

# NEUROCIRCUITRY OF ADDICTION

PETER W. KALIVAS

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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

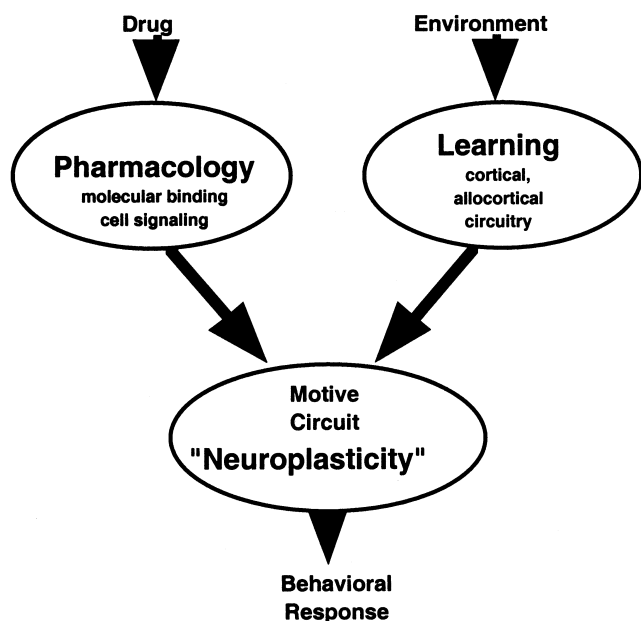
part the difficulty of integration arises because the veracity of each molecular neuroplastic event must be tested in animal models of addiction; a labor-intensive process often employing imprecise tools for selective *in vivo* manipulation of cell biology. Moreover, this problem is compounded by the 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

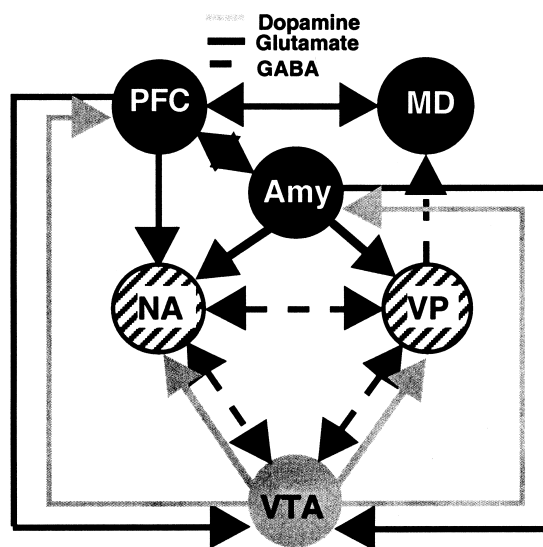
### Molecular Binding Site of the Drug

The molecular site of action and the immediate sequence of cellular events have been successfully decoded for many



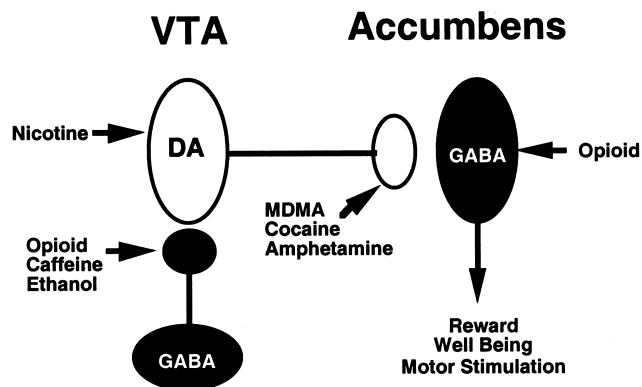
**FIGURE 95.1.** Collaboration between the pharmacology of a drug of abuse and environmental stimuli. Depiction of the impact that both the molecular binding site of a drug and environmental stimuli have on the neuroplasticity associated with drug addiction.

