by increases in dopaminergic synaptic transmission and weakened by decreases. These dopaminergic neurons are excited by glutamatergic cells in the prefrontal cortex and amygdala as well as from cholinergic cells in the laterodorsal tegmental and pedunculopontine nuclei of the hindbrain, and are inhibited by local GABAergic cells within or just caudal to the ventral tegmental area. Brain stimulation is thought to activate dopaminergic neurons in the ventral tegmental area in part through the activation of these hindbrain cholinergic neurons. Blockade of this cholinergic input reduces the rewarding effects of the electrical stimulation. While most attention has focused on dopamine pathways in mediating brain stimulation reward, it is important to emphasize the involvement of non-dopaminergic pathways as well.

The strength of brain stimulation reward is indicated by the finding that starving rats provided with brief daily access to food will forego eating to press a lever for brain stimulation. The heedless pursuit of an artificial goal to the detriment of a biological need is one of many parallels between self-stimulation and drug abuse. Indeed, drugs of abuse augment the rewarding effects of activation of dopaminergic pathways with brain stimulation (Figure 43–1C,D). Lower frequencies of stimulating currents accompanied by cocaine or nicotine administration—both of which enhance dopaminergic neurotransmission through different mechanisms—produce a rate of lever pressing equivalent to that obtained during self-stimulation at higher stimulating currents in the absence of these drugs. These results indicate that cocaine and nicotine amplify the effects of neuronal activation elicited by microstimulation.

Dopamine May Act as a Learning Signal

An earlier view of the function of dopamine was that it conveyed "hedonic signals" in the brain and that, in humans, it was directly responsible for subjective pleasure. From this point of view, addiction would reflect the habitual choice of short-term pleasure despite a host of long-term life problems that emerge. In fact, however, new research indicates that the hedonic principle cannot easily explain the persistence of drug use by addicted persons as negative consequences mount.

The effects of dopamine have proven to be far more complex than was first thought. Dopamine can be released by aversive as well as by rewarding stimuli, and the short latency component of a dopamine neuron's response may not be related to the rewarding or aversive qualities of a stimulus at all. Moreover, rodents lacking dopamine—rats in which dopamine is depleted by 6-hydroxydopamine and mice genetically engineered so that they cannot produce dopamine—continue to exhibit hedonic responses to sucrose. Dopamine delivery itself is not currently considered to produce hedonic qualities. Instead, the degree to which a particular sensory stimulus is rewarding is thought to be processed by a broad network of brain areas, spanning sensory cortices of different modalities, association cortex, prefrontal cortex (in particular, orbitofrontal regions), and many subcortical areas such as the amygdala, hippocampus, nucleus accumbens, and ventral pallidum.

Many of the brain areas whose activity is modulated by reward anticipation or receipt receive dopaminergic input. What information do dopaminergic neurons transmit to these brain areas? Wolfram Schultz and his colleagues discovered that dopaminergic neurons often have a complex and changing pattern of responses to rewards during learning. In one experiment, Schultz trained monkeys to expect juice at a fixed interval after a visual or auditory cue. Before the monkeys learned the predictive cues, the appearance of the juice was unexpected and produced a transient increase in firing above basal levels by ventral tegmental area dopaminergic neurons. As the monkeys learned that certain cues predict the juice, the timing of the firing changed. The neurons no longer fired in response to presentation of the juice—the reward—but earlier, in response to a predictive visual or auditory cue. If a cue was presented but the reward was withheld, firing paused at the time the reward would have been presented. In contrast, if a reward exceeded expectation or was unexpected, because it appeared without a prior cue, firing was enhanced (Figure 43–2).

These observations suggest that dopamine release in the forebrain serves not as a pleasure signal but as a *prediction error* signal. A burst of dopamine would signify a reward or reward-related stimulus that had not been predicted; pauses would signify that the predicted reward is less than expected or absent. If a reward is just as expected based on environmental cues, dopaminergic neurons would maintain their tonic (baseline) firing rates. Alterations in dopamine release are thus thought to modify future responses to stimuli to maximize the likelihood of obtaining rewards and to minimize fruitless pursuits. For natural rewards, like the sweet juice consumed by the monkeys in Schultz's experiments, once the environmental cues for a reward are learned, dopaminergic neuron firing returns toward baseline levels. Schultz has interpreted this to mean that as long as nothing changes in the environment, there is nothing more to learn and therefore no need to alter behavioral responses.

