

The Neural Basis of Addiction: A Pathology of Motivation and Choice

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Objective: A primary behavioral pathology in drug addiction is the overpowering motivational strength and decreased ability to control the desire to obtain drugs. In this review the authors explore how advances in neurobiology are approaching an understanding of the cellular and circuitry underpinnings of addiction, and they describe the novel pharmacotherapeutic targets emerging from this understanding.

Method: Findings from neuroimaging of addicts are integrated with cellular studies in animal models of drug seeking.

Results: While dopamine is critical for acute reward and initiation of addiction, end-stage addiction results primarily from cellular adaptations in anterior cingulate and orbitofrontal glutamatergic projections to the nucleus accumbens. Patho-

physiological plasticity in excitatory transmission reduces the capacity of the prefrontal cortex to initiate behaviors in response to biological rewards and to provide executive control over drug seeking. Simultaneously, the prefrontal cortex is hyperresponsive to stimuli predicting drug availability, resulting in supraphysiological glutamatergic drive in the nucleus accumbens, where excitatory synapses have a reduced capacity to regulate neurotransmission.

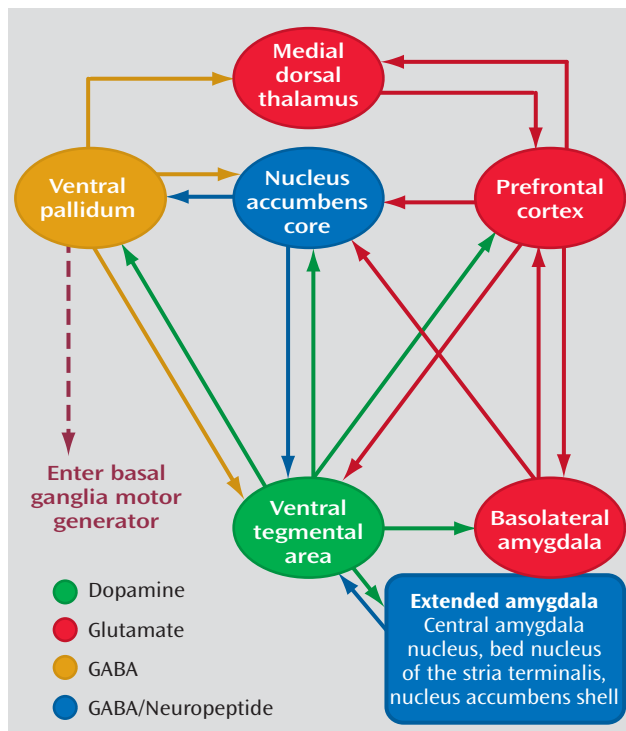
Conclusions: Cellular adaptations in prefrontal glutamatergic innervation of the accumbens promote the compulsive character of drug seeking in addicts by decreasing the value of natural rewards, diminishing cognitive control (choice), and enhancing glutamatergic drive in response to drug-associated stimuli.

(*Am J Psychiatry* 2005; 162:1403–1413)

Among the most insidious characteristics of drug addiction is the recurring desire to take drugs even after many years of abstinence. Equally sinister is the compromised ability of addicts to suppress drug seeking in response to that desire even when confronted with seriously adverse consequences, such as incarceration. The enduring vulnerability to relapse is a primary feature of the addiction disorder and has been identified as a point where pharmacotherapeutic intervention may be most effectively employed (1). In order to fashion rational pharmacotherapies it is necessary to understand the neurobiological underpinnings of craving, relapse, choice, and control, and the last decade has seen significant advances toward achieving this goal. However, as the pursuit for the neural basis of addiction advances, it is clear that the search intimately involves understanding the neurobiological basis of motivation and choice for biological rewards, such as food and sex, as well as more cognitively and experientially based rewards, such as friendship, family, and social status. Moreover, the fact that vulnerability to relapse in addicts can persist after years of abstinence implies that addiction is caused by long-lasting changes in brain function as a result of pharmacological insult (repeated drug use), genetic disposition, and environmental associations made with drug use (learning). Therefore, comprehending the basis of addiction also requires understanding physiological mecha-

nisms of enduring neuroplasticity. Accordingly, this review begins with an overview of the neural circuitry and mechanisms of neuroplasticity that underlie the generation of adaptive behavioral responses to motivationally relevant events.

After outlining the neurobiology of motivated behavior, we will describe the pathological dysregulation of cellular and circuitry functions produced by addiction. As early as the 1970s it became clear that the acute administration of most drugs of abuse increases dopamine transmission in the basal ganglia (2), which is essential for these drugs to reinforce behavior, and thereby promote addiction (3, 4). Therefore, dopamine projections to the basal ganglia and cortex are important in facilitating the encoding of learned associations necessary for the development of addiction (5). In contrast, once a person is addicted the uncontrollable urge to obtain drugs and relapse arises from a pathological form of the plasticity in excitatory transmission (6–9). Alterations in excitatory transmission occur physiologically when learned associations with motivationally relevant events are formed. Similarly, addicts' extreme difficulty in resisting the desire to use drugs of abuse is encoded by changes in excitatory synapses, and it will be proposed that the molecular underpinnings of dysregulated excitatory transmission may be fruitful pharmacotherapeutic targets in ameliorating addiction.