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).  $\mu$ -opioid receptors are found in high density on presynaptic terminals of GABAergic interneu-



**FIGURE 95.2.** The circuit thought to be critical for mediating both natural and drug reward behavior. Amy, amygdala; MD, mediodorsal thalamus; NA, nucleus accumbens; PFC, prefrontal cortex; VP, ventral pallidum; VTA, ventral tegmental area.

rons 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,



**FIGURE 95.3.** Sites of action by addictive drugs to augment mesoaccumbens dopamine transmission.

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 GABAA receptor agonists, including benzodiazepines and barbiturates, do not appear to stimulate dopamine cells or increase dopamine release (30). Also, although systemic administration of  $\mu$ -opioids clearly activates dopamine transmission by disinhibiting dopamine cell activity, it is equally clear that stimulating  $\mu$ -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.

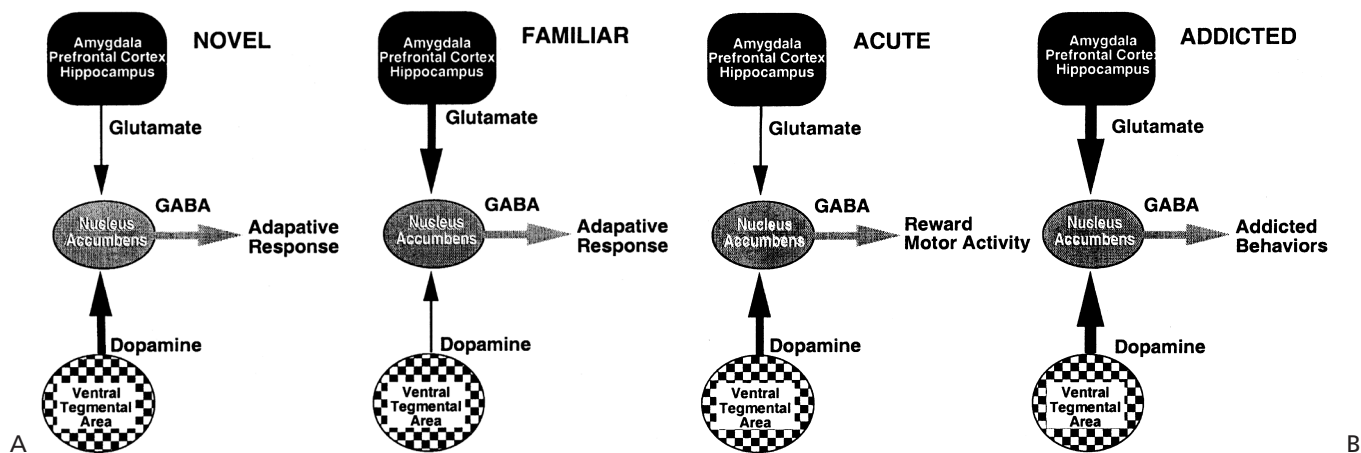
Evaluating potential nondopaminergic substrates for initiating addiction-related neuroplasticity points most directly to modulating GABA transmission. Figure 95.2 illustrates that dopamine terminals in the nucleus accumbens synapse on GABAergic cells. Moreover, these GABAergic cells innervate GABAergic 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  $\mu$ -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 circuitry 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 phencyclidine 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 molecular site of drug action and environmental stimuli associated with the effect of the drug. In this way, cortical and allocortical 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 morphologic changes in dendritic branching and synaptic connectivity 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 secondary 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 manipulations these specific cellular neuroadaptations can be evaluated *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 dependent 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 physiologic neuroadaptive processes associated with the development of habitual behavioral responses to previously novel motivationally relevant natural stimuli (Fig. 95.4). Moreover, 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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## REFERENCES

