cues. Sensitized incentive salience is posited to produce intense wanting of drugs activated by drug-associated cues (Robinson & Berridge 1993, 2003). The incentive-sensitization theory is consistent with the view that associative learning mechanisms bind specific cues to drug wanting and drug seeking; indeed the theory depends on there being neural mechanisms that produce associations. This theory can also be viewed as consistent with reinforcement-learning theories in which dopamine release functions as a reward prediction-error signal; both reinforcement-learning theories and the incentive-sensitization theory can be taken to hold that the experience of a reward enhances the incentive salience of the cues that predict that reward (Montague et al. 2004). Nonetheless, the concept of sensitization does not address the encoding of detailed information about drug cues or the ability of cues to activate specific drug-seeking behavioral repertoires, except insofar as sensitization is subsumed into associative learning models. Associative learning mechanisms can explain the encoding of specific cues, their overvaluation in PFC, and their connection with specific prepotent drug-seeking behaviors that develop over time and depend on the dorsal striatum (Tiffany 1990, Berke & Hyman 2000, Everitt et al. 2001, Everitt & Robbins 2005, Vanderschuren et al. 2005). Insofar as sensitization might cause enhanced dopamine release in response to drugs and drug cues, it would hasten the consolidation of

drug-related associations but would not contribute to their specificity. Despite these explanatory gaps as a core explanation for addiction, and the lack of compelling evidence to date for sensitization in humans, sensitization remains a useful and important experimental model of drug-induced changes in reward circuits as described below.

## CELLULAR AND MOLECULAR MECHANISMS OF ADDICTION

As implied by the discussion above, candidate molecular and cellular mechanisms of addiction at the behavioral and systems levels ultimately must explain (a) how repeated episodes of dopamine release consolidate drug-taking behavior into compulsive use, (b) how drug-related cues come to control behavior, and (c) how risk of relapse, even from a drug-free state, can persist for years. Intracellular signaling mechanisms that produce synaptic and other forms of neural plasticity [e.g., changes in the intrinsic, global excitability of individual neurons (Nestler & Aghajanian 1997, Zhang & Linden 2003)] can convert drug-induced signals, such as dopamine release, into long-term alterations in neural function. Here we focus on synapse-specific Hebbian forms of plasticity.

Synaptic plasticity is complex, but it can be heuristically divided into mechanisms that change the strength or “weight” of existing connections and those that might lead to synapse formation or elimination and remodeling of the structure of dendrites or axons (Chklovskii et al. 2004, Malenka & Bear 2004). Such processes are hypothesized to produce long-term changes in neural circuits and therefore long-term alterations in behavior. One of the interesting fallouts from research into the cellular and molecular basis of associative memory as a candidate mechanism of addiction is the striking convergence with mechanisms implicated in other forms of memory (e.g., hippocampus-dependent memory). This convergence suggests neurons have a finite repertoire of molecular mecha-

nisms for encoding information and that the behavioral consequences of any given alteration depends on the precise neural circuits in which it occurs (Berke & Hyman 2000, Hyman & Malenka 2001, Nestler 2002).

## MECHANISMS OF CELLULAR PLASTICITY

As described above, the specificity of drug cues and their relationship to specific drug-seeking behavioral sequences suggest at least some of the mechanisms underlying addiction must be associative and synapse specific. The best-characterized candidate mechanisms for changing synaptic strength that are both associative and synapse specific are LTP and long-term depression (LTD). These mechanisms have been hypothesized to play critical roles in many forms of experience-dependent plasticity, including various forms of learning and memory (Martin et al. 2000, Malenka & Bear 2004). Such mechanisms of synaptic plasticity could lead subsequently to the reorganization of neural circuitry by altering gene and protein expression in neurons that receive enhanced or diminished signals as a result of LTP or LTD. LTP and LTD have thus become important candidate mechanisms for the drug-induced alterations of neural circuit function that are posited to occur with addiction (Hyman & Malenka 2001). There is now good evidence that both mechanisms occur in the VTA, and also in the NAc and other targets of VTA dopamine neurons as a consequence of drug administration.

**Synaptic plasticity in the ventral tegmental area.** The first suggestion that synaptic plasticity in reward circuitry, and in particular in the VTA, might play an important role in the development of drug-related behavior was the observations that administration of NMDA receptor (NMDAR) antagonists, including direct administration into the VTA, prevents the development of sensitization to psychostimulants (reviewed in Vanderschuren & Kalivas 2000, Wolf 1998).

Because NMDARs were known to be critically involved in triggering major forms of LTP and LTD (Malenka & Bear 2004), these findings suggested that addictive drugs might trigger synaptic plasticity in the VTA. Consistent with this idea, lesions of the PFC, which provides excitatory afferents to the VTA, can block sensitization (Wolf et al. 1995, Cador et al. 1999, Tzschentke & Schmidt 1999), whereas electrical stimulation of these afferents can mimic repeated drug exposure by sensitizing animals to cocaine (Schenk & Snow 1994).