Experiments using functional magnetic resonance imaging in humans have provided further evidence

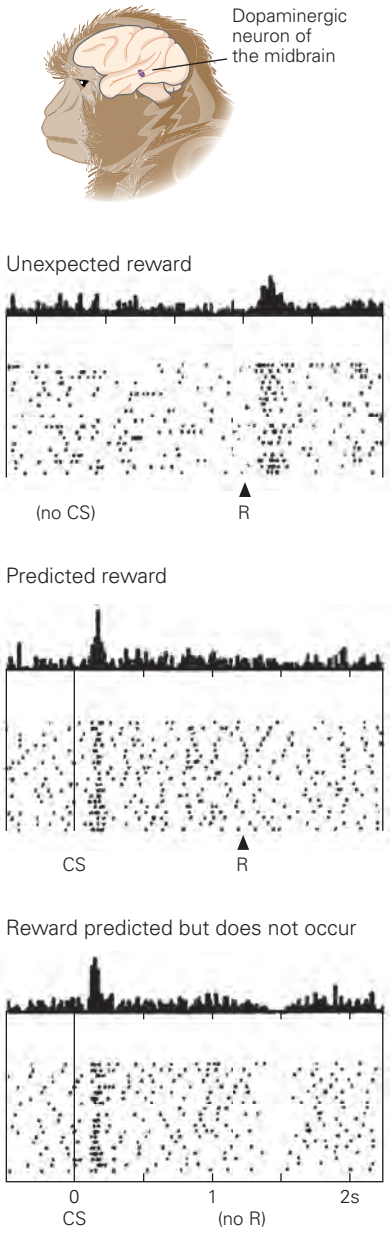

Figure 43–2 Dopaminergic neurons report an error in reward prediction. Graphs show firing rates recorded from midbrain dopaminergic neurons in awake, active monkeys. **Top:** A drop of sweet liquid is delivered without warning to a monkey. The unexpected reward (**R**) elicits a response in the neurons. The reward can thus be construed as a positive error in reward prediction. **Middle:** The monkey has been trained that a conditioned stimulus (**CS**) predicts a reward. In this record, the reward occurs according to the prediction and does not elicit a response in the neurons because there is no error in the prediction of reward. The neurons are activated by the first appearance of a predicting stimulus but not by the reward. **Bottom:** A conditioned stimulus predicts a reward that fails to occur. The dopaminergic neurons show a decrease in firing at the time the reward would have occurred. (Reproduced, with permission, from Schultz, Dayan, and Montague 1997. Copyright © 1997 AAAS.)

that dopaminergic agonists and antagonists modulate reward learning and the blood oxygen level–dependent (BOLD) signal in the nucleus accumbens. However, in some experiments, mice that lack a dopamine synthesis gene can still learn where to find a sugar or cocaine reward, suggesting that dopamine is not required for all forms of reward learning. In addition, rodents who receive amphetamines to elevate presynaptic dopamine levels over a more extended time interval exhibit enhanced "wanting" behavior (ie, increased responding in the presence of a Pavlovian cue predicting sucrose reward).

These considerations have led some investigators to suggest that dopamine has a broader role than simply driving reinforcement learning by providing prediction-error signals. Indeed, several recent studies have demonstrated considerable variation in the response properties of different subpopulations of midbrain dopaminergic neurons. Some neurons are activated by both rewarding and aversive stimuli, while others are activated preferentially by one of the two types of stimuli, and still others show opposite responses (activated by rewards and suppressed by aversive stimuli). There is some evidence that these neuronal differences are related to differences in afferent inputs and efferent projections between subpopulations of dopaminergic neurons. Understanding the precise role of this complex mixture of dopamine signals—in learning, in driving goal-directed behavior, and especially in more complex forms of learning that involve longer timescales of sequences of actions to acquire distant rewards—remains an active area of investigation.

Unlike natural rewards, addictive drugs cause dopamine release in the reward circuitry no matter how often they are consumed, and the magnitude of this release is often greater than that seen with natural rewards—dopamine is released even when the drug no longer produces subjective pleasure. To the brain, consumption of addictive drugs might always signal "better than expected" and in this way would continue to influence behavior to maximize drug seeking and drug taking. If this idea is correct, it might explain why drug seeking and consumption become compulsive and why the life of the addicted person becomes focused increasingly on drug taking at the expense of all other pursuits.

Drug Addiction Is a Pathological Reward State

Drug addiction is a chronic and sometimes fatal syndrome characterized by compulsive drug seeking and consumption despite serious negative consequences such as medical illness and inability to function in the

family, workplace, or society. Many drug addicts are aware of the destructive nature of their addiction but are unable to alter their addictive behavior despite numerous attempts at treatment.

An interesting feature of drug addiction is that only a minute fraction of all chemical substances can cause the syndrome. These so-called drugs of abuse do not share a common chemical structure, and they produce their effects by binding to different protein targets in the brain. Rather, these diverse substances can each cause a similar behavioral syndrome of addiction because their actions converge on the brain circuits that control reward and motivation (Figure 43–3).

Advances in understanding these actions have come about in large part based on studies of laboratory animals that self-administer the same drugs that cause addiction in humans. In fact, when animals are given free and unlimited access to these drugs, a subset will lose control over drug consumption—which becomes increasingly involuntary—at the expense of eating and sleeping, and some will even die by overdose. Drug self-administration and other animal models of addiction (Box 43–1) have made it possible to study both the neural circuitry through which drugs of abuse act to produce their initial rewarding effects and the molecular and cellular adaptations that drugs induce in this circuitry after repeated exposures cause an addiction-like syndrome. Over the past decade, these studies in animals, together with brain imaging studies in human addicts, have provided an increasingly complete view of the addiction process.