1. Koob GF, Nestler EJ. The neurobiology of drug addiction. *J Neuropsychiatry Clin Neurosci* 1997;9:482–497.
2. White FJ, Kalivas PW. Neuroadaptations involved in amphetamine and cocaine addiction. *Drug Alcohol Depend* 1998;51:141–154.
3. Nestler EJ, Hope BT, Widnell KL. Drug addiction: a model for the molecular basis of neural plasticity. *Neuron* 1993;11:995–1006.
4. Childress AR, Mozley PD, McElgin W, et al. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 1999;156:11–18.
5. O'Brien CP, Childress AR, McLellan AT, et al. Classical conditioning in drug-dependent humans. *Ann NY Acad Sci* 1992;654:400–415.
6. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Rev* 1998;28:309–369.
7. Kalivas P, Cornish J, Ghasemzadeh M. Cocaine craving and paranoia: a combination of pharmacology and learning. *Psychiatry Ann* 1998;28:569–576.
8. Berke J, Hyman S. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 2000;25:515–532.
9. Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res Rev* 1986;11:157–198.
10. Wise RA, Rompre PP. Brain dopamine and reward. *Annu Rev Psychol* 1989;40:191–215.
11. Koob GF, Goeders NE. Neuroanatomical substrates of drug self-administration. In: Cooper SJ, Lieberman JM, eds. *The neuropharmacological basis of reward*. Clarendon, UK: Oxford Press, 1989:214–263.
12. Reith MEA, Meisler BE, Sershen H, et al. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. *Biochem Pharmacol* 1986;35:1123–1129.
13. Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res Rev* 1997;25:192–216.
14. Mereu G, Yoon K-WP, Boi V, et al. Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. *Eur J Pharmacol* 1987;141:395–399.
15. Gysling K, Wang RY. Morphine-induced activation of A10 dopamine neurons in the rat brain. *Brain Res* 1983;277:119–127.
16. Dilts RP, Kalivas PW. Autoradiographic localization of mu-opioid and neurotensin receptors within the mesolimbic dopamine system. *Brain Res* 1989;488:311–327.
17. Westfall TC, Mereu G, Vickery L, et al. Regulation by nicotine of midbrain dopamine neurons. *Prog Brain Res* 1989;79:173–185.
18. Clarke PBS, Pert A. Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. *Brain Res* 1985;348:355–358.
19. Nisell M, Nomikos GG, Svensson TH. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regu-