These experiments set the stage for a direct test of the hypothesis that addictive drugs cause plasticity at excitatory synapses in the VTA. It was, of course, important to first establish that LTP and LTD could be elicited at these synapses (Bonci & Malenka 1999, Jones et al. 2000, Thomas et al. 2000). Whereas LTP in the VTA turned out to be dependent on NMDARs, LTD appeared to be caused by the activation of voltage-dependent calcium channels. These results focused further attention on LTP in the VTA. To directly determine whether *in vivo* administration of an addictive drug could cause LTP in the VTA, animals were given cocaine, and synaptic responses were recorded from dopaminergic cells in acute brain slices prepared 24 h later (Ungless et al. 2001). Differences in synaptic strength between cocaine- and saline-treated animals were assayed by measuring the relative ratio of synaptic currents mediated by AMPA receptors (AMPA) versus NMDARs. The AMPA/NMDA ratio was significantly elevated in cocaine-treated animals. Similar to hippocampal LTP, this change in synaptic strength was blocked by an NMDAR antagonist and reflected a modification of postsynaptic AMPARs (Ungless et al. 2001). Moreover, there was diminished ability to further enhance excitatory postsynaptic currents by attempting to induce LTP, suggesting these synapses had already undergone LTP. This cocaine-induced synaptic modification was not permanent but lasted between 5 and 10 days, even when cocaine was administered

repeatedly (Borgland et al. 2004). The transient nature of this synaptic plasticity is consistent with the idea that these drug-induced adaptations in the VTA are not permanent but instead are an initial step in the neural processes leading to addiction (Vanderschuren & Kalivas 2000, Everitt & Wolf 2002, Kauer 2004).

If this cocaine-induced synaptic plasticity in the VTA is generally important for the development of addiction, it should occur in response to other drugs as well. This prediction was confirmed by demonstrating that, in addition to cocaine, *in vivo* administration of amphetamine, nicotine, morphine, or ethanol all caused a similar increase in the AMPA/NMDA ratio in dopaminergic cells (**Figure 6**) (Saal et al. 2003). In contrast, the nonaddictive psychotropic drugs fluoxetine and carbamazepine did not cause detectable synaptic modifications in the VTA.

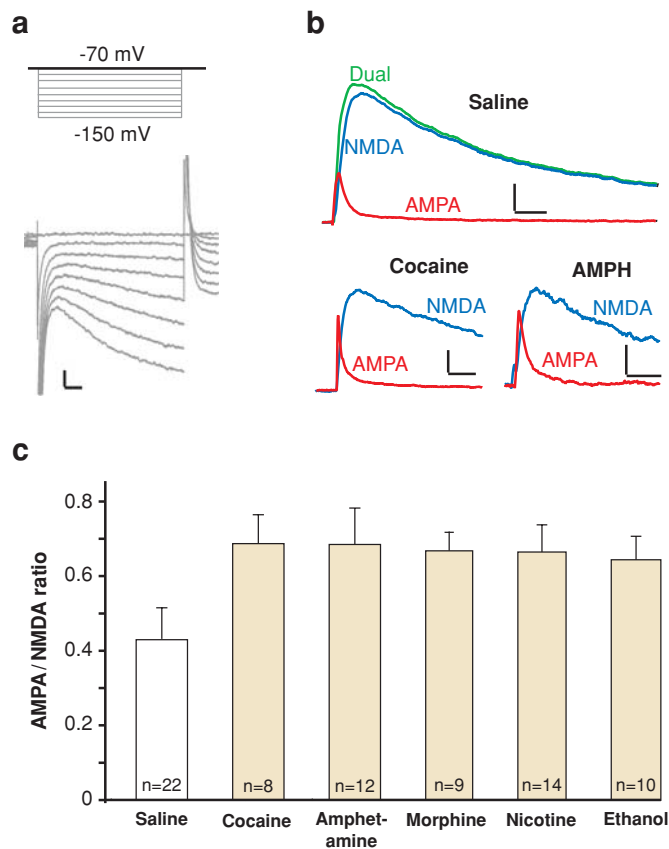
What might be the normal function of LTP in dopamine neurons? A clue came from the observations discussed above: In both humans and animal models, reinstatement of drug seeking and self-administration after drug withdrawal can be triggered by drug-associated cues (Wikler & Pescor 1967, Tiffany 1990, O'Brien et al. 1998, Berke & Hyman 2000) or by stress (Piazza & Le Moal 1998, Shaham et al. 2000). Stress can even facilitate initial drug taking, perhaps by enhancing the rewarding properties of addictive drugs (Piazza & Le Moal 1998). Therefore, the effect of exposing animals to an acute stress was examined; similar to addictive drugs, stress caused an increase in synaptic strength on dopamine neurons (Dong et al. 2004). The synaptic potentiation of dopamine neurons caused by cocaine and stress both involve an upregulation of AMPARs (Ungless et al. 2001, Dong et al. 2004). However, the effect of stress was blocked by administration of the glucocorticoid receptor antagonist mifepristone (Saal et al. 2003) but not by a D1DR antagonist, whereas cocaine-induced LTP on dopamine neurons was blocked by a D1DR antagonist (Dong et al. 2004) but not



by mifepristone (Saal et al. 2003). These results suggest the actions of cocaine in the VTA are unlikely to be a result of a stress response.

