Addiction can be defined as drug-induced changes in the central nervous system (CNS) that produce maladaptive alterations in spontaneous behavior and in the behavioral response to readministration of that drug. Maladaptive behaviors include those identified as criteria for addiction in the DSM-IV. In general what most psychiatric metrics describe as addiction associated behaviors is the emergence of behaviors to obtain drug reward at the expense of engaging in behaviors to seek natural rewards, ranging from biological rewards such as sex to cultural rewards such as stable personal relationships. The substitution of drug reward for natural reward suggests that the neuropathology of addiction may reside in the same neural systems that mediate the detection and acquisition of natural rewards. This postulate forms a primary premise in the search for the neurobiological basis of addiction, and has revealed a circuit consisting of interconnections among limbic cortex, basal ganglia, and brainstem nuclei that is pathologically modified by repeated drug administration. The drug-induced changes in the structure and function of this circuit are progressive, and to some extent parallel the development of the behavioral characteristics of addiction.

Over the last decade neurobiologists have come to describe the behavioral transition to addiction as a drug-induced neuroplastic process (1–3). In parallel with the development and expression of addictive behaviors, the neurobiology of these two components of the transition to addiction can be described as: (a) the sequence of molecular events that establish the neuroplastic changes leading to addiction, and (b) the neuroplastic changes themselves. Accordingly, a number of molecular neuroplastic alterations have been identified in the brain after repeated drug administration, and some of these appear to be important in the development and/or expression of addictive behaviors. However, the process of identifying drug-induced changes is accelerating and producing a deluge of information that is proving increasingly difficult to integrate into a coherent sequence of neuroplastic changes that mediate addiction. In part the difficulty of integration arises because the veracity of each molecular neuroplastic event must be tested in animal models of addiction; a labor-intensive process often employing imprecise tools for selective \textit{in vivo} manipulation of cell biology. Moreover, this problem is compounded by the fact that the neuroadaptations associated with use of a drug of abuse are not entirely predicated on the pharmacology of the drug. It has become increasingly clear that in addition to drug pharmacology, the environmental regulation of the drug-induced changes is a critical factor in the development and expression of addiction (4–6).

Although a critical role for environment in the manifestation of addicted behaviors has been obvious for decades in the behavioral evaluation of addiction in humans and animal models, only recently has the drug–environment interface been directly evaluated as critical in the cellular neuroadaptations mediating addiction (7,8). The realization that the neuroplasticity defining addiction arises as a collaboration between repeated drug administration and environmental associations is contributing to the construction of a template to help organize and integrate the emerging tide of data that describes the cellular adaptations potentially mediating addiction. Figure 95.1 illustrates how learning to associate environmental stimuli with the molecular action of a drug impinges on brain circuitry to elicit neuroplastic changes producing addiction. Figure 95.1 is used to organize this chapter into the three current arenas of investigation into the neurobiology of addiction: (a) the molecular site of action by a drug and the immediate consequences of drug administration to intracellular signaling and synaptic transmission; (b) the circuitry involved in learning and how this integrates with the molecular action of drugs of abuse; and (c) the overall circuitry of reward that contains both molecular sites of drug action and learning circuits, and forms the site of pathologic change mediating addiction.