- lated by nicotinic receptors in the ventral tegmental area. *Synapse* 1994;16:36–44.
20. Lovinger DM. Alcohols and neurotransmitter gated ion channels: past, present and future. *Naunyn-Schmiedeberg's Arch Pharmacol* 1997;356:267–282.
  21. Fadda F, Rossetti Z. Chronic ethanol consumption: from neuroadaptation to neurodegeneration. *Progr Neurobiol* 1998;56:385–431.
  22. Yim HJ, Schallert T, Randall PK, et al. Comparison to local and systemic ethanol effects on extracellular dopamine concentration in rat nucleus accumbens by microdialysis. *Alcohol Clin Exp Res* 1998;22(2):367–374.
  23. Bunney E, Appel S, Brodie M. Cocaine potentiates ethanol-induced excitation of dopaminergic reward neurons in the ventral tegmental area. *J Pharmacol Exp Ther* 2000;293(2):383–389.
  24. Bailey CP, Manely SJ, Watson S, et al. Chronic ethanol administration alters activity in ventral tegmental area neurons after cessation of withdrawal hyperexcitability. *Brain Res* 1998;803(1, 2):144–152.
  25. Brodie M, McElvain M, Bradshaw Bunney E, et al. Pharmacological reduction of small conductance calcium-activated potassium current (sK) potentiates the excitatory effect of ethanol on ventral tegmental area dopamine neurons. *J Pharmacol Exp Ther* 1999;290(1):325–333.
  26. Gonzales RA, Weiss F. Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. *J Neurosci* 1998;18(24):10663–10671.
  27. Weinrieb R, O'Brien C. Naltrexone in the treatment of alcoholism. *Annu Rev Med* 1997;48:477–487.
  28. Swift R. Drug therapy for alcohol dependence. *N Engl J Med* 1999;340:1482–1490.
  29. French ED, Ceci A. Non-competitive N-methyl-D-aspartate antagonists are potent activators of ventral tegmental A10 dopamine neurons. *Neurosci Lett* 1990;119:159–162.
  30. Zhang H, Weng X, Rosenberg HC. Characterization of substantia nigra pars reticulata neurons based on response to iontophoretically applied GABA and flurazepam. *Life Sci* 1993;53:1911–1919.
  31. Olds ME. Reinforcing effects of morphine in the nucleus accumbens. *Brain Res* 1982;237:429–440.
  32. Ettenberg A, Pettit HO, Bloom FE, et al. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. *Psychopharmacology* 1982;78:204–209.
  33. Svingos AL, Moriwaki A, Wang JB, et al. mu-opioid receptors are localized to extrasynaptic plasma membranes of GABAergic neurons and their targets in the rat nucleus accumbens. *J Neurosci* 1997;17:2585–2594.
  34. David V, Cazala P. Anatomical and pharmacological specificity of the rewarding effect elicited by microinjections of morphine into the nucleus accumbens of mice. *Psychopharmacology* 2000;150(1):24–34.
  35. Mogenson GJ, Brudzynski SM, Wu M, et al. From motivation to action: A review of dopaminergic regulation of limbic-nucleus accumbens-pedunclopontine nucleus circuitries involved in limbic-motor integration. In: Kalivas PW, Barnes CD, eds. *Limbic motor circuits and neuropsychiatry*. Boca Raton, FL: CRC Press, 1993:193–236.
  36. Kalivas PW, Churchill L, Klitenick MA. The circuitry mediating the translation of motivational stimuli into adaptive motor responses. In: Kalivas PW, Barnes CD, eds. *Limbic motor circuits and neuropsychiatry*. Boca Raton, FL: CRC Press, 1993:237–287.
  37. Mitchell JB, Gratton A. Opioid modulation and sensitization of dopamine release elicited by sexually relevant stimuli: a high-speed chronoamperometric study in freely behaving rats. *Brain Res* 1990;551:20–27.
  38. Tabor MT, Fibiger HC. Feeding-evoked dopamine release in the nucleus accumbens: regulation by glutamatergic mechanisms. *Neuroscience* 1997;76:1105–1112.
  39. Mermelstein PG, Becker JB. Increased extracellular dopamine in the nucleus accumbens and striatum of the female rat during paced copulatory behavior. *Behav Neurosci* 1995;109:354–365.
  40. Cabib S, Puglisi-Allegra S. Different effects of repeated stressful experiences on mesocortical and mesolimbic dopamine metabolism. *Neuroscience* 1996;73:375–380.
  41. Doherty MD, Gratton A. NMDA receptors in nucleus accumbens modulate stress-induced dopamine release in nucleus accumbens and ventral tegmental area. *Synapse* 1997;26:225–234.
  42. Kalivas PW, Duffy P. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. *Brain Res* 1995;675:325–328.
  43. Richardson NR, Gratton A. Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. *J Neurosci* 1996;16:8160–8169.
  44. Kuczenski RSD. Dynamic changes in sensitivity occur during the acute response to cocaine and methylphenidate. *Psychopharmacology* 1999;147(1):96–103.
  45. Marshall DL, Redfern PH, Wonnacott S. Presynaptic nicotinic modulation of dopamine release in the three ascending pathways studied by in vivo microdialysis: comparison of naive and chronic nicotine-treated rats. *J Neurochem* 1997;68:1511–1519.
  46. Kalivas PW, Duffy P, White S. MDMA elicits behavioral and neurochemical sensitization in rats. *Neuropsychopharmacology* 1998;18:469–479.
  47. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common m1 opioid receptor mechanism. *Science* 1997;276:2048–2050.
  48. Schultz W. Predictive reward signal of dopamine neurons. *Am J Physiol* 1998;80:1–27.
  49. Deutch AY, Tam S-Y, Roth RH. Footshock and conditioned stress increase in 3,4-dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not substantia nigra. *Brain Res* 1985;333:143–146.
  50. Sorg BA, Davidson DL, Kalivas PW, et al. Repeated daily cocaine alters subsequent cocaine-induced increase of extracellular dopamine in the medial prefrontal cortex. *J Pharmacol Exp Ther* 1997;281:54–61.
  51. Graybiel A. The basal ganglia and chunking of action repertoires. *Neurobiol Learning Memory* 1998;70:119–136.
  52. Jog M, Kubota Y, Connolly C, et al. Building neural representations of habits. *Science* 1999;286:1745–1749.
  53. Silva A, Geise K, Fedorov N, et al. Molecular, cellular and anatomical substrates of place learning. *Neurobiol Learning Memory* 1998;70:44–61.
  54. McGaugh J. Memory—a century of consolidation. *Science* 2000;287:248–251.
  55. Becker J, Morris R. Working memory(s). *Brain Cogn* 1999;41:1–8.
  56. Eichenbaum H. The hippocampus and mechanisms of declarative memory. *Behav Brain Res* 1999;103:123–139.
  57. Sesack SR, Pickel VM. In the medial nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. *Brain Res* 1990;527:266–272.
  58. Sesack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminal in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. *J Comp Neurol* 1992;320:145–160.