FIGURE 1. Neural Circuitry Mediating the Activation of Goal-Directed Behavior

The Neurobiology of Adaptive Behavior

Seeking food and companionship and avoiding physical and psychological discomfort are examples of motivated adaptive behaviors. Motivated behavior classically implies both an activation of the organism by environmental or interoceptive stimuli and a directed behavioral output (10). Thus, the neurobiological search for the antecedents of motivated behavior involves defining the neural substrates that 1) attach sufficient importance (saliency) to an integrated stimulus that behavior is “activated” and 2) “direct” this state of activation toward a specific behavioral response. While we have made substantial progress toward identifying the neural circuits and cellular foundations responsible for activating behavior, we have been only marginally effective at understanding the substrates that cause one behavior to be favored over another behavior (direction of behavior).

Activation of Behavior

Neurobiology has focused on three brain regions in the activation of behavior: the amygdala, prefrontal cortex, and nucleus accumbens. The amygdala emerged from studies showing involvement in fear-motivated behaviors (11), while the nucleus accumbens was identified from a connection with reward-motivated behaviors (12). The prefrontal cortex is less involved in establishing whether a stimulus is positive or negative (valence); rather, it regulates the overall motivational salience and determines the

intensity of behavioral responding (13, 14). More recent studies have blurred the linkage between positive and negative emotional valence in the amygdala and nucleus accumbens, and they have revealed a neuronal circuit consisting of glutamatergic interconnections among the amygdala, nucleus accumbens, and prefrontal cortex and dopaminergic afferents to all three regions (15, 16). Figure 1 illustrates this circuit and includes three additional components. The accumbens has dense projections carrying γ -aminobutyric acid (GABA) and neuropeptides to the ventral pallidum that are critical for the expression of motivated behaviors (17). Another GABA/neuropeptide component of the circuit is the extended amygdala, which is a cluster of interconnected nuclei, including the central amygdala nucleus, bed nucleus of the stria terminalis, and shell of the nucleus accumbens, that is in part a conduit for environmental and interoceptive stressors (18). It is important to note that while the shell of the accumbens possesses some functional and anatomical characteristics of the extended amygdala (especially in terms of the neurocircuitry of addiction), it is also anatomically distinct from the other nuclei in terms of some aspects of connectivity and histochemistry (19). Finally, there is a series subcircuit consisting of GABA-ergic projections from the ventral pallidum to the mediodorsal thalamus and a reciprocal glutamatergic projection between the thalamus and prefrontal cortex that mediates reintegration of information exiting the circuit back into the prefrontal cortex (20).

Dopamine and the ventral tegmental area. Projections from the ventral tegmental area release dopamine throughout the circuit in response to a motivationally relevant event (21, 22). The release of dopamine signals the circuit to initiate adaptive behavioral responses to the motivational event, and in doing so it facilitates cellular changes that establish learned associations with the event (5). In this way the organism can more effectively emit an adaptive behavioral response should the event reoccur. However, in contrast to repeated drug administration, as a motivational event becomes familiar by repeated exposure, dopamine release is no longer induced by that particular event (23). In this case, although the behavioral response remains goal directed, it is well learned and further dopamine-induced neuroplastic changes are not necessary. However, it is important to note that conditioned stimuli predicting the event continue to trigger release of dopamine (23–25). Therefore, in most natural situations where learned associations accompany a repeatedly encountered motivational event, dopamine will likely be released as part of the overall experience. In sum, dopamine can be seen as serving two functions in the circuit: 1) to alert the organism to the appearance of novel salient stimuli, and thereby promote neuroplasticity (learning), and 2) to alert the organism to the pending appearance of a familiar motivationally relevant event, on the basis of learned associations made with environmental stimuli predicting the event (23, 26).

Amygdala. The amygdala is especially critical in establishing learned associations between motivationally relevant events and otherwise neutral stimuli that become predictors of the event (27). Interactions between the basolateral and central amygdala nucleus involve autonomic and endocrine associations by means of projections from the central nucleus to the brainstem, the hypothalamus, and dopamine neurons in the ventral tegmental area (28, 29). In contrast, the glutamatergic projections from the basolateral amygdala to the prefrontal cortex and accumbens are required for learned associations to influence more complex behavioral responses (16, 20). The functional integration between the amygdala and prefrontal cortex has been demonstrated in many neuroimaging studies in which healthy subjects were exposed to stimuli associated with motivationally relevant events, ranging from food and sex to social cooperation (30–32).

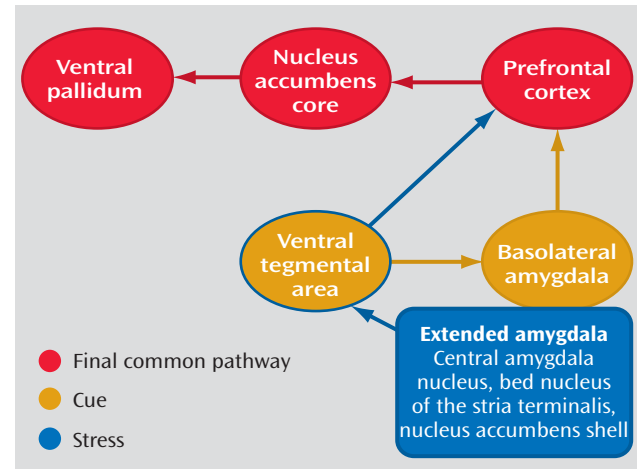
Prefrontal cortex. The anterior cingulate and ventral orbital cortices in the prefrontal cortex are recruited by motivationally relevant events, as well as stimuli that predict such events, and contribute to whether a behavioral response will be emitted and the relative intensity of that response (14, 33). Consistent with involvement of dopaminergic afferents, the activation of the prefrontal cortex by rewarding stimuli is strongly influenced by the predictability of the reward (34, 35).