All Drugs of Abuse Target Neurotransmitter Receptors, Transporters, or Ion Channels

A great deal is known about the initial interactions of addictive drugs with the nervous system. Virtually all of the proteins with which such drugs interact have been cloned and characterized (Table 43–1).

Each class of drug of abuse produces a different range of acute behavioral effects, consistent with the fact that each class acts on different targets and that these targets have distinct patterns of expression throughout the nervous system and peripheral tissues. Cocaine and other psychostimulants are activating and can cause cardiac side effects because their targets

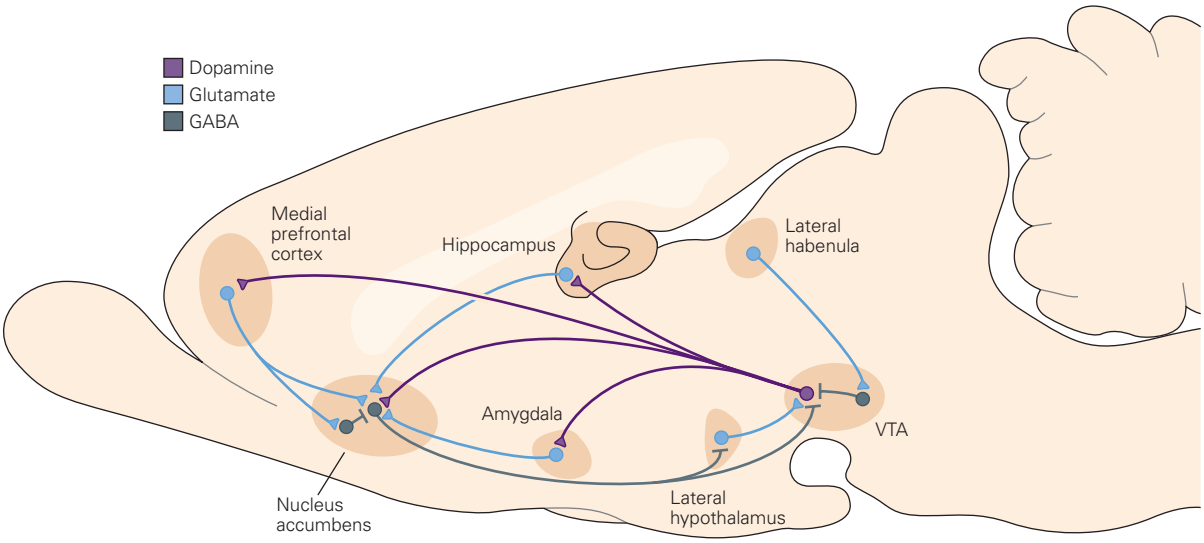

Figure 43–3 Brain reward circuits. A schematic drawing of the major dopaminergic, glutamatergic, and γ-aminobutyric acid (GABA)-ergic connections to and from the ventral tegmental area (VTA) and nucleus accumbens (NAc) in the rodent brain. The primary reward circuit includes dopaminergic projections from the VTA to the NAc. The VTA projections release dopamine in response to reward-related stimuli (and in some cases aversion-related stimuli). There are also GABAergic projections from the NAc to the VTA, with some in a direct pathway innervating the VTA and some in an indirect pathway innervating the VTA via intervening GABAergic neurons in the ventral pallidum (not shown). The NAc also contains numerous types of interneurons. The NAc receives dense innervation from glutamatergic monosynaptic circuits from the medial prefrontal cortex, hippocampus, lateral habenula, and amygdala, among other regions. The VTA receives such inputs from the amygdala and prefrontal cortex and from several brain stem nuclei that use the transmitter acetylcholine (not shown). It also receives the peptidergic terminals of neurons in the lateral hypothalamus as well as other inputs. These various inputs control aspects of reward-related perception and memory. (Adapted from Russo and Nestler 2013.)

Box 43–1 Animal Models of Drug Addiction

Several animal models have played an important role in understanding how addictive drugs produce reward acutely and an addiction-like syndrome after repeated exposures.

Drug Self-administration

The reinforcing effects of a drug can be demonstrated in experiments in which animals perform a task (eg, press a lever) to receive an intravenous drug injection. In addition to studying acquisition of this behavior, scientists assess how hard an animal will work to deliver the drug by use of progressive ratio procedures, where each successive drug dose requires an increasing number of lever presses.

Animals reach a so-called break point when they stop self-administering the drug. After weeks or months of withdrawal from or extinction of drug self-administration, animals display a relapse-like behavior: They will press the stimulation lever, which no longer delivers the drug, in response to a test dose of the drug, cues associated previously with the drug (a light or tone), or stress. These various self-administration behaviors are considered the best-validated models of human addiction.

Conditioned Place Preference

Animals learn to associate a particular environment with passive exposure to drugs. For example, a rodent will spend more time on the side of a box where it was given cocaine than on the side where it received saline. This paradigm offers an indirect measure of potency of a drug reward and demonstrates the strong cue-conditioned effects of addictive drugs.