59. Wolf ME. The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Progr Neurobiol* 1998; 54(6):679–720.
60. Vanderschuren L, Kalivas P. Alterations in dopaminergic and glutamatergic signaling in the induction and expression of behavioral sensitization. *Psychopharmacology* 2000;151:99–120.
61. Grant S, London ED, Newlin DB, et al. Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci USA* 1996;93:12040–12045.
62. Kilts CD, Schweitzer JB, Quinn CK, et al. Functional anatomy of drug craving in human cocaine addiction. *Am J Psychiatry* 1998.
63. Nurmi M, Ashizawa T, Sinclair JD, et al. Effect of prior ethanol experience on dopamine overflow in accumbens of AA and ANA rats. *Eur J Pharmacol* 1996;315(3):277–283.
64. Szumlinski K, Maisonneuve I, Glick S. The potential anti-addictive agent, 18 methoxycoronaridine, blocks the sensitized locomotor and dopamine responses produced by repeated morphine treatment. *Brain Res* 2000;864(1):13–23.
65. George TP, Verrico CD, Roth RH. Effects of repeated nicotine pre-treatment on mesoprefrontal dopaminergic and behavioral responses to acute footshock stress. *Brain Res* 1998;801(1–2): 36–49.
66. Volkow N, Wang G, Fowler J, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature* 1997;386:830–833.
67. Wang G, Volkow N, Fowler J, et al. Reproducibility of repeated measures of endogenous dopamine competition with [<sup>11</sup>C]raclopride in the human brain in response to methylphenidate. *J Nucl Med* 1999;40:1285–1291.
68. Horgor BA, Giles MK, Schenk S. Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. *Psychopharmacology* 1992;107:271–276.
69. Itzhak Y, Martin JL. Effects of cocaine, nicotine, dizocilpine and alcohol on mice locomotor activity: cocaine-alcohol cross-sensitization involves upregulation of striatal dopamine transporter binding sites. *Brain Res* 1999;818(2):204–211.
70. Beitner-Johnson D, Guitart X, Nestler EJ. Common intracellular actions of chronic morphine and cocaine in dopaminergic brain reward regions. In: Kalivas PW, Samson HH, eds. *The neurobiology of drug and alcohol addiction* (Annals of the New York Academy of Sciences, Volume 654). New York: New York Academy of Science, 1992:70–87.
71. Nestler E, Aghajanian G. Molecular and cellular basis addiction. *Science* 1997;278:58–63.
72. Bonci A, Williams JT. A common mechanism mediates long-term changes in synaptic transmission after chronic cocaine and morphine. *Neuron* 1996;16:631–639.
73. Erdtmann-Vourliotis M, Mayer P, Riechert U, et al. Prior experience of morphine application alters the *c-fos* response to MDMA ('ecstasy') and cocaine in the rat striatum. *Mol Brain Res* 2000;77(1):55–64.
74. Prasad BM, Ulibarri C, Sorg BA. Stress-induced cross-sensitization to cocaine: effect of adrenalectomy and corticosterone after short- and long-term withdrawal. *Psychopharmacology* 1998; 136:24–33.
75. Mitchell JB, Stewart J. Facilitation of sexual behaviors in the male rat associated with intra-VTA injections of opiates. *Pharmacol Biochem Behav* 1990;35:643–650.
76. Segal DS, Schuckit MA. Animal models of stimulant-induced psychosis. In: Creese I, ed. *Stimulants: neurochemical, behavioral, and clinical perspectives*. New York: Raven Press, 1983:131–167.
77. Markou A, Weiss F, Gold LH, et al. Animal models of drug craving. *Psychopharmacology* 1993;112:163–182.