Nucleus accumbens. The accumbens contains two functionally distinct subcompartments, termed the shell and core (36). The shell is strongly interconnected with the hypothalamus and ventral tegmental area and is correspondingly important in regulating ingestive behaviors (21, 36). Reciprocal dopamine innervation from the ventral tegmental area to the accumbens shell is important in modulating motivational salience and contributes to establishing learned associations between motivational events and concurrent environmental perceptions (37, 38). In contrast, the core compartment is anatomically associated with the anterior cingulate and orbitofrontal cortex and appears to be a primary site mediating the expression of learned behaviors in response to stimuli predicting motivationally relevant events (36, 39). Moreover, the obligatory involvement of the accumbens core in expressing adaptive behavior depends not on dopaminergic afferents but, rather, on glutamatergic afferents from the prefrontal cortex (40). Although not an obligatory event, dopamine is released into the core in response to stimuli predicting a rewarding event and likely modulates the expression of adaptive behaviors (41, 42).

Direction of Behavior

While our understanding of brain mechanisms responsible for activating goal-directed behavior is considerable, the mechanisms by which the circuit in Figure 1 determines or “chooses” the direction of behavior are less clear. Choice is initiated in part by means of the prefrontal cortex, as some studies have shown that activation of the

FIGURE 2. Neural Circuitry Mediating Drug Seeking^a



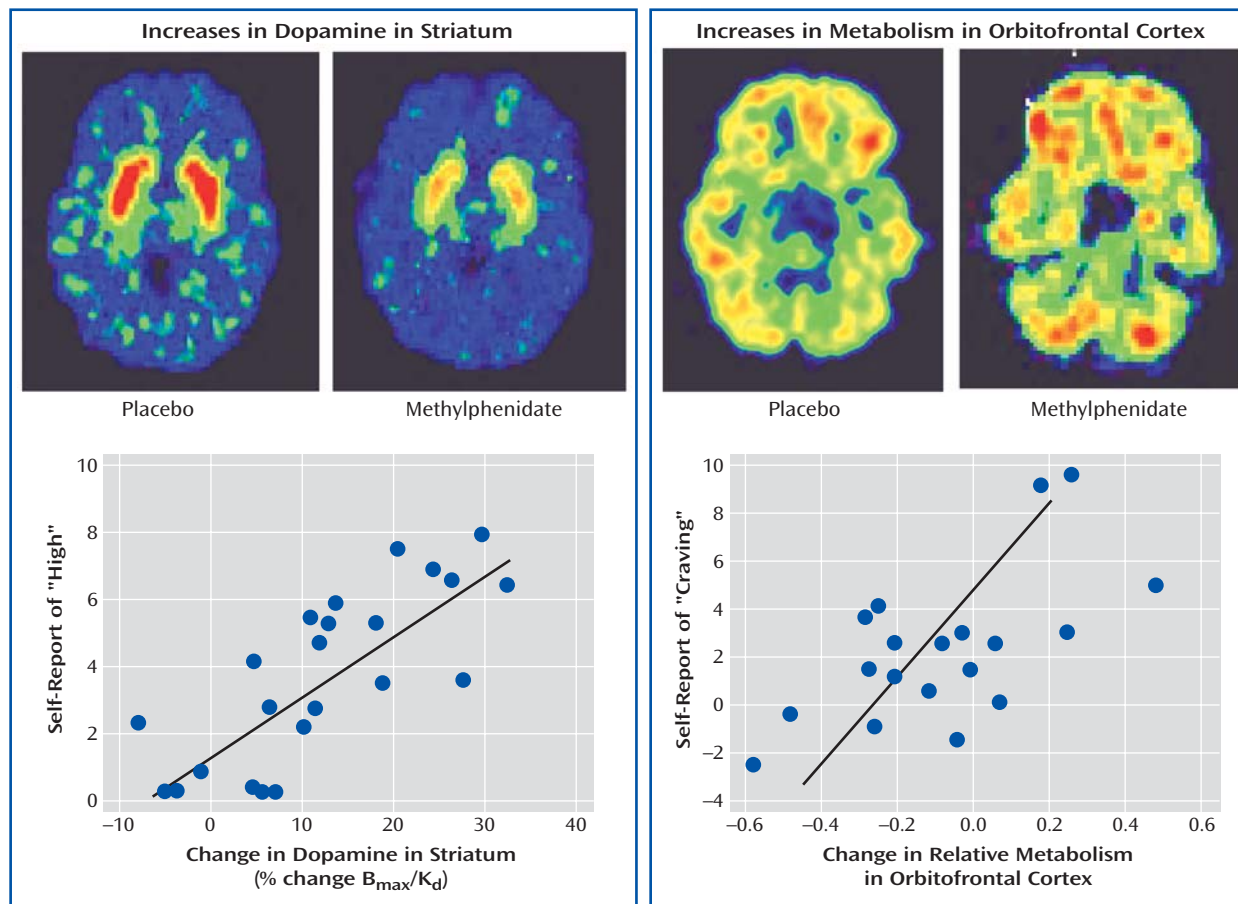
^a The series projection from the prefrontal cortex to the nucleus accumbens core to the ventral pallidum is a final common pathway for drug seeking initiated by stress, a drug-associated cue, or the drug itself (which increases dopamine release in the prefrontal cortex).