**PHARMACOLOGY**

**Molecular Binding Site of the Drug**

The molecular site of action and the immediate sequence of cellular events have been successfully decoded for many...
drugs of abuse. Ethanol remains a notable exception where a number of candidate binding sites are currently being evaluated for a role in addiction. In contrast, for many drugs of abuse a reasonably accurate portrait of site of action has emerged. Over the last two decades a common direct or indirect action by drugs on dopamine transmission in the projection from the ventral mesencephalon (ventral tegmental area, VTA) to the forebrain has consistently been proposed and experimentally evaluated (8–11). This historic focus arose from studies employing lesions and the administration of dopamine receptor antagonists that converged on the potential importance of the dopamine projections in mediating natural, electrical, and drug reward. Figure 95.2 illustrates the dopamine projections most frequently evaluated in this regard and includes axon terminations in the amygdala, nucleus accumbens, prefrontal cortex (PFC), and ventral pallidum that arise from cell bodies in the VTA. Examination of the known binding sites for drugs of abuse reveals for some drugs a clear relationship between drug binding site and dopamine transmission (Fig. 95.3). Thus, amphetamine-like psychostimulants inhibit the binding of dopamine to the dopamine transporter and thereby elevate extracellular dopamine (12,13). Nicotine binds directly to acetylcholine nicotinic receptors on dopamine cells to increase the firing frequency of the mesocorticolimbic dopamine neurons (14). μ-opioid receptors are found in high density on presynaptic terminals of GABAergic interneurons and GABAergic axonal afferents to the VTA (15–19). Stimulation of these receptors inhibits the tonic and stimulated release of GABA, thereby increasing the firing frequency of the dopamine neurons. Alcohol modulates GABA-gated chloride conductance, as well as sodium and calcium conductances gated by glutamate (20,21). By promoting chloride conductance and inhibiting glutamate gated sodium and calcium fluxes alcohol is generally found to be inhibitory on neuronal activity. However, electrophysiologic and neurochemical studies reveal that alcohol increases dopamine cell firing and dopamine release in axon terminal fields via an action within the VTA (22–25). Thus,
it has been hypothesized that alcohol may act preferentially on GABAergic interneurons in the VTA to disinhibit dopamine cells. Moreover, recent evidence demonstrates that the capacity of alcohol to elevate dopamine transmission is blocked by opioid receptor antagonists (26). This indicates that alcohol is directly or indirectly increasing enkephalin release in the VTA, thereby disinhibiting dopamine cell firing. Indeed, this mechanism is likely to contribute to the therapeutic efficacy of opioid antagonist naltrexone in attenuating relapse in alcohol addiction (27,28).

By inhibiting the NMDA subtype of the glutamate receptor, phencyclidine may decrease the activity of GABAergic interneurons in the VTA and thereby activate dopamine cell firing (29). Although these data strongly indicate a common action of drugs of abuse to stimulate dopamine transmission, notable exceptions exist. Of the major classes of drugs of abuse, the allosteric GABA receptor agonists, including benzodiazepines and barbiturates, do not appear to stimulate dopamine cells or increase dopamine release (30). Also, although systemic administration of μ-opioids clearly activates dopamine transmission by disinhibiting dopamine cell activity, it is equally clear that stimulating μ-opioid receptors located postsynaptic to the dopamine projection in the nucleus accumbens is sufficient to elicit behaviors that are characteristic of addiction (31–34). Thus, the historic focus on dopamine transmission has identified an initial substrate for most drugs of abuse. However, the exceptions to this rule point clearly to the conclusion that, although an action on dopamine transmission may be a sufficient substrate to initiate drug-induced neuroplasticity relevant to addiction, other substrates are also sufficient.

Evaluating potential nondopaminergic substrates for initiating addiction-related neuroplasticity points most directly to modulating GABA transmission. Figure 95.2 illustrates that dopamine terminals in the nucleus accumbens synapse on GABAergic cells. Moreover, these GABAergic cells innervate GABAergic neurons in the VP. Indeed, Fig. 95.2 shows that there is a topographically organized interconnection among the nucleus accumbens, VP, and VTA that is GABAergic (35,36). Given the apparent importance of modulating dopamine transmission in this circuit in the neuroplasticity leading to addiction, it seems reasonable that directly modulating the GABAergic subcircuit with opioids or allosteric GABAergic agonists may also produce neuroplastic changes relevant to the development of addiction. Although substantial evidence exists for μ-opioids that this is true (31–34), this hypothesis has not yet been evaluated for benzodiazepines or barbiturates.

**Pharmacologic Versus Physiologic Release of Dopamine**

Studies in animal models measuring the *in vivo* release of dopamine with microdialysis reveal that natural rewarding or aversive stimuli increase dopamine release in the nucleus accumbens (6,37–42). However, the physiologic release of dopamine stimulated by environmental stimuli is of substantially less magnitude and duration than the pharmacologic release elicited by most drugs of abuse (22,43–47). The importance of excessive pharmacologic release of dopamine can be extrapolated from what is known about the behavioral situations that elicit physiologic activation of mesoaccumbens dopamine transmission. Dopamine release and cell firing are increased by the presentation of novel and motivationally relevant environmental stimuli (6,48).