78. Zhang X-F, Hu X-T, White FJ, et al. Increased responsiveness of ventral tegmental area dopamine neurons to glutamate after repeated administration of cocaine or amphetamine is transient and selectively involves AMPA receptors. *J Pharmacol Exp Ther* 1997;281:699–706.
79. Corrigal WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Res* 1994;653:278–284.
80. Gallegoa RA, Lee R-S, Criado JR, et al. Adaptive responses of  $\gamma$ -aminobutyric acid neurons in the ventral tegmental area to chronic ethanol. *J Pharmacol Exp Ther* 1999;291(3): 1045–1052.
81. Ohmori T, Abekawa T, Koyama T. Environment modifies the expression of behavioral sensitization produced by methamphetamine: behavioral and neurochemical studies. *Behav Pharmacol* 1995;6:133–142.
82. Pierce RC, Kalivas PW. Amphetamine produces sensitized locomotion and dopamine release preferentially in the nucleus accumbens shell of rats administered repeated cocaine. *J Pharmacol Exp Ther* 1996;275:1019–1029.
83. Pierce RC, Kalivas PW. Repeated cocaine modifies the mechanism by which amphetamine releases dopamine. *J Neurosci* 1997;17:3254–3261.
84. Iwata S-I, Hewlett GHK, Ferrell ST, et al. Enhanced dopamine release and phosphorylation of synapsin I and neuromodulin in striatal synaptosomes after repeated amphetamine. *J Pharmacol Exp Ther* 1997;283:1445–1452.
85. Kantor L, Hewlett Keikilani GH, et al. Enhanced amphetamine- and K<sup>+</sup>-mediated dopamine release in rat striatum after repeated amphetamine: differential requirements for Ca<sup>2+</sup> and calmodulin-dependent phosphorylation and synaptic vesicles. *J Neurosci* 1999;19(10):3801–3808.
86. Nestler EJ, Aghajanian GK. Molecular and cellular basis of addiction. *Science* 1997;278:58–63.
87. Mackler SA, Korutla L, Cha XY, et al. NAC-1 is a brain POZ/BTB protein that can prevent behavioral sensitization in rat. *J Neurosci* 2000;20:6210–6217.
88. Hurd YL, Herkenham M. Molecular alterations in the neostriatum of human cocaine addicts. *Synapse* 1993;13:357–369.
89. Ketz M, Chen, J, Carlezon WA, et al. Expression of the transcription factor *dFosB* in the brain controls sensitivity to cocaine. *Nature* 1999;401:272–276.
90. Brakeman PR, Lanahan AA, O'Brien R, et al. Homer: a protein that selectively binds metabotropic glutamate receptors. *Nature* 1997;386:221–223.
91. O'Brien R, Xu D, Petralia RS, et al. Synaptic clustering of AMPA receptors by the extracellular immediate early gene product *Narp*. *Neuron* 1999;23:309–323.
92. Jentsch JD, Taylor JR, Elsworth JD, et al. Altered frontal cortical dopaminergic transmission in monkeys after subchronic phencyclidine exposure: involvement in frontostriatal cognitive deficits. *Neuroscience* 1999;90(3):823–832.
93. Beyer CE, Steketee JD. Dopamine depletion in the medial prefrontal cortex induces sensitized-like behavioral and neurochemical responses to cocaine. *Brain Res* 1999;833(2):133–141.
94. Vezina P, Blanc G, Glowinski J, et al. Blockade of D-1 dopamine receptors in the medial prefrontal cortex produces delayed effects on pre- and postsynaptic indices of dopamine function in the nucleus accumbens. *Synapse* 1994;16:104–112.
95. Schenk S, Horgor BA, Peltier R, et al. Supersensitivity to the reinforcing effects of cocaine following 6-hydroxydopamine lesions to the medial prefrontal cortex in rats. *Brain Res* 1991; 543:297–235.
96. Jentsch K, Taylor J. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* 1999;146: 373–390.
97. Tran-Nguyen LTL, Fuchs RA, Coffey GP, et al. Time-depen-