prefrontal cortex precedes behavior (33, 43, 44). Glutamatergic efferents from the prefrontal cortex stimulate behavioral output by accessing accumbens-thalamocortical circuitry (45, 46). It has long been proposed that distinct neuronal ensembles within the accumbens encode the relationship between discrete stimuli and behavioral responses (47). However, only recently was it demonstrated that different subsets of neurons in the accumbens respond differentially to cues associated with distinct motivationally relevant stimuli, such as water versus cocaine (48). How these ensembles are formed and organized is unclear. However, the intensity and quality of behavioral output are strongly influenced by both dopaminergic and glutamatergic input to the accumbens, and activity at these synapses produces morphological changes in the dendrites of accumbens spiny cells (49). Changes in dendritic spine density occur in cellular and in vivo models of learning, and they correlate roughly with excitatory synaptic contacts (50). In addition to morphological changes, in vitro models of neuroplasticity reveal intracellular changes that can augment or diminish excitatory transmission (51, 52). Recent studies demonstrate that addiction is associated with neuroplasticity in these cellular mechanisms of synaptic organization, and we will discuss them in detail.

Addiction: Dysregulation in the Motive Circuit

Repeated use of addictive drugs induces reorganization in the circuit shown in Figure 1 to establish behaviors characteristic of addiction, and Figure 2 illustrates connections in the circuit that are particularly critical for craving and drug seeking. In preclinical studies the most widely used animal model is training rodents to self-administer a drug

FIGURE 3. PET Brain Images Showing the Effects of Intravenous Methylphenidate on Extracellular Dopamine in the Striatum and on Regional Glucose Metabolism in Cocaine-Addicted Subjects^a



^a Extracellular dopamine in the striatum was assessed by measuring [¹¹C]raclopride binding. Regional brain glucose metabolism was assessed by measuring [¹⁸F]fluorodeoxyglucose metabolism. Increases with methylphenidate were determined by calculating the difference between methylphenidate and placebo conditions. As shown in the scattergrams, although methylphenidate's increases in dopamine in the striatum are associated with the "high," the activation of the orbitofrontal cortex is associated with drug craving.

(18). The behavior is extinguished, making it possible to reinstate drug seeking by exposing the animals to stimuli similar to those that elicit craving in human addicts, such as a cue previously associated with drug delivery, a mild stressor, or a single dose of the drug (18). In great measure the circuit in Figure 2 was assembled by inactivating specific nuclei in animals tested for reinstatement of drug seeking, as well as using cerebral blood flow or blood-oxygenation-level-dependent responses in addicts elicited by the presentation of cues previously associated with drug use (15). Three general principles emerge from the circuit in Figure 2.

Final Common Pathway

First, this glutamatergic projection is a final common pathway for initiation of drug seeking. Inactivation of the prefrontal cortex in rats prevents the reinstatement of drug seeking by all three modalities of reinstating stimuli (29, 53–55). Further supporting an obligatory role of this projection in drug seeking, AMPA glutamate receptor antagonists in the nucleus accumbens prevent drug- and

cue-induced reinstatement (40, 56, 57). Moreover, increased release of glutamate in the nucleus accumbens occurs following drug- and stress-primed reinstatement, and treatments that prevent the release of glutamate also prevent drug seeking (29, 58). Within the accumbens the region most strongly associated with drug seeking is the core subcompartment, consistent with the role of this region in emitting learned behavioral responses (see the preceding). Neuroimaging studies support a strong linkage between the prefrontal cortex and drug seeking. The magnitude of change in metabolic activity in both the orbitofrontal and anterior cingulate cortices statistically correlates with the intensity of the self-reported cue-induced craving (33, 35, 59, 60). It is interesting that the craving-associated increase in prefrontal activity is on a drug-free background of reduced activity (13, 15, 61, 62). Moreover, activation of the anterior cingulate and orbitofrontal cortex in addicts is inhibited in experimental situations of decision making (63, 64) and in response to biologically relevant rewards, such as sexually evocative cues (30). To-

gether, these data indicate that dysregulation in the anterior cingulate and orbitofrontal cortex is critically involved in the prepotent motivation by stimuli predicting drug availability relative to stimuli associated with biological rewards, as well as the difficulty experienced by addicts in cognitive control over drug seeking. Indeed, just as hyperactivity of the anterior cingulate and orbitofrontal cortex contributes to compulsive behaviors in patients with obsessive-compulsive disorders, the relative hypermetabolism in response to drug-related stimuli could trigger compulsive drug intake (65).

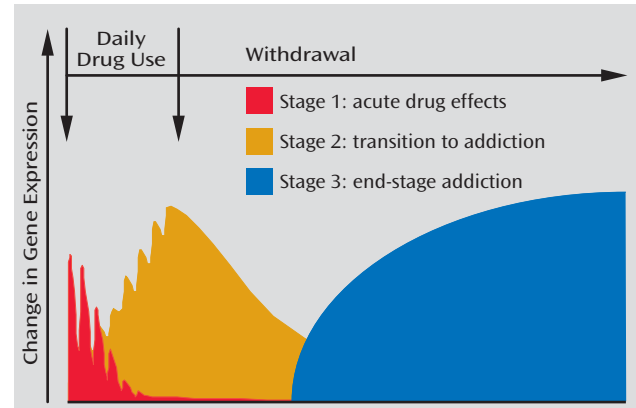
Modality-Dependent Subcircuits

The second principle in the circuitry of drug seeking is that different modes of stimuli inducing drug seeking involve distinct components of the circuit. In contrast to the obligatory role of the glutamate projection from the prefrontal cortex to the accumbens core in drug seeking, distinct nuclei in Figure 2 regulate reinstatement in response to selective stimuli. For example, cue-primed drug seeking requires involvement of the basolateral amygdala (66–68), while stress- and drug-primed drug seeking do not (29, 55, 69). Also, stress-induced drug seeking selectively engages nuclei in the extended amygdala (29, 70). Consistent with a role for the amygdala in recognition of cue association with drug use and not in determining cue salience or the intensity of the behavioral responding, neuroimaging studies reveal that the amygdala is not consistently correlated with the reported intensity of craving (33, 59, 71).