This has contributed to the notion that enhanced dopamine release in the nucleus accumbens signals the appearance of an important event that requires the creation and engagement of an adaptive behavioral strategy. This signal is supplied to numerous forebrain structures constituting the limbic cortex and basal ganglia (Fig. 95.2) and presumably initiates the recruitment of cortically derived memories and cognitive strategies, as well as motor output. In doing so, dopamine plays a role in initiating and establishing neuroplastic changes associated with developing behavioral strategies necessary to adapt to novel stimuli. One characteristic of the activation of dopamine transmission by environmental stimuli is that the release of dopamine diminishes with repeated exposure to the same stimulus as the organism establishes an adaptive behavioral response (40,49,50). Thus, dopamine contributes to the establishment of neuroplastic changes that mediate behavioral adaptation to relevant environmental stimuli, but may not be necessary for the expression of those behaviors. Rather, once a behavioral response to a stimulus has been established, the stimulus elicits the behavior via interactions among the limbic cortex, thalamus, and basal ganglia, with less involvement by mesocorticolimbic dopamine transmission (51,52). The transition from dopamine-dependent to behaviors less dependent on dopamine is illustrated in Fig. 95.4 as the transition in neural substrates mediating behavioral responding to a novel and familiar stimulus.

Given the apparent role of dopamine release in establishing adaptive behavioral responses and the magnitude of dopamine release elicited by most drugs of abuse, it is perhaps not surprising that nonphysiologic neuroadaptations ensue, culminating in the maladaptive behaviors characteristic of addiction. Moreover, given that the physiologic release of dopamine is elicited by novel and salient environmental stimuli to facilitate the creation of enduring behavioral strategies, it is reasonable that the pharmacologic magnitude of drug-induced release would result in the addict developing potent learned associations between the dopamine-releasing drug experience and environmental stimuli. This strong association may contribute to the intense cravings that can be induced by environmental stimuli the addict has learned to associate with the drug experience.
FIGURE 95.4. Changes in the role of mesencephalic versus cortical input to the nucleus accumbens with repeated exposure to natural motivational stimuli (A) and drug reward (B). Both a novel stimulus and acute drug administration increase dopamine transmission. After repeated exposure the natural stimulus produces little or no increase in extracellular dopamine and the behavioral response to the stimulus arises primarily from cortical and allocortical interactions with the basal ganglia. Similarly, repeated drug use results in a recruitment of cortico-accumbens circuitry, but is also associated with augmented dopamine transmission. It is postulated that a portion of the pathology of addiction arises from both an overstimulated cortico-accumbens projection and a hyperresponsive mesoaccumbens dopamine projection.

LEARNING

Circuitry of Learning

A complete review of the current knowledge of the neural circuitry involved in learning and memory is beyond the scope of this chapter (53–56); however, it is clear that cortical regions receiving dopaminergic axon terminations, such as the prefrontal and anterior cingulate cortex and allocortical nuclei (including the hippocampus and amygdala) play distinct yet integrated roles in memory and learning. As illustrated in Fig. 95.2, these cortical and allocortical nuclei have relatively dense glutamatergic projections to the nucleus accumbens and synapse on the same neurons that receive dopaminergic afferents from the VTA (57,58). This arrangement provides an anatomic substrate whereby learned information can be integrated and guide adaptive behavioral responding to environmental stimuli. Whether or not these glutamatergic afferents to the nucleus accumbens influence the behavioral effects of drugs of abuse and play a role in the neuroplasticity associated with the development and expression of addictive behaviors is a subject of much recent interest (13,59). For example, antagonists of the NMDA subtype of glutamate receptors block the development of behavioral neuroadaptations (e.g., behavioral sensitization of motor activity) to the repeated administration of most drugs of abuse, including alcohol, psychostimulants, and opioids (59,60). Moreover, it has been shown that drug craving induced in addicts by environmental stimuli previously paired with the drug experience is associated with metabolic activation of the anterior cingulate and amygdala (4,61,62). The apparent recruitment of glutamatergic cortical regions by a drug-associated stimulus concurrent with the manifestation of behavioral characteristics of addiction argues for a transition from primarily dopamine-dependent behaviors elicited by acute drug administration to primarily glutamate-dependent behaviors produced by drug or environmental stimuli in drug addicts. Thus, as illustrated in Fig. 95.4, the development of addiction may consist in part of a transition from dopamine- to glutamate-dependent behaviors akin to what occurs during adaptation to biologically relevant environmental stimuli, such as food, sex, and stress. However, given the initial pharmacologic activation of dopamine transmission produced by most drugs of abuse, the ensuing recruitment of cortical glutamatergic neurons may also contain nonphysiologic constituents that contribute to the pathology of addiction. Moreover, repeated administration of most drugs of abuse, including psychostimulants, opioids, alcohol, and nicotine, increases the capacity of subsequent drug administration to release dopamine in the nucleus accumbens (2,63,65). This neurochemical reverse-tolerance or sensitization is opposite to what typically occurs with repeated exposure to motivationally relevant environmental stimuli, such as food, sex, and stress, and probably also contributes to the expression of addiction-related behaviors. Of note, the indirect measurement of dopamine release using methylphenidate-induced displacement of radiolabeled D2 receptor antagonist revealed an apparent decrease in dopamine release in cocaine addicts compared with control subjects (66). Assuming the veracity of D2 ligand displacement as an in vivo
measure of dopamine release (67), this indicates a potentially important distinction between data in animal models and human cocaine addicts.