Locomotor Sensitization

All drugs of abuse stimulate locomotion in rodents upon initial drug exposure, with increasing locomotor activation seen after repeated drug doses. Since the neural circuitry that mediates locomotor responses to drugs of abuse partly overlaps with the circuitry that mediates reward and addiction, locomotor sensitization provides a model with which to study plasticity in this circuitry during a course of chronic drug exposure.

Intracranial Self-Stimulation

Animals will work (eg, press a lever) to deliver electrical current into parts of the brain's reward circuitry (see Figure 43–1). Drugs of abuse reduce the stimulation threshold for such self-stimulation, meaning that in the presence of drug animals will work for stimulation frequencies that have no effect under control conditions.

(monoamine transporters) are expressed in peripheral nerves that innervate the heart. In contrast, opiates are sedatives and potent analgesics because their targets (opioid receptors) are expressed in sleep and pain centers.

Nevertheless, all drugs of abuse acutely induce reward and reinforcement, and this shared action reflects the fact that the drugs, despite their very different initial targets, induce some common functional effects on the brain's reward circuitry (Figure 43–4). The best established of these shared initial effects is increased dopaminergic neurotransmission in the nucleus accumbens, albeit via different mechanisms. For example, cocaine produces this effect by blocking dopamine reuptake transporters located on the terminals of the ventral tegmental neurons, whereas opiates activate ventral tegmental area dopamine neuron cell bodies by inhibiting nearby GABAergic interneurons.

Opiates also produce reward through dopamine-independent actions (eg, by activating opioid receptors on nucleus accumbens neurons themselves). All other drugs of abuse act through a combination of dopamine-dependent and -independent mechanisms (eg, activation of endogenous opioid and cannabinoid signaling) to produce some of the same functional effects on nucleus accumbens neurons. Importantly, by increasing dopaminergic neurotransmission, all such drugs also produce some of the same functional effects mediated by activation of dopamine receptors on the many other projection targets of ventral tegmental dopamine neurons (Figure 43–3), actions that are also instrumental in reward and in initiating some of the deleterious actions of repeated drug exposure.

Repeated Exposure to a Drug of Abuse Induces Lasting Behavioral Adaptations

The acute rewarding actions of drugs of abuse do not account for addiction. Rather, addiction is mediated by the brain's adaptations to the repeated exposure to such acute actions. Two main questions in the field

Table 43–1 Major Classes of Addictive Drugs

Class	Source	Molecular target	Examples
Opiates	Opium poppy	μ opioid receptor (agonist)[1]	Morphine, methadone, oxycodone, heroin, many others
Psychomotor stimulants	Coca leaf Synthetic[2] Synthetic	Dopamine transporter (antagonist)[3]	Cocaine Amphetamines Methamphetamine
Cannabinoids	Cannabis	CB1 cannabinoid receptors (agonist)	Marijuana
Nicotine	Tobacco	Nicotinic acetylcholine receptor (agonist)	Tobacco
Ethyl alcohol	Fermentation	$GABA_A$ receptor (agonist), NMDA-type glutamate receptor (antagonist), and multiple other targets	Various beverages
Phencyclidine-like drugs	Synthetic	NMDA-type glutamate receptor (antagonist)	Phencyclidine (PCP, angel dust)
Sedative/hypnotics	Synthetic	$GABA_A$ receptor (positive allosteric modulator)	Barbiturates, benzodiazepines
Inhalants	Varied	Unknown	Glues, gasoline, nitrous oxide, others

[1]The signaling pathways induced by μ receptor activation differ between opiates, differences that might be related to different addiction liabilities. Additionally, most opiates activate the δ opioid receptor, although the action at μ receptors is most important for reward and addiction.
[2]The original synthesis of amphetamine was based on the natural plant product ephedrine.
[3]While cocaine is an antagonist of the transporter, amphetamine and methamphetamine act differently: They are substrates for the transporter and, once in the nerve terminal cytoplasm, act to stimulate dopamine release.
GABA, γ-aminobutyric acid; **NMDA**, *N*-methyl-D-aspartate.
Note: Caffeine can produce mild physical dependence but does not result in compulsive use. Some illegal drugs that are abused can be harmful but do not generally produce addiction; these include the hallucinogens lysergic acid diethylamide (LSD), mescaline, psilocybin, and 3,4-methylenedioxymethamphetamine (MDMA), popularly known as ecstasy.

remain: What specific adaptations mediate the behavioral syndrome of addiction, and why are some individuals more likely to become addicted?

We know—in both animals and humans—that roughly 50% of the risk for addiction across all drugs of abuse is genetic, but the specific genes that confer risk remain largely unknown. As for most other common chronic conditions, the genetic risk for addiction is highly complex, reflecting the combined actions of hundreds of genetic variations, each of which has a very small effect. The other 50% of the risk, while incompletely understood, involves a host of environmental factors including early life stress, stress throughout life, and peer pressure.