Requirement for Dopamine Transmission

The last principle is that all three modalities of drug-seeking stimuli require dopamine transmission. Since drug seeking is inhibited by inactivation of the ventral tegmental area regardless of the stimulus modality employed, the mesocorticolimbic dopamine projection is obligatory for reinstatement (29, 55, 72). However, while the rewarding effects accompanying the acute administration of most drugs of abuse depend on increased dopamine release in the accumbens (2, 3), the reinstatement of drug seeking requires dopamine release in the prefrontal cortex and amygdala (29, 53, 55, 73), not in the nucleus accumbens core (40, 55, 57). Dopamine release in the prefrontal cortex is antecedent to activation of the projection from the prefrontal cortex to the accumbens core since preventing cortical dopamine release prevents glutamate release in the nucleus accumbens by a stress or drug prime (29, 58). Also, reinstatement elicited by dopamine release in the prefrontal cortex is blocked by glutamate antagonists in the accumbens core (56). Data from imaging studies support the idea that once a person is addicted, dopamine release into the accumbens is not critical for craving. By using positron emission tomography and the $D_{2/3}$ dopamine receptor ligand [^{11}C]raclopride in combination with a dopamine reuptake inhibitor such as methylphenidate, it is possible to estimate dopamine release. These studies

FIGURE 4. The Three Stages of Addiction^a



^a Acute drug effects occur widely in dopamine terminal fields in the circuit shown in Figure 1. Neuroadaptations mediating the transition from recreational drug use to addiction endure for a finite period after discontinuation of repeated drug administration and initiate the changes in protein expression and function that emerge during withdrawal and underlie the behavioral characteristics of end-stage addiction, such as craving, relapse, and reduced ability to suppress drug seeking.

have corroborated in humans that increases in dopamine in the striatum are associated with the reinforcing effects of stimulants (as evidenced by self-reported “high”) (Figure 3). However, in relation to comparison subjects, cocaine-addicted subjects showed less dopamine release in parallel with fewer self-reports of a methylphenidate-induced “high” (74). In contrast, an intense methylphenidate-induced cocaine craving in cocaine abusers but not in comparison subjects indicates that addiction is associated not with either enhanced drug-induced dopamine release in the striatum or an augmented pleasurable response to the drug but, rather, with enhanced motivation to procure the drug. As predicted by the animal studies, methylphenidate-induced craving in cocaine-addicted subjects is not associated with dopamine increases in the striatum but with increased activity in the orbitofrontal cortex (Figure 3). In addition, further contributing to the hypofunction of striatal dopamine is low D_2 receptor availability in the striatum of addicted subjects (65). Given the role we have described for dopamine transmission in the accumbens, to signal the salience of novel motivational events, the decrease in dopamine release and reception combined with the reduced activation of the prefrontal cortex in response to biologically relevant stimuli (see the preceding) may explain the reduced sensitivity of addicted subjects to “natural” reinforcers.

Stages of Addiction

The portrait of addiction drawn by the studies we have discussed indicates that dopamine release in the accumbens is required for the drug high and for the initiation of addiction but that repeated use of a drug causes gradual

recruitment of the prefrontal cortex and its glutamatergic efferents to the accumbens.

The switch from dopamine- to glutamate-based behavior reveals that the development of addiction occurs in a chronological sequence during which different parts of the circuit are preeminent. Similarly, cellular adaptations occur in a chronological sequence. Three temporally sequenced stages of addiction are illustrated in Figure 4: 1) acute drug effects, 2) transition from recreational use to patterns of use characteristic of addiction, and 3) end-stage addiction, which is characterized by an overwhelming desire to obtain the drug, a diminished ability to control drug seeking, and reduced pleasure from biological rewards.

Stage 1: Acute Drug Effects

The acute rewarding effects of drugs involve supraphysiological dopamine release throughout the motive circuit, which induces changes in cell signaling. The prototype signaling cascade in this regard is D₁ dopamine receptor stimulation resulting in the activation of cAMP-dependent protein kinase (PKA), PKA-induced phosphorylation of the transcriptional regulator cAMP response element binding protein (CREB), and the induction of immediate early gene products, such as cFos (75, 76). The induction of Fos and other immediate early genes promotes short-term neuroplastic changes in response to the acute drug injection that persist for a few hours or days after drug administration (77). Thus, these molecular consequences of acute drug administration are widely distributed in the motive circuit and initiate cellular events leading up to addiction, but they do not mediate the enduring behavioral consequences of addiction.