Little else is known about the detailed mechanisms by which drugs of abuse and stress trigger synaptic potentiation in dopamine neurons except that it occurs within 2 h of drug administration, and it requires intact neural circuitry. For example, treatment of brain slices (which interrupt normal circuitry) with amphetamine for 2 h is insufficient to generate LTP (Faleiro et al. 2004). Considering all of the available data, it would appear that multiple *in vivo* circuit, cellular, and molecular mechanisms are involved in processes by which LTP is triggered in dopamine neurons, with the different drugs of abuse and stress employing distinct mechanisms that lead to a similar net result.

Of course, a critical question is whether this drug-induced LTP in dopamine neurons has any important functional consequences. This is a challenging question to answer definitively—after all, despite three decades of work it has been difficult to prove hippocampal LTP is critically involved in hippocampal-dependent learning and memory (Martin et al. 2000, Malenka & Bear 2004). Nonetheless, several lines of evidence support the idea that synaptic plasticity in the VTA is behaviorally relevant. First, as mentioned above, blockade of glutamate receptors in the VTA prevents behavioral sensitization as well as conditioned place preference in response to cocaine (Kim et al. 1996, Harris & Aston-Jones 2003). Second, cocaine- and stress-induced LTP in dopamine neurons do not occur in genetically engineered mice that lack the AMPAR subunit GluR1, and these mice also exhibit defects in conditioned place preference in response to cocaine (Dong et al. 2004). Third, overexpression of GluR1 in the VTA using viral vectors—a manipulation that in the hippocampus can mimic the induction of LTP (Malinow & Malenka 2002)—enhances the rewarding and motivational effects of drugs of abuse (Carlezon et al. 1997, Carlezon & Nestler 2002, Choi et al. 2003). Based on



**Figure 6**

Excitatory synaptic responses in dopamine neurons are modified by addictive drugs. (a) A sample whole-cell voltage clamp recording from midbrain slices showing that hyperpolarizing voltage steps (*top*) generate a family of inward  $I_h$  currents (*bottom*), which are characteristic of dopamine cells. (b) Examples of excitatory postsynaptic currents recorded from dopamine neurons. Top traces show superimposed examples of the total synaptic current recorded at +40 mV, the pure AMPA receptor-mediated synaptic current and the pure NMDA receptor-mediated synaptic current. This recording was made from a midbrain slice prepared from an animal that had received a saline injection 24 h earlier. Bottom traces show AMPA receptor- and NMDA receptor-mediated synaptic currents recorded from dopamine (DA) neurons in slices prepared from animals that had received cocaine or amphetamine (AMPH) injections 24 h earlier. The AMPA/NMDA ratio is calculated by measuring the peaks of the respective synaptic currents. (c) The bars show the mean ( $\pm$ SEM) AMPA/NMDA ratio of DA cells in slices prepared from animals that had received saline or drug injections 24 h earlier. All drugs of abuse caused a significant increase in the AMPA/NMDA ratio, which reflects an increase in basal excitatory synaptic strength. Modified with permission from Saal et al. (2003).

results, we propose that the LTP induced in dopamine neurons by addictive drugs or stress may play an important, although transient, role in enhancing the rewarding properties of these drugs.

How do addictive drugs or stress cause LTP? While the answer to this question is unknown, there are the following hints. Amphetamine blocks LTD at VTA synapses (Jones et al. 2000) and also blocks inhibitory postsynaptic potentials mediated by metabotropic glutamate receptors (Paladini et al. 2001). Nicotine both directly excites VTA dopamine neurons (Calabresi et al. 1989, Pidoplichko et al. 1997) and enhances glutamate release from excitatory afferents to the VTA (Mansvelter & McGehee 2000). Opiates, conversely, acutely hyperpolarize GABAergic interneurons within the VTA that synapse on and inhibit dopamine neurons, a mechanism that causes disinhibition of VTA neurons (Johnson & North 1992). Finally, corticotropin-releasing factor, the levels of which increase during stress, can acutely enhance NMDAR-mediated synaptic responses (Ungless et al. 2003). All of these cellular actions promote the firing of VTA dopamine neurons and facilitate the generation of LTP. One possible mechanism tying increased firing to LTP is the phosphorylation of transcription factor CREB (cAMP response element binding protein), which is induced in the VTA by several addictive drugs (Shaw-Lutchman et al. 2002, 2003; Walters et al. 2003, 2005). The activation of CREB leads to increased expression of the GluR1 AMPAR subunit in the VTA (Olson et al. 2005), which may contribute to the LTP observed.