**NEUROPLASTICITY**

**Motivational Circuitry as a Site of Addiction Pathologies**

The circuit shown in Fig. 95.2 contains interconnections among mesencephalic dopamine, cortical glutamate, and subcortical (basal ganglia) GABA neurons that can permit the transition from dopamine- to glutamate-dependent behaviors. This circuit has been a focus for research aimed at determining how the neuroplastic changes produced in various nuclei by repeated drug action at a molecular level are integrated with environmental stimuli to form the maladaptive behaviors characteristic of addiction. Studies in this regard are most numerous for psychostimulants; the findings employing this class of addictive drugs provide the primary buttresses of the model. However, emerging data with other drugs of abuse are generally consistent with this view; moreover, there is an abundance of behavioral data supporting the possibility that the neuroplastic changes elicited by repeated administration of one drug impinge on circuity shared with a different drug of abuse. For example, the repeated administration of some drugs of abuse promotes the acquisition of addiction-related behaviors to another mechanistically similar drug of abuse (68,69). Similarly, a number of overlapping cellular neuroadaptations, such as changes in G proteins, tyrosine hydroxylase, and certain immediate early genes, have been identified after repeated exposure to different drugs of abuse (70–73). Also, a number of studies indicate behavioral and neurochemical overlap between the effects of repeated drug administration and motivationally relevant environmental stimuli (e.g., cross-sensitization and cross-tolerance to stress) (65,69,74,75).

**Drug-Induced Changes in Presynaptic and Postsynaptic Dopamine Transmission**

As described in the preceding, most addictive drugs produce significant elevations in cortical and subcortical dopamine transmission, and repeated drug-induced dopamine release causes enduring alterations in presynaptic and postsynaptic dopamine transmission. These changes have been characterized using animal models of addiction, including behavioral sensitization studies involving repeated investigator administered drug, as well as studies in which the acquisition, maintenance, and reinstatement of drug self-administration is measured (9,76,77). The majority of studies have endeavored to identify changes in nucleus accumbens dopamine transmission. However, in light of evidence implicating cortical and allocortical brain regions in addiction, more recent studies have come to focus dopamine innervation of the prefrontal cortex and amygdala. In general, in animal models the repeated administration of drugs of abuse, including amphetamine-like psychostimulants, alcohol, nicotine, and opioids, produces an enduring increase in the capacity of subsequent drug injection or an environmental stimulus, such as stress or sex, to release dopamine in the nucleus accumbens (13,37,63–65). The enhanced releasability may result in part from increased excitability of dopamine cells (24,78–80), but also clearly involves increased presynaptic release, as evidence by the enhanced release of dopamine from synaptosomes or after direct drug administration into the accumbens (81,82). Following repeated amphetamine and cocaine administration the elevated presynaptic release of dopamine arises from enhanced presynaptic calcium signaling through calmodulin kinase II (83–85). A number of enduring changes in postsynaptic dopamine signaling have also been identified. Most of these changes can be traced to alterations in gene expression following stimulation of the D1 receptor-signaling cascade (2,86). Interestingly, among the genes showing changed expression are protein products, including preprodynorphin, NAC-1, and delta-Fos-B, that appear to dampen enhanced dopamine transmission and/or the expression of behaviors potentially related to addiction, such as motor sensitization and conditioned place preference (87–89). This poses the likelihood that many changes produced by repeated drug administration are not necessarily promoting addictive behaviors but may constitute homeostatic alterations to minimize the impact of pathologic neuroadaptations elicited by repeated drug injection. In addition to changes in gene expression in the nucleus accumbens that affect dopamine transmission, repeated administration of psychostimulants also increases or decreases the synthesis of proteins affecting glutamate transmission that may alter postsynaptic corticofugal neurotransmission (see the following). This includes drug-induced changes in glutamate receptor subunits, as well as proteins involved in the trafficking and signaling of glutamate receptors (13,59,90,91).