Stage 2: Transition to Addiction

The transition from recreational drug use to addiction is associated with changes in neuron function that accumulate with repeated administration and diminish over days or weeks after discontinuation of drug use. The most well-studied molecular adaptation in this category is D₁-receptor-mediated stimulation of proteins with long half-lives, such as Δ FosB (78). Δ FosB is a transcriptional regulator that modulates the synthesis of certain AMPA glutamate receptor subunits and cell-signaling enzymes (79, 80). Recently, the pattern of gene expression induced by long-term induction of Δ FosB was shown to overlap considerably with the pattern of changes induced in the accumbens by chronic cocaine administration, strongly implicating Δ FosB in mediating the transition to addiction (81). In addition to the effects of Δ FosB, elevation of the GluR1 glutamate receptor subunit in the ventral tegmental area for a few days after discontinuation of cocaine administration may contribute to the development of addiction (82). Also, there are alterations in the content and function of various proteins directly involved in dopamine transmission that endure for a few days after drug administration

stops; these proteins include tyrosine hydroxylase, dopamine transporters, RGS9-2, and D₂ autoreceptors (83, 84). However, these changes in dopamine transmission appear to be compensatory and may not directly mediate the transition to addiction.

Stage 3: End-Stage Addiction

Vulnerability to relapse in end-stage addiction endures for years and results from equally enduring cellular changes. It is interesting that, like the locomotor sensitization and drug-seeking behaviors associated with addiction (85, 86), changes in protein content and/or function in this category often become greater with increasing periods of withdrawal (87–89). This temporal characteristic is consistent with the possibility that the more temporary changes in protein expression that mediate the transition to addiction (see the preceding) may induce changes in protein expression that convert vulnerability to relapse from temporary and reversible into permanent features of addiction.

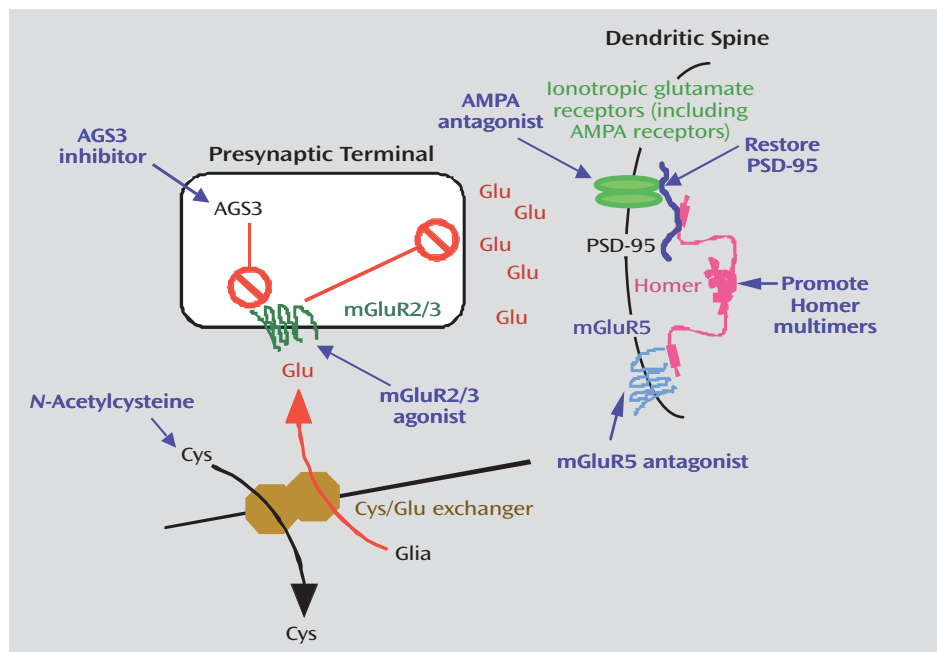
Cellular Adaptations in Glutamatergic Projection From Prefrontal Cortex to Accumbens That Mediate Drug Seeking

The involvement of the glutamate projection from the prefrontal cortex to the accumbens core as a final common pathway for initiating drug seeking poses molecular changes in the projection as potential mediators of the uncontrollable desire to take drugs that characterizes addiction. Moreover, the search for cellular changes in the projection from the prefrontal cortex to the accumbens that are involved in the recruitment of this pathway by repeated drug use may reveal pharmacological targets for ameliorating craving and relapse.

Prefrontal Cortex

Withdrawal from repeated administration of psychostimulants or opioids results in dysmorphisms in the dendritic tree of pyramidal cells in the prefrontal cortex (49, 90). The enduring drug-induced morphological plasticity indicates long-lasting alterations in neurotransmission (91). Accordingly, there is reduced cell signaling through transmitter receptors coupled to G_i (a G protein subtype) (92, 93) that is mediated in part by an elevation in the G protein binding protein AGS3 (87). It is important that an elevated AGS3 level increases the activity of prefrontal glutamatergic projections to the nucleus accumbens and that normalizing the level of AGS3 in cocaine-addicted rats prevents the reinstatement of drug seeking (87). Recently, it was postulated that the increased excitability of pyramidal cells may result from AGS3 inhibition of D₂ receptor signaling and a corresponding relative increase in D₁ signaling (94). Supporting this possibility are the findings that D₁ receptor blockade in the prefrontal cortex prevents the reinstatement of drug seeking (53) and that

FIGURE 5. Potential Pharmacotherapeutic Targets for Normalizing Dysregulated Glutamate Release and Postsynaptic Responsiveness in the Nucleus Accumbens to Ameliorate Cocaine Craving and Relapse^a



^a Glu=glutamate, Cys=cysteine.

withdrawal from repeated amphetamine administration renders pyramidal cells more excitable (95).