This focus on LTP does not indicate this is the only functionally important adaptation in the VTA possibly relevant to addiction. Inhibitory synaptic transmission is also affected by chronic administration of addictive drugs. For example, in naive animals D1DR activation enhances the GABA<sub>B</sub> receptor-mediated inhibitory postsynaptic potential (IPSP) in dopamine neurons via presynaptic enhancement of GABA release. However, in animals

chronically treated with cocaine or morphine, D1DR stimulation decreases this IPSP, an effect that appears to be a result of changes in extracellular adenosine levels (Bonci & Williams 1996). The increase in adenosine tone in the VTA induced by chronic cocaine treatment also reduces the IPSP mediated by metabotropic glutamate receptors but not excitatory postsynaptic currents (Fiorillo & Williams 2000). These sorts of changes, such as the acute changes listed above, would also make VTA dopamine neurons more likely to fire in response to excitatory afferent inputs. Indeed, differences in the basal impulse activity of dopamine neurons strongly correlate with locomotor responses to a novel environment and cocaine self-administration, which suggests individual differences in properties of VTA dopamine neurons may modify individual responses to addictive drugs (Marinelli & White 2000).

**Synaptic plasticity in the nucleus accumbens.** It is known that LTP and LTD occur at excitatory synapses on medium spiny neurons, the major cell type in the NAc (Kombian & Malenka 1994, Thomas et al. 2000), including a novel form of endocannabinoid mediated LTD (eCB-LTD) (Robbe et al. 2002). That said, much less work has been performed on drug effects in the NAc than in the VTA. In one study chronic (5 days) cocaine administration followed by 10–14 days of withdrawal caused a decrease in the AMPA/NMDA ratio (Thomas et al. 2001). This decrease in synaptic strength was detected in the NAc shell but not in the core and appeared to be LTD-like because the magnitude of LTD was reduced in the cocaine-treated animals. Additional electrophysiological assays suggest the cocaine-induced LTD, similar to the LTD observed in other brain structures (Malenka & Bear 2004), involves downregulation of AMPARs (Thomas et al. 2001). Little is known about the precise mechanisms by which this LTD in the NAc occurs and whether other addictive drugs cause similar changes. Similarly the functional

consequences of this synaptic modification are unknown, although behavioral experiments involving molecular manipulations of synaptic proteins in the NAc may be relevant. Specifically, overexpression of GluR1, expected to increase synaptic strength, facilitated the extinction of cocaine-seeking responses (Sutton et al. 2003) and also made cocaine aversive, rather than rewarding (Kelz et al. 1999). Conversely, manipulations expected to reduce AMPA currents had the opposite effect. This suggests that cocaine-induced LTD may normally enhance the motivational and behavioral effects of cocaine and other drugs of abuse. The findings that chronic cocaine treatment decreases levels of the synaptic scaffold protein PSD-95 in the striatum and that mice lacking PSD-95 show enhanced locomotor responses to cocaine (Yao et al. 2004) can be viewed as consistent with this hypothesis if, as found in the hippocampus (Nakagawa et al. 2004), decreased PSD-95 levels lead to a depression of basal excitatory synaptic transmission. Indeed, blocking the generation of LTD in the NAc prevents the expression of amphetamine-induced sensitization (Brebner et al. 2005).

Cocaine administration has also been shown to alter the levels of several other proteins known to be important for postsynaptic specializations at excitatory synapses. Examples include Homer (Berke et al. 1998), which helps cluster glutamate receptors and associated signaling proteins at the synapse, and F-actin (filamentous actin), which is thought to provide critical support of dendritic spines (Kalivas 2004, Kalivas et al. 2005). Recent studies have demonstrated potent effects of Homer isoforms on behavioral responses to cocaine (Szumlinski et al. 2004, 2005).

These studies emphasize the complex changes that occur in NAc neurons with respect to postsynaptic responses to glutamate as a consequence of drug exposure. There are also suggestions that glutamatergic innervation of the NAc is altered in addiction. Thus stimulants putatively impair glutamatergic transmission from the PFC

including the OFC, as evidenced by the “hypofrontality” (decreased metabolism in the PFC) observed in much neuroimaging of human addicts (Volkow & Fowler 2000, Kalivas et al. 2005). Drug-induced adaptations within cortical regions, which remain understudied, likely underlie part of this cortical pathology. In addition, there is recent evidence that local changes in the NAc may also contribute. Thus, prolonged withdrawal from chronic cocaine decreases activity of the cystine-glutamate transporter in glial cells located within this brain region (Baker et al. 2003). This decrease would lead to reduced basal levels of extracellular glutamate in NAc by decreasing the exchange of extracellular cystine for intracellular glutamate. A major goal of current research is to integrate the many observed drug-induced changes in pre- and postsynaptic glutamatergic transmission to the NAc to better understand the net effect of the glutamate system in addiction.