- dent changes in cocaine-seeking behavior and extracellular dopamine levels in the amygdala during cocaine withdrawal. *Neuropsychopharmacology* 1998;19:48–59.
98. Harmer CJ, Hitchcott PK, Morutto SL, et al. Repeated d-amphetamine enhances stimulated mesoamygdaloid dopamine transmission. *Psychopharmacology* 1997;132:247–254.
  99. Grimm J, See R. Dissociation of primary and secondary reward-relevant limbic nuclei in an animal model of relapse. *Neuropsychopharmacology* 2000;22(5):473–479.
  100. Hitchcott P, Harmer C, Phillips G. Enhanced acquisition of discriminative approach following intra-amygdala d-amphetamine. *Psychopharmacology* 1997;132:237–246.
  101. Brown EE, Robertson GS, Fibiger HC. Evidence for conditional neuronal activation following exposure to a cocaine-paired environment: role of forebrain limbic structures. *J Neurosci* 1992;12:4112–4121.
  102. Neisewander JL, Baker DA, Fuchs RA, et al. Fos protein expression and cocaine seeking behavior in rats after exposure to a cocaine self-administration environment. *Neuroscience* 2000;20(2):798–805.
  103. Yang C, Seamans J, Gorelova N. Developing a neuronal model for the pathology of schizophrenia based on the nature of electrophysiological actions of dopamine in the prefrontal cortex. *Neuropsychopharmacology* 1999;21(2):161–194.
  104. Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 1995;376:572–575.
  105. Taber MT, Das S, Fibiger HC. Cortical regulation of subcortical dopamine release: mediation via the ventral tegmental area. *J Neurochem* 1995;65:1407–1410.
  106. Karreman M, Moghaddam B. The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. *J Neurochem* 1996;66:589–598.
  107. Brake W, Flores G, Francis D, et al. Enhanced nucleus accumbens dopamine and plasma corticosterone stress responses in adult rats with neonatal excitotoxic lesions to the medial prefrontal cortex. *Neuroscience* 2000;96(4):687–695.
  108. Pierce RC, Bell K, Duffy P, et al. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J Neurosci* 1996;16:1550–1560.
  109. Reid MS, Hsu KJ, Berger SP. Cocaine and amphetamine preferentially stimulate glutamate release in the limbic system: studies on the involvement of dopamine. *Synapse* 1997;27:95–105.
  110. Kalivas PW, Duffy T. Repeated cocaine administration alters extracellular glutamate levels in the ventral tegmental area. *J Neurochem* 1998;70:1497–1502.
  111. Cornish J, Kalivas P. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neurosci* 2000;20:RC89.
  112. Tzschentke T, Schmidt W. Differential effects of discrete sub-area-specific lesions of the rat medial prefrontal cortex on amphetamine- and cocaine-induced behavioral sensitization. *Cereb Cortex* 2000;10:488–498.
  113. Brown EE, Fibiger HC. Differential effects of excitotoxic lesions of the amygdala on cocaine-induced conditioned locomotion and conditioned place preference. *Psychopharmacology* 1993;113:123–130.
  114. Everitt BJ, Robbins TW. Amygdala-ventral striatal interactions and reward-related processes. In: Aggleton JP, ed. *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction*. New York: Wiley-Liss, 1992:401–429.
  115. Gaffan D, Murray EA. Amygdala interaction with the medio-dorsal nucleus of the thalamus and the ventromedial prefrontal cortex in stimulus-reward associative learning in the monkey. *J Neurosci* 1990;8:3144–3150.
  116. Robinson TE, Kolb B. Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. *J Neurosci* 1997;17:8491–8497.
  117. Robinson T, Kolb B. Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats. *Synapse* 1999;33(2):160–162.