Nucleus Accumbens: Presynaptic Adaptations

In the nucleus accumbens there are two categories of adaptation in glutamate transmission, those that promote presynaptic glutamate release and those altering postsynaptic responsiveness to released glutamate. Increased release of glutamate in response to a stimulus that induces drug seeking arises in part from adaptations that reduce inhibitory presynaptic regulation by metabotropic glutamate (mGluR2/3) inhibitory autoreceptors (96, 97), and perhaps from alterations in the organization of vesicles in presynaptic terminals (98–100). There is a reduction in basal extracellular glutamate in the nucleus accumbens after withdrawal from cocaine that results from reduced glial cystine-glutamate exchange (96). The cystine-glutamate exchanger is the rate-limiting step in glutathione synthesis (101) and is responsible for the majority of extracellular glutamate outside the synaptic cleft (102). Thus, the exchanger is the primary contributor to maintenance of tone on mGluR2/3 inhibitory autoreceptors and thereby inhibits the release of synaptic glutamate (103). It is noteworthy that activation of cystine-glutamate exchange by procysteine drugs prevents the reinstatement of drug seeking by restoring extrasynaptic glutamate and stimulating inhibitory presynaptic mGluR2/3 (96, 103).

Nucleus Accumbens: Postsynaptic Adaptations

Postsynaptic responses to glutamate in the accumbens of animals withdrawn from cocaine reveal enduring adap-

tations in postsynaptic receptor associated proteins (postsynaptic density) that can alter glutamate receptor intracellular signaling and trafficking to the membrane. This includes reductions in scaffolding proteins such as PSD-95 (104) and Homer (89, 105). Together, these changes in postsynaptic density proteins may account for the dendritic dysmorphisms produced in the accumbens by withdrawal from psychostimulants or morphine (49, 90). The cellular ramifications of changes in postsynaptic density induced by cocaine withdrawal remain to be fully investigated. However, animals with constitutive *Homer2* gene deletion show remarkable similarities to animals withdrawn from chronic cocaine, including reduced cystine-glutamate exchange, increased AGS3 levels, increased releasability of glutamate, as well as augmented behavioral responsiveness to cocaine (106). Moreover, many of the effects of *Homer2* gene deletion are normalized when *Homer2* is restored to the accumbens by viral transfection. Similarly, the deletion of the PSD-95 gene augments the acute behavioral response to cocaine (104).

Potential New Targets for Pharmacotherapeutic Amelioration of Addiction

The enduring changes in proteins regulating excitatory transmission in the projection from the prefrontal cortex to accumbens core point to a number of novel targets for treating addiction. However, it is important to remember that additional pharmacotherapies could target other components of the circuit shown in Figure 2 that pertain

selectively to stress- or cue-induced relapse. These include drugs that 1) decrease the motivational value of the drug, 2) increase the salience and motivational value of nondrug reinforcers, or 3) inhibit conditioned responses to stimuli predicting drug availability. Most advanced in this regard are drugs that restore inhibitory presynaptic regulation of excitatory transmission as a means to interfere with the enhanced salience of the drug or drug-related cues. Figure 5 illustrates that this has been approached by three different mechanisms, all of which have been shown to reduce drug seeking in the reinstatement model of relapse. Procyteine drugs such as *N*-acetylcysteine have been used clinically to stimulate cystine-glutamate exchange and restore glutathione following acetaminophen overdose (107). *N*-Acetylcysteine administration to rats withdrawn from cocaine self-administration restores glutamatergic tone on mGluR2/3 inhibitory presynaptic receptors and abolishes cocaine-induced reinstatement of drug seeking (96). It is noteworthy that in animal models it is effective only in cocaine-trained subjects and is without effect on control animals or animals trained in a food-seeking paradigm (96). Direct stimulation of mGluR2/3 with systemically active agonists also reduces the reinstatement of drug seeking (108). Finally, a portion of decreased mGluR2/3 inhibitory tone on presynaptic glutamate release arises from the increased levels of AGS3 produced by withdrawal from repeated cocaine, and restoring AGS3 levels to normal in the prefrontal cortex blocks cocaine-induced reinstatement of drug seeking (87). Unfortunately, the pharmacological techniques for manipulating AGS3 levels in vivo require intracellular transduction of active protein, and the currently available technologies to accomplish this (e.g., Tat fusion proteins, viral transfection, or oligonucleotide/iRNA infusions) are not available for clinical use.

The changes in postsynaptic proteins induced by cocaine withdrawal also point to potential pharmacotherapeutic interventions. Notably, blockade of AMPA glutamate receptors in the nucleus accumbens prevents cocaine- or cue-primed reinstatement of drug seeking in animal models (40, 56, 57). In addition, while tests in the reinstatement model have not yet been conducted, restoration of the scaffolding proteins Homer and PSD-95 may also inhibit drug seeking (104, 106). Unfortunately, akin to AGS3, reagents to manipulate scaffolding proteins are not yet available for use in humans. A final promising discovery is that mice with a deletion of the mGluR5 gene show reduced responsiveness to cocaine (109), and systemic administration of an mGluR5 antagonist reduces cocaine and nicotine self-administration (110).