There are several other drug-induced physiological adaptations in the NAc that may be functionally important. For example, there is evidence that chronic cocaine treatment decreases the intrinsic excitability of NAc cells by modifying several different voltage-dependent conductances (Zhang et al. 1998, 2002; Hu et al. 2004), effects possibly mediated in part via CREB (see below). The behavioral relevance of these effects is suggested by the recent finding that suppression of NAc cell excitability by *in vivo* overexpression of  $K^+$  channels greatly enhances locomotor responses to acute cocaine (Dong et al. 2006). Chronic cocaine treatment also enhanced the presynaptic inhibition of excitatory synaptic transmission by dopamine (Beurrier & Malenka 2002), while decreasing the potency of adenosine (Manzoni et al. 1998). Amphetamine, conversely, which normally blocks the generation of LTP in the NAc, no longer has this effect in animals chronically treated with the drug (Li & Kauer 2004). Of particular interest are the findings that *in vivo* administration of cocaine or cannabinoids (e.g., THC) inhibits the

generation of eCB-LTD in the NAc (Hoffman et al. 2003, Fourgeaud et al. 2004, Mato et al. 2004). In the dorsal striatum, this eCB-LTD has Hebbian properties and is strongly modulated by dopamine (Kreitzer & Malenka 2005) in a manner consistent with theoretical predictions that dopamine may gate long-term synaptic plasticity in the striatum and provide a mechanism by which learning-induced circuit modifications become operational only when the appropriate “reward/teaching” signal occurs (Schultz 1998, Montague et al. 2004). Thus, disruption of this form of plasticity or its inappropriate generation by drugs of abuse and their associated cues may be particularly important during the development of addiction.

**Plasticity in other brain regions.** As described above, the NAc is not the only dopamine target involved in addiction. The PFC, dorsal striatum, and amygdala also play critical roles. Addictive drugs act on the PFC to produce pathological valuations and to interfere with top-down control of behavior (see above). Although dopamine appears to influence LTP and LTD in the PFC (Otani et al. 1998; Gurden et al. 1999, 2000; Huang et al. 2004), little is known about the mechanisms by which addictive drugs modify synaptic properties in this region. It appears that the membrane excitability of PFC pyramidal neurons is significantly affected by chronic cocaine administration due to the modulation of several voltage-dependent conductances (Dong et al. 2005, Nasif et al. 2005). Such a change would have a significant effect on neural circuit behavior in the PFC and its regulation of the NAc.

Dopamine has been reported to modulate synaptic plasticity in several other brain regions including the amygdala (Bissiere et al. 2003) and hippocampus (Huang & Kandel 1995, Otmakhova & Lisman 1996). Several addictive drugs have been reported to impair hippocampal LTP (e.g., Roberto et al. 2002, Pu et al. 2002), although cocaine exposure has been reported to enhance LTP

(Thompson et al. 2002) under some circumstances but not others (Thompson et al. 2004, 2005). An intriguing recent finding is that, at excitatory synapses in the bed nucleus of the stria terminalis (BNST), a brain area closely related to the amygdala that projects to the VTA, self-administration of cocaine or palatable food increased the AMPA/NMDA ratio (Dumont et al. 2005). This result suggests another synaptic modification that, similar to LTP in VTA dopamine neurons, might promote reward-seeking behaviors.

The molecular basis of alterations in synaptic weights outside the VTA and NAc has received insufficient attention to date. There is evidence that addictive drugs induce CREB activity in the prefrontal and other regions of frontal cortex, amygdala, and BNST, among other regions (see below). However, we do not know the functional effects of the observed CREB activation. Chronic cocaine administration is reported to induce AGS3 (activator of G protein signaling 3) in PFC after a prolonged withdrawal period (Bowers et al. 2004). AGS3 is a negative regulator of G<sub>i</sub>-coupled receptors, which suggests cocaine induction of the protein would enhance sensitivity of prefrontal cortical neurons to signals mediated via D<sub>2</sub> dopamine and opioid receptors. Further studies of drug-induced molecular adaptations in the PFC, amygdala, hippocampus, and other brain regions are a high priority for future research.