Historically, the adaptations induced by repeated drug exposure have been described by a series of pharmacological terms. *Tolerance* refers to the diminishing effect of a drug after repeated administration at the same dose or to the need for an increase in dose to produce the same effect. *Sensitization*, also known as reverse tolerance, occurs when repeated administration of the same drug dose elicits escalating effects. *Dependence* is defined as an adaptive state that develops in response to repeated drug administration and is unmasked during *withdrawal*, which occurs when drug taking stops. The symptoms of withdrawal vary from drug to drug and include effects opposite to a drug's acute actions. Tolerance, sensitization, and dependence/withdrawal are seen with many drugs that are not addicting. For instance, two drugs used to treat hypertension, the β-adrenergic antagonist propranolol and the α_2-adrenergic agonist clonidine, produce strong dependence as evidenced by severe hypertension upon their sudden withdrawal.

Drugs of abuse are unique in causing tolerance, sensitization, and dependence/withdrawal in reward- and motivation-related behaviors, and these behaviors contribute to the syndrome of addiction. Reward tolerance, which can be viewed as homeostatic suppression of endogenous reward mechanisms in response to repeated drug exposure, is one factor leading to escalating patterns of drug use. Motivational dependence, which is manifested as negative emotional (eg, depression- and anxiety-like) symptoms seen during early drug withdrawal and also mediated by

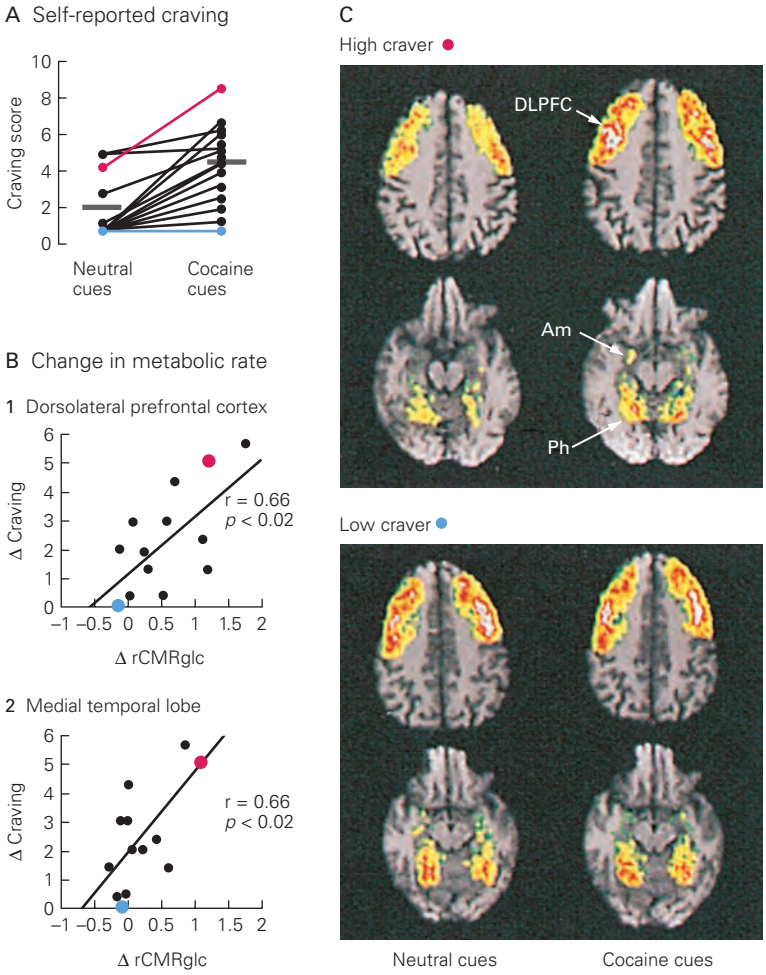

Figure 43–4 Positron emission tomography (PET) imaging reveals neural correlates of cue-induced cocaine craving. (Adapted, with permission, from Grant et al. 1996.)

A. Subjects were shown neutral or cocaine-related cues and asked, "How do you rate your craving or urge for cocaine on a scale of 1–10?" The mean craving score (**horizontal bar**) is significantly higher for exposure to cocaine-related cues than for exposure to neutral stimuli, even though the magnitude of the response across individuals varies considerably. Two subjects, identified by **red** and **blue dots**, represent high-level and low-level craving, respectively.

B. Changes in self-reported craving are correlated with changes in metabolic rate in the dorsolateral prefrontal cortex and medial temporal lobe during exposure to cocaine-related cues. The abscissa plots the difference in metabolic rate between the two sessions (activity with cocaine cues minus activity with neutral cues). Metabolic rate is measured as the regional cerebral metabolic rate for glucose (**rCMRglc**). The ordinate plots the difference between the average of the responses to the question, "Do you have a craving or urge for cocaine?" in separate sessions with neutral and cocaine-related cues. (Each session lasted 30 minutes, and in each session, the question was asked three times.)