In addition to the nucleus accumbens, more recent studies have examined the effect of repeated drug administration on dopamine transmission in the PFC. In general, repeated systemic drug administration reduces the releasability of dopamine in the PFC. Such a blunting of stimulus- or drug-induced dopamine transmission in the PFC has been most clearly shown after repeated cocaine and phenycyclidine administration (50,92). Further implicating reduced cortical dopamine transmission, destruction of dopamine afferents to or blockade of dopamine receptors in the PFC promotes behavioral sensitization and drug self-administration (93–95). Moreover, the blunting of PFC dopamine transmission may be related to the cognitive dysfunction and increased impulsivity often associated with drug addiction (96).

The effect of repeated drug administration has also been evaluated in the amygdala, and in contrast with the PFC an
augmentation or no change in drug-stimulated dopamine release after repeated drug administration has been observed (97,98). Although the effect of repeated drug administration on dopamine release in the PFC and amygdala differs, the changes in dopamine transmission in both structures may contribute to expression of addictive behavior. Although reduced dopamine transmission in the PFC may contribute to cognitive dysfunction in some addicts (see the preceding), enhanced release of dopamine in the amygdala may contribute to the strong learned associations made between drug taking and environmental stimuli that have been repeatedly paired with drug taking. Supporting this possibility, stimulation of dopamine transmission in the amygdala increases stimulus-reward associations, whereas the inhibition of dopamine transmission blocks cue-induced reinstatement of lever pressing for cocaine (99,100). Thus, the sensitized release of dopamine in the amygdala may contribute to cue-induced relapse, a conclusion directly supported by imaging studies showing that drug craving in addicts is associated with metabolic activation of the amygdala (4,61,62), and in experimental animal models where drug-associated cues have been shown to increase glucose uptake or c-fos synthesis in the amygdala (101,102).

**Prefrontal and Anterior Cingulate Cortex**

As outlined above, there is an enduring change in dopamine transmission in the PFC associated with repeated administration of some drugs of abuse. Efforts to deduce the effect of dopamine transmission in the PFC have generally revealed that the actions of dopamine are state-dependent. This is reflected by distinct electrophysiologic effects of dopamine when pyramidal cells in the cortex are relatively active or inactive (e.g., up or down state) and by a biphasic dose–response effect of dopamine agonists and antagonists on cognition (103,104). Although the effects of dopamine are state-dependent, dopamine clearly has the capacity to modulate excitatory glutamatergic projections to the nucleus accumbens and VTA (105–107). Thus, the long-term alterations in PFC dopamine transmission by repeated drug use change corticofugal glutamate transmission.

A variety of emerging data indicate that glutamatergic projections to the nucleus accumbens and VTA may be altered by repeated drug administration and that this is consequential in behaviors associated with addiction. Thus, repeated cocaine administration elicits a reduction in basal extracellular glutamate in the nucleus accumbens, whereas subsequent drug exposure results in enhanced glutamate release in both the nucleus accumbens and VTA that depends on dopamine receptor stimulation (108–110). Moreover, the blockade of glutamate receptors in the nucleus accumbens inhibits the expression of behavioral sensitization to cocaine, as well as the capacity of systemic cocaine to elicit drug craving using a reinstatement model of craving in rodents (108,111). Also, lesions of the PFC have been shown to block behavioral sensitization to cocaine and morphine, as well as increase extracellular glutamate produced by cocaine in cocaine-pretreated subjects (13,112). Taken together with the imaging data in human cocaine addicts showing an association between cocaine craving and metabolic activity in the anterior cingulate cortex (4,61), the data to date point toward a critical role in addiction for neuroadaptations in glutamate transmission in the projection from the PFC to the mesoaccumbens dopamine system. Moreover, recent studies may indicate a prepotent role in cocaine addiction for glutamate over dopamine in the nucleus accumbens, although a role for this projection has been more difficult to demonstrate for some drugs of abuse, notably amphetamine (59).