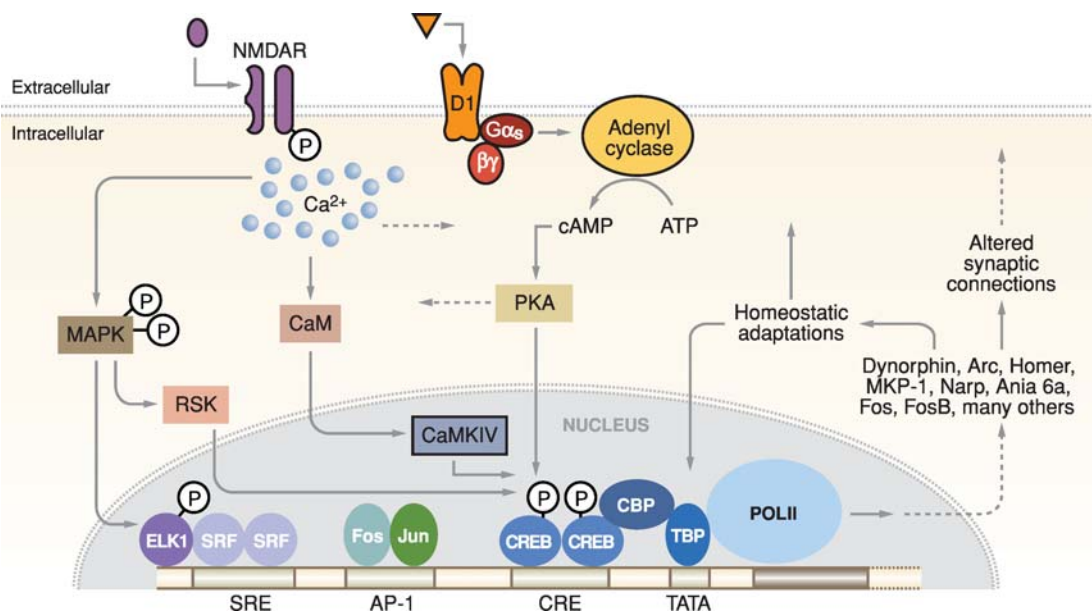
## MOLECULAR MECHANISMS OF PLASTICITY

As with hippocampal long-term memory, it has been difficult to identify the molecular mechanisms underlying the persistent associative memories central to addiction. Despite progress in identifying examples of drug-induced LTP and LTD in and potentially relevant changes in dendritic morphology in the NAc (Robinson & Kolb 2004), we have little molecular information as to how memories are encoded or stored for prolonged periods of time.

As with other forms of memory, it is hypothesized that changes in gene expression or protein translation play an important role in memory storage (Berke & Hyman 2000, Nestler 2001). At the extremes of time course, two types of gene regulation could contribute to long-term memory, including the hypothesized pathological memory processes underlying addiction: (a) long-lived up- or downregulation of the gene expression, perhaps reflecting alterations in chromatin (Kumar et al. 2005), and (b) transient bursts of gene expression (or protein translation) that produce physical remodeling of synapses and the reorganization of circuits. Both types of alterations in gene expression, as well as some intermediate forms, have been observed in response to addictive drugs, although we are still at relatively early stages of relating spe-

cific changes in gene expression to cellular and behavioral aspects of addiction. Several transcriptional and translational changes have been reported in response to drugs of abuse; here we focus on two transcription factors that have been related to specific aspects of reward and reward-related learning.

The transcription factor most studied in the context of learning and memory is CREB. CREB binds to CRE (cAMP response element) sites located in the promoter regions of certain genes (Impey et al. 2004, Zhang et al. 2005). CREB is activated upon its phosphorylation by protein kinase A, CaM-kinases (e.g., CaMKIV), or growth factor-associated kinases, which indicates that CREB is a point of convergence of numerous neurotransmitter-intracellular signaling pathways (Figure 7). Gene knockout studies have shown that



**Figure 7**

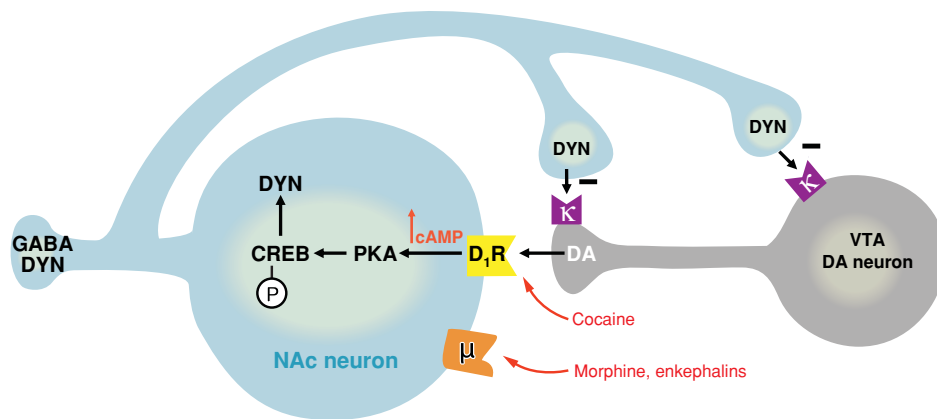
Regulation of gene expression by dopamine and glutamate. Stimulation of D1 dopamine receptors and glutamate receptors in the striatal neurons activates second messenger cascades and gene expression (Konradi et al. 1996). Shown in the cell nucleus is a model of binding sites from the cFos promoter including a serum response element (SRE), activator protein-1 element (AP-1), and a cyclic AMP (cAMP) response element (CRE). In addition to c-Fos a wide variety of other genes are activated, including the prodynorphin gene [which contains multiple CREs (Cole et al. 1995)], Fos B, Homer, Narp, and the splicing factor Ania 6a (Berke et al. 1998, 2001). CBP, CREB binding protein; CREB, cAMP response element binding protein; MAPK, MAP kinase; NMDAR, NMDA receptor; PKA, protein kinase A; TBP, TATA binding protein. Modified from Berke & Hyman (2000).