C. When subjects report a craving for cocaine, metabolic activity increases in the dorsolateral prefrontal cortex (**DLPFC**) and in two medial temporal lobe structures, the amygdala (**Am**) and parahippocampal gyrus (**Ph**). Pseudocolored PET images of metabolic activity are spatially aligned with high-resolution structural magnetic resonance images. Metabolic rate markedly increased in the amygdala and parahippocampal gyrus in one subject who reported a large increase in craving during presentation of cocaine-related cues (**red dots** in parts **A** and **B**). This effect is not evident in a subject who reported no increase in craving while exposed to the cocaine-related cues (**blue dots** in parts **A** and **B**). Metabolic activity outside the dorsolateral prefrontal cortex and medial temporal lobe is not shown.

suppressed endogenous reward mechanisms, is a leading factor in driving the return to drug use, or *relapse*. Reward sensitization, which typically occurs after longer withdrawal periods, can trigger relapse in response to exposure to the drug itself or to drug-associated cues (eg, being with people or in a place where drug was previously used).

Interestingly, a given drug can produce all of these adaptations—tolerance, sensitization, and dependence—simultaneously, due to different acute effects of the drug; this phenomenon emphasizes the involvement of multiple cell types and circuits in mediating a drug's global actions. The key challenge for neuroscientists is to identify the changes in specific types of neurons and glia—and in their consequent contributions to circuit function—that are induced by repeated drug exposure and that mediate the behavioral features that define a state of addiction.

Lasting Molecular Adaptations Are Induced in Brain Reward Regions by Repeated Drug Exposure

An extensive literature shows that repeated exposure to a drug of abuse in animal models alters the levels of many neurotransmitters and neurotrophic factors, their receptors and intracellular signaling pathways, and transcriptional regulatory proteins throughout the brain's reward circuitry. Most of these changes cannot be studied in living patients—only a small number of neurotransmitters and receptors can be assessed in patients with brain imaging—although studies of postmortem human brain tissue are being used increasingly to validate findings from animal models. Most of the reported research has focused on the ventral tegmental area and nucleus accumbens, although an increasing number of studies are examining other parts of the reward circuitry.

The most robust experimental findings are available for psychostimulants and opiates, probably because the changes induced by these drugs are larger in magnitude than those of other drugs of abuse. This likely reflects the greater inherent addictiveness of psychostimulants and opiates: With equivalent exposures, a larger fraction of people will become addicted to these drugs as compared with other classes of abused substances. Nevertheless, given the dominant public health consequences of alcohol, nicotine, and marijuana addictions, more attention should be given to these drugs.

Below, we summarize this large literature by focusing on a small number of drug-induced adaptations that have been linked causally to specific behavioral features of addiction in animal models. As will be clear in the next section, the present research focus is on relating these and many other molecular changes to synaptic and circuit adaptations also implicated in addiction.

Upregulation of the cAMP-CREB Pathway

Several drugs of abuse activate G_i protein–linked receptors, such as the D_2 dopamine receptor; the μ, δ, and κ opioid receptors; and the CB1 cannabinoid receptor. This means that, to a certain extent, many drugs of abuse will activate G_i protein–linked signaling pathways, with effects such as inhibition of adenylyl cyclase (Chapter 14), in the nucleus accumbens and other target neurons.

Work over the past two decades has established that, after repeated exposure, the affected neurons adapt to this sustained suppression of the cyclic adenosine monophosphate (cAMP) pathway by upregulating it, including induction of certain isoforms of adenylyl cyclase and protein kinase A. Repeated drug exposure likewise induces upregulation of the transcription factor CREB, which is normally activated by the cAMP pathway. Such upregulation of the cAMP-CREB pathway can be seen as a molecular mechanism of tolerance and dependence: It restores normal activity of these pathways despite the presence of a drug (tolerance and dependence), and when the drug is removed, the upregulated pathway is unopposed, causing abnormally high activity of the pathway (withdrawal) (Figure 43–5). Indeed, upregulation of the cAMP-CREB pathway in nucleus accumbens neurons has been shown to mediate both reward tolerance and motivational dependence and withdrawal in animal models.

Induction of ΔFosB

ΔFosB is a member of the Fos family of transcription factors. It is a truncated product of the *FosB* gene generated through alternative splicing. In contrast to all other members of the Fos family, which are induced rapidly and transiently in response to many perturbations in neural activity or cell signaling, ΔFosB is induced only slightly by initial presentation of stimuli. However, with repeated drug exposure, ΔFosB accumulates in neurons because of its unusual stability, unique among all Fos family proteins.