**Amygdala-Thalamo-Cortical Circuit**

There is substantial evidence for a role by the amygdala in mediating the conditioning of behavior to obtain a natural or drug reward (99,113,114). Thus, pharmacologically inhibiting neurotransmission within the amygdala prevents the capacity of a cocaine cue to elicit drug-seeking behavior in rodents, and amygdala lesions blunt the expression of conditioned place preference produced by many drugs of abuse. There are two likely connections from the amygdala that are mediating the relationship between learned associations and rewarding stimuli. The first is an interconnected relationship with the amygdala, mediodorsal thalamus, and PFC. Various data suggest that this subcircuit is critical for the formation of learned associations with rewarding stimuli (115). The second connection is among the amygdala, VTA, and nucleus accumbens. Although this subcircuit is important in unconditioned responses to most drugs of abuse (see the preceding), many studies indicate that it is critical for the expression of behaviors elicited by conditioned stimuli to obtain reward, as well as cue-induced drug relapse (114). Although both circuits probably contribute to stimulus-induced drug relapse, the relative role of each may depend on the type of stimulus. For example, relapse precipitated by a low dose of drug, especially a drug known to activate dopamine transmission, is likely to involve the dopamine projection from the VTA to the amygdala, whereas cue-induced relapse may be more involved with the influence the amygdala brings to bear on the thalamocortical projection (99,111).

**CONCLUSION AND FUTURE DIRECTIONS**

The last decade has witnessed the emergence of a number of seminal developments in our understanding of the circuitry mediating addiction. Primary among these is that there exists substantial overlap in the circuits mediating behavioral responses to non-drug and drug reward (Figs. 95.2 and 95.4), and that the pathology of addiction arises to a great
extent from neuroplasticity within this common circuit. The second critical development is that neuroplasticity to
drug reward arises from an interaction between the molecul-
ar site of drug action and environmental stimuli associated
with the effect of the drug. In this way, cortical and allocorti-
cal circuitry important in learning and memory is recruited
and undergoes neuroplastic alterations in response to drugs
of abuse. The studies outlined in this chapter describe
changes in neurotransmission and cell signaling that may
be critical in changing the functional status of the circuit
illustrated in Fig. 95.2. Accompanying these intracellular
and neurochemical neuroadaptations, it is also important
to note the recent studies of Robinson and coworkers (116,
117), which show that akin to normal learning, repeated
exposure to psychostimulants or opioids produces morpho-
logic changes in dendritic branching and synaptic connect-
ity in many nuclei (Fig. 95.2). Although neurobiologists
are well engrossed in identifying neuroplastic changes in
various nuclei (Fig. 95.2), there is a lag in understanding
how these alterations result in a change in the function of
the circuit as a whole. The circuit shown in Fig. 95.2 is
highly interconnected and topographically organized (35,
36). Thus, a change in the function of a cell group in one
nucleus is likely to impact on the status of neurons in other
nuclei. Predicting and experimentally evaluating these sec-
ondary interactions and how they determine the appearance
of addictive behavior will be the arena of study over the
next decade. This arena can be approached from molecular
technologies at one end and imaging studies at the other.
The imaging experiments help to define functional subcircuits
within the overall reward and learning circuitry, whereas
the molecular studies can identify specific cellular
neuroadaptations. Using pharmacologic and genetic manip-
ulations these specific cellular neuroadaptations can be evalu-
ated in vivo animal models of addiction to determine the
relevance of the changes in addictive behaviors and on cellular
adaptations in interconnected nuclei within the reward and
learning circuits.

As an initial foray into integrative thinking it is becoming
clear that there is a distinction between the effects of acute
drug and repeated administration on the circuit shown in
Fig. 95.2. In the analysis of the literature outlined in the preceding,
this distinction was characterized as a transition
from dopamine-dependent effects to behaviors more depend-
ent on cortical glutamate transmission. Although this is
an oversimplification based on too few experiments using
too few classes of drugs of abuse, it is similar to the physio-
logic neuroadaptive processes associated with the develop-
ment of habitual behavioral responses to previously novel
motivationally relevant natural stimuli (Fig. 95.4). More-
over, involvement of cortical and allocortical brain regions
in addiction imparts a mandate that future researchers to
consider the neurobiology of learning and memory as an
equal partner with drug neuropharmacology in developing
effective therapy for addiction.

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