CREB is required for long-term behavioral memory in diverse animal species (e.g., see Yin & Tully 1996, Mayford & Kandel 1999, Josselyn et al. 2004, Carlezon et al. 2005). The target genes and cellular pathways through which CREB exerts effects on memory are not known; one potentially significant candidate in mammalian hippocampus is the NMDA glutamate receptor signaling pathway (Marie et al. 2005).

CREB is phosphorylated and activated in several reward-related regions (e.g., VTA, amygdala, and frontal cortex) by acute and chronic administration of stimulant and opiate drugs (Konradi et al. 1994; Cole et al. 1995; Shaw-Lutchman et al. 2002, 2003; Walters et al. 2003; Olson et al. 2005). The induction of CREB activity appears to become greater and more persistent with repeated drug exposures. The functional significance of this effect is best established within the NAc. Here, the ability of stimulants to induce CREB is mediated via activation of D1DR (Konradi et al. 1994, Cole et al. 1995); the mechanism underlying opiate induction of CREB is not

known but could also be dopamine dependent. However, CREB induction in the NAc does not appear to be shared by all addictive drugs; nicotine and ethanol have been reported to decrease CREB activity in this region (Brunzell et al. 2003, Pandey 2004). Virally mediated overexpression of CREB in the NAc decreases an animal's sensitivity to the rewarding effects of cocaine or morphine, whereas reduction in CREB activity—via overexpression of mCREB, a dominant negative mutant—causes opposite effects (Carlezon et al. 1998, Barrot et al. 2002). Studies utilizing inducible overexpression of CREB or mCREB in bitransgenic mice (McClung & Nestler 2003) or partial genetic knockdown of CREB (Walters & Blendy 2001) have yielded similar findings.

At least some of the CREB-mediated decrease in the rewarding properties of drugs is mediated by the induction of prodynorphin mRNA, which encodes the dynorphin peptides (Cole et al. 1995). Dynorphin acts on  $\kappa$  opioid receptors on VTA neurons to decrease dopamine release (Figure 8). Thus,



**Figure 8**

Induction of dynorphin peptides by dopamine. Cocaine and amphetamine have been shown to activate prodynorphin gene expression in the nucleus accumbens (NAc) and dorsal striatum via D1 dopamine receptors stimulation, the cyclic AMP pathway, and the phosphorylation of CREB (cAMP response element binding protein) (Cole et al. 1995). The resulting dynorphin peptides are transported to presynaptic terminals including terminals found on recurrent collateral axons that feed back on dopaminergic neurons. Dynorphin peptides are agonists at inhibitory  $\kappa$  opiate receptors, resulting in decreased dopamine release. As described in the text, this mechanism may contribute to emotional and motivational aspects of drug withdrawal.

persistent activation of CREB, and the resulting induction of dynorphin, in response to long-term drug exposure would appear to represent a mechanism of tolerance and possibly dependence leading to dysphoria during drug withdrawal (dependence) (Carlezon et al. 2005). The effects of CREB are also mediated via changes in the intrinsic electrical excitability of NAc neurons: CREB overexpression increases excitability of the neurons, whereas mCREB has the opposite effect (Dong et al. 2005). Further work is needed to identify the ion channels that mediate this effect and to understand, at the neural circuit level, how CREB-induced increases in NAc excitability decrease sensitivity to drug reward.

A possible role for CREB in several other brain regions in the addiction process has been mentioned above. The best-established role is in the locus coeruleus, the major noradrenergic nucleus in brain, which normally regulates an animal's attention and vigilance. Opiate induction of CREB in this brain region is one mechanism underlying opiate physical dependence and withdrawal (see *Upregulation of the cAMP Pathway: A Molecular Mechanism of Opiate Dependence*) (Nestler & Aghajanian 1997). CREB is also known to be induced by chronic administration of addictive drugs in the VTA (Olson et al. 2005, Walters et al. 2005), where its effect on drug sensitivity is complex: CREB can either promote or diminish sensitivity to the behavioral effects of cocaine and opiates depending on whether it is induced in more rostral or caudal subregions of this nucleus (Olson et al. 2005). One target gene for CREB in the VTA appears to be GluR1, which may mediate some of the effects of drugs on LTP-like phenomena as discussed above. An important need for future research is to better understand the actions of CREB in amygdala, frontal cortical regions, BNST, and other areas of brain where addictive drugs are known to induce its activity (Shaw-Lutchman et al. 2002, 2003; Brunzell et al. 2003; Pandey 2004).

Addictive drugs are also known to induce members of the Fos family of transcription factors (for references, see McClung et al. 2004). Fos family proteins form heterodimers with Jun family proteins that bind to activator protein-1 (AP-1) sites present within the promoters of certain genes. Fos proteins are encoded by immediate early genes, which show very rapid, but transient, induction in response to diverse types of stimuli. Acute administration of virtually any addictive drug increases the expression of several Fos and Jun family members and increases AP-1 binding activity in the NAc and dorsal striatum (McClung et al. 2004). One possible mechanism of drug action is via dopamine activation of D<sub>1</sub> receptors and the subsequent activation of the cAMP pathway (Konradi et al. 1996), although alternative mechanisms have not been adequately explored. Maximal induction of these Fos proteins occurs within 1–2 h of drug administration and returns to normal levels within 8–12 h, which means that induction of these proteins could contribute to the initial remodeling of synapses that may occur with short-term drug exposure, but this remains hypothetical.