This phenomenon occurs within neurons of the nucleus accumbens and several other brain reward areas after repeated exposure to virtually any drug of abuse, including cocaine and other psychomotor stimulants, opiates, nicotine, ethanol, cannabinoids, and phencyclidine. Recent studies involving the selective

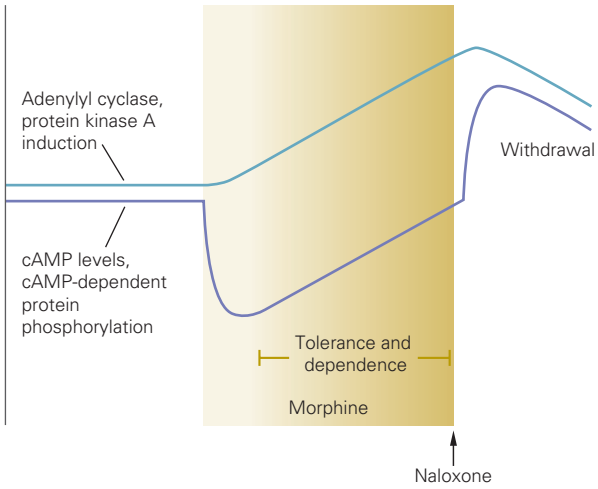

Figure 43–5 Upregulation of the cAMP-CREB pathway is a molecular mechanism underlying drug tolerance and dependence. Morphine or other μ opioid receptor agonists acutely inhibit the functional activity of the cyclic adenosine monophosphate (**cAMP**) pathway in brain reward neurons, as indicated, for example, by cellular levels of cAMP or protein kinase A (PKA)–dependent phosphorylation of substrates such as CREB. With continued drug exposure (**shading**), functional activity of the cAMP-CREB pathway is gradually upregulated and increases far above control levels upon removal of the drug (eg, by administration of the μ opioid receptor antagonist naloxone). These changes in the functional state of the cAMP-CREB pathway are mediated via the induction of adenylyl cyclase and PKA and activation of PKA substrates such as CREB in response to repeated drug administration. Induction of these proteins accounts for the gradual recovery in the functional activity of the cAMP-CREB pathway seen during chronic drug exposure (tolerance and dependence) and for the elevated activity of the cAMP-CREB pathway seen upon removal of the drug (withdrawal). First demonstrated for opiate drugs, similar regulation is seen in response to several other types of drugs of abuse. (Reproduced, with permission, from Nestler et al. 2020.)

expression or knockdown of ΔFosB in the nucleus accumbens of adult mice have provided direct evidence that induction of ΔFosB mediates reward sensitization, including increased drug self-administration and relapse. This is yet another example of a common adaptation to drugs of abuse that contributes to aspects of addiction shared across numerous drugs of abuse.

CREB and ΔFosB are two of many transcription factors implicated in drug addiction. Ongoing research is focused on characterizing the chromatin regulatory mechanisms through which these factors cooperate to regulate the expression of specific genes in the affected neurons and glia. Work is also underway to understand how these target genes drive their associated behavioral abnormalities via altered expression of proteins involved in synaptic, cell, and circuit function (Figure 43–6).

Lasting Cellular and Circuit Adaptations Mediate Aspects of the Drug-Addicted State

Repeated exposure to a drug of abuse can alter a neural circuit in two major ways. One mechanism, referred to as whole-cell or homeostatic plasticity, involves altering the intrinsic excitability of a nerve cell that will ultimately alter functioning of the larger circuit of which it is a part. It is easy to imagine how whole-cell plasticity in neurons within the brain's reward circuitry might mediate aspects of reward tolerance, sensitization, and dependence and withdrawal.

The other mechanism is synaptic plasticity, where connections between particular neurons are either strengthened or weakened. These synapse-specific adaptations could mediate the features of addiction that involve maladaptive memories, such as memories of the association of drug exposure with a host of environmental cues. This pathological learning and memory can increasingly focus an individual on the drug at the expense of natural rewards. Most attention in the field to date has concentrated on synaptic plasticity.

Synaptic Plasticity

As discussed elsewhere in this book, two major forms of synaptic plasticity have been described at glutamatergic synapses: *long-term depression* (LTD) and *long-term potentiation* (LTP). Over the past two decades, the molecular basis of both adaptations has been established, with distinct mechanisms underlying each of several distinct subtypes of LTD and LTP that occur throughout the nervous system. We now know that several types of drugs of abuse, in particular psychomotor stimulants and opiates, cause LTD- and LTP-like changes at particular classes of glutamatergic synapses in the brain's reward circuitry, with most work to date focused on the ventral tegmental area and nucleus accumbens.

Changes in the nucleus accumbens show interesting time-dependent adaptations as a function of drug withdrawal. At early withdrawal points (hours to days), glutamatergic synapses on neurons of the nucleus accumbens display LTD-like changes, which evolve into LTP-like changes after longer periods of withdrawal (weeks to months). Drug-induced LTD- and LTP-like adaptations in the nucleus accumbens involve morphological changes similar to those in other brain regions (mostly the hippocampus and cerebral cortex) where LTD and LTP occur in association with morphological changes in individual dendritic spines. During early withdrawal, LTD-like responses occur coincidently with increased numbers of