The ability to induce these Fos family proteins in the NAc and dorsal striatum is attenuated upon repeated drug treatment, whereas the increased AP-1 binding activity persists for weeks after drug treatment ceases (Hope et al. 1992, Daunais & McGinty 1994). This persistent AP-1 binding activity is caused by the long-lived expression of biochemically modified isoforms of  $\Delta$ FosB (Hope et al. 1994, Hiroi et al. 1997).  $\Delta$ FosB is a unique Fos family member because of its extraordinary stability, which is mediated in part by its phosphorylation by casein kinase II (see McClung et al. 2004). Sustained induction of  $\Delta$ FosB is a common consequence of long-term drug exposure, which has been documented for cocaine, amphetamine, morphine, nicotine, ethanol, cannabinoids, and phencyclidine.  $\Delta$ FosB could represent a type of molecular switch that contributes to relatively prolonged aspects of drug addiction.

Studies of transgenic mice in which  $\Delta$ FosB, or an antagonist of  $\Delta$ FosB, is induced in adult animals selectively within the NAc and dorsal striatum demonstrate that  $\Delta$ FosB expression increases an animal's sensitivity to the rewarding and locomotor-activating effects of cocaine and morphine and may increase drug seeking as well (Kelz et al. 1999, Colby et al. 2003, Peakman et al. 2003, McClung et al. 2004, Zachariou et al. 2006).  $\Delta$ FosB causes this behavioral phenotype via the regulation of numerous target genes, which are just now beginning to be identified and characterized (McClung & Nestler 2003). Interestingly, some of these target genes have been related to the decreased glutamate sensitivity (Kelz et al. 1999) and increased dendritic spine densities (Norrholm et al. 2003) within NAc neurons.

A major gap in our knowledge is that none of the molecular changes observed after chronic drug exposure persist as long as the altered reward-related behaviors. Thus, even the  $\Delta$ FosB signal, one of the longest-lived molecular changes identified to date, recovers to normal within 6–8 weeks of drug withdrawal. This gap in knowledge is similar to the situation in the broader learning and memory field: As stated above we have little insight into the nature of the highly stable molecular and cellular events that underlie potentially life-long memories. One possibility is that synaptic remodeling could be very stable and outlive the molecular events (e.g., CREB phosphorylation, induction of  $\Delta$ FosB) that first initiated them. Another possibility, not incompatible with the first, is that the initial molecular events may trigger more long-lived changes in the structure of chromatin, which then drive more persistent changes in gene expression, synaptic structure, and ultimately behavior. Post-translational modifications (e.g., acetylation, phosphorylation, methylation) of histones at the promoters of particular genes, and methylation of DNA, may activate or suppress gene expression for long periods of time (Felsenfeld & Groudine 2003). Some modifications in histones at drug-regulated pro-

motors may be mediated by  $\Delta$ FosB (Kumar et al. 2005). These findings support a scheme whereby drug-induced perturbation of cellular signaling pathways in NAc neurons, mediated via dopamine and other neurotransmitter signals of reward, lead to waves of regulation of gene expression. Initial drug exposure causes the rapid activation of transcription factors (CREB, acute Fos-Jun proteins), which gradually gives rise to somewhat different transcription factors induced by repeated drug administration (CREB,  $\Delta$ FosB). These transcription factors, in turn, cause the remodeling of chromatin at specific target genes, which ultimately drives the extremely stable cellular and behavioral plasticity that defines a state of addiction. Work is now needed to probe the validity of this scheme and delineate the specific transcription factors, chromatin remodeling mechanisms, and target genes involved.

## CONCLUSIONS

Much progress has been made in understanding the neural substrates of drug addiction, but much remains to be learned, and much integration needs to go on among information at the molecular, cellular, systems, and behavioral levels. The pursuit of mechanisms underlying addiction has been hampered by the limitations of current animal models and thus requires that basic investigators exchange ideas with those involved in human experimental biology and clinical research. It is clear that neurotransmitters other than dopamine must play important roles in regulating hedonic states and even in reward-related learning. However, the current models of addiction, with dopamine at the center, have proven fruitful. Given its widespread projections within the forebrain, dopamine action can help us understand the progression from pleasurable experimentation with drugs to a long-lived compulsion as persistent associative memories are formed in circuits involving the NAc, PFC, amygdala, and dorsal striatum. The model of addiction as a usurpation of



normal systems of associative memory underlying reward-related learning and behavior has helped organize a great deal of experimental information, as we review here, while providing a compelling notion of what happens in the addicted brain.

## DISCLOSURE OF BIAS

R.M. is on the Scientific Advisory Boards of Merck & Co., Inc. and Renovis, Inc.

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