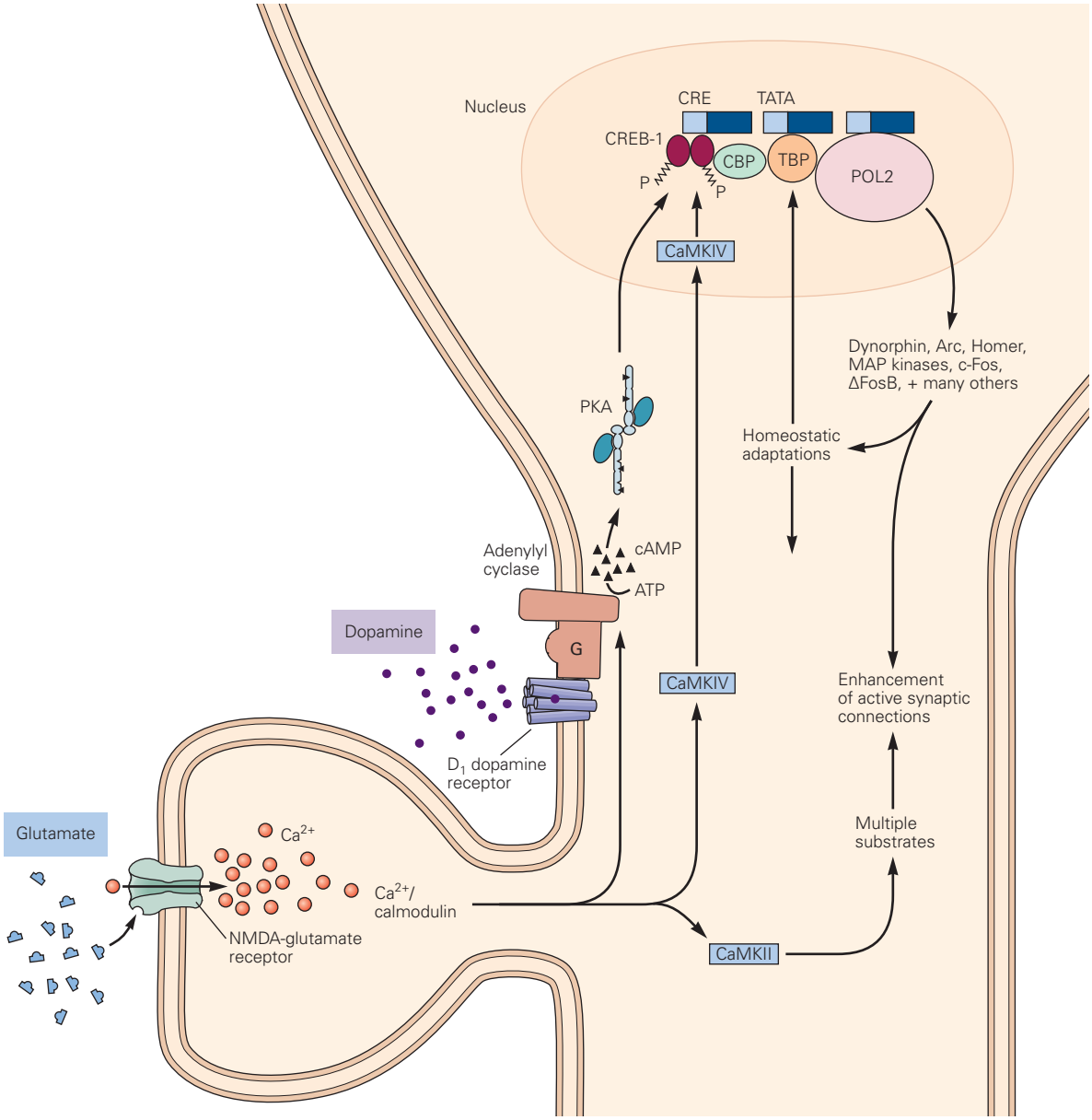

Figure 43–6 Dopamine- and glutamate-activated intracellular signaling pathways implicated in drug addiction. NMDA-type glutamate receptors permit Ca^{2+} entry, which binds calmodulin. The Ca^{2+}/calmodulin complex activates two types of Ca^{2+}/calmodulin-dependent protein kinases, CaMKII in the cytoplasm and CaMKIV in the cell nucleus. Certain dopamine receptors activate a stimulatory G protein that in turn activates adenylyl cyclase to produce cyclic adenosine monophosphate (**cAMP**). The cAMP-dependent protein kinase A (**PKA**) catalytic subunit can enter the nucleus. Once activated in the nucleus, both PKA and CaMKIV phosphorylate and thus activate cAMP response element binding protein (**CREB**). CREB recruits CREB-binding protein (**CBP**) and many other chromatin regulatory proteins and thereby activates the RNA polymerase II–dependent transcription of many genes, giving rise to proteins that can alter cellular function. Arc and Homer are localized in synaptic regions; mitogen-activated protein (**MAP**) kinases are protein kinases that control numerous cellular processes; Fos and ΔFosB are transcription factors; and dynorphin is a type of endogenous opioid peptide. These proteins are thought to contribute both to homeostatic responses to excessive dopamine stimulation and to the morphological and functional changes in synapses associated with memory formation. (Abbreviations: **ATP**, adenosine triphosphate; **NMDA**, *N*-methyl-D-aspartate; **POL 2**, RNA polymerase 2; **TBP**, TATA binding protein.)