Summary

The cardinal behavioral feature of drug addiction is continued vulnerability to relapse after years of drug abstinence. Vulnerability arises from an intense desire for the

drug and reduced capacity to control that desire. Addiction can be viewed as a pathology in how importance is attached to stimuli that predict drug availability and how the brain regulates (chooses) behavioral output in response to those stimuli. Thus, end-stage addiction is characterized by the excessive motivational importance of drug seeking. The glutamatergic projection from the prefrontal cortex to the accumbens is a final common pathway for eliciting drug seeking. This anatomical locus of pathology is consistent with behavioral dysregulation in addiction, since the prefrontal-accumbens projection is credited with providing the properties of motivational salience and direction to normal goal-directed behavior. Recently, some of the cellular mediators of the pathology in the prefrontal-accumbens glutamate projection have been identified. These include 1) alterations in G protein signaling in the prefrontal cortex that increase the excitability of neurons projecting to the accumbens, 2) augmented presynaptic glutamate release in the accumbens due to reduced inhibitory presynaptic regulation and increased releasability of synaptic vesicles, and 3) alterations in postsynaptic proteins that result in rigid dendritic morphology and signaling. These findings combined with functional imaging studies in addicts reveal a situation whereby prefrontal regulation of behavior is reduced in basal conditions, thereby contributing to the reduced salience of nondrug motivational stimuli and reduced decision-making ability. However, when stimuli predicting drug availability are presented, there is profound activation of the prefrontal cortex and glutamatergic drive to the nucleus accumbens. Combined with the cellular neuroadaptations in the accumbens that render excitatory synapses relatively immune to regulation, the increased prefrontal drive contributes overpowering motivational salience to drug-associated stimuli and correspondingly impels craving and drug seeking. The combined functional and cellular evidence predicts that pharmacotherapeutic agents regulating prefrontal glutamatergic drive to the nucleus accumbens have the potential to ameliorate both the excessive motivational importance given to stimuli that predict drug availability and the reduced capacity of addicts to inhibit drug intake.

Presented at the 157th annual meeting of the American Psychiatric Association, New York, May 1–6, 2004. Received July 7, 2004; revision received Aug. 26, 2004; accepted Sept. 9, 2004. From the Department of Neurosciences, Medical University of South Carolina; and the National Institute on Drug Abuse, Bethesda, Md. Address correspondence and reprint requests to Dr. Kalivas, Department of Neurosciences, Medical University of South Carolina, 173 Ashley Ave., BSB-403, Charleston, SC 29425; kalivas@musc.edu (e-mail).

Supported in part by National Institute on Drug Abuse grants DA-12513, DA-05369, and DA-03906.

References

1. O'Brien C: Drug addiction and drug abuse, in *The Pharmacological Basis of Therapeutics*. Edited by Hardman J, Limbird L, Gilman AG. New York, McGraw-Hill, 2001, pp 621–642

2. Wise RA, Rompre PP: Brain dopamine and reward. *Annu Rev Psychol* 1989; 40:191–225
3. Koob GF, Le Moal M: Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001; 24:97–129
4. Robinson TE, Berridge KC: Addiction. *Annu Rev Psychol* 2003; 54:25–53
5. Jay TM: Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. *Prog Neurobiol* 2003; 69:375–390
6. Pierce RC, Kalivas PW: A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res Brain Res Rev* 1997; 25:192–216
7. Thomas MJ, Beurrier C, Bonci A, Malenka RC: Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nat Neurosci* 2001; 4:1217–1223
8. Wolf ME: The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Prog Neurobiol* 1998; 54:679–720
9. Winder DG, Egli RE, Schramm NL, Matthews RT: Synaptic plasticity in drug reward circuitry. *Curr Mol Med* 2002; 2:667–676
10. Lashley KS: Experimental analysis of instinctive behavior. *Psychol Rev* 1938; 45:445–471
11. Kluver H, Bucy PC: Preliminary analysis of functions of the temporal lobes in monkeys. *Arch Neurol Psychiatry* 1939; 42:979–1000
12. Olds J, Milner P: Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 1954; 47:419–427
13. Jentsch JD, Taylor JR: Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)* 1999; 146:373–390
14. Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR: Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc Natl Acad Sci USA* 2002; 99:523–528
15. Goldstein RZ, Volkow ND: Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 2002; 159:1642–1652
16. Cardinal RN, Parkinson JA, Hall J, Everitt BJ: Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 2002; 26:321–352
17. Mogenson GJ, Brudzynski SM, Wu M, Yang CR, Yim CCY: From motivation to action: a review of dopaminergic regulation of limbic-nucleus accumbens-pedunculo-pontine nucleus circuitries involved in limbic-motor integration, in *Limbic Motor Circuits and Neuropsychiatry*. Edited by Kalivas PW, Barnes CD. Boca Raton, Fla, CRC Press, 1993, pp 193–236
18. Shalev U, Grimm JW, Shaham Y: Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol Rev* 2002; 54:1–42
19. Zahm DS: An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. *Neurosci Biobehav Rev* 2000; 24:85–105
20. McFarland K, Kalivas PW: Motivational systems, in *Handbook of Psychology*, vol 3. Edited by Gallagher M, Nelson RJ. Hoboken, NJ, John Wiley & Sons, 2003, pp 379–404
21. Robinson TE, Berridge KC: The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 1993; 18:247–291
22. McClure SM, Daw ND, Montague PR: A computational substrate for incentive salience. *Trends Neurosci* 2003; 26:423–428
23. Schultz W: Predictive reward signal of dopamine neurons. *J Neurophysiol* 1998; 80:1–27
24. Phillips PE, Stuber GD, Heien ML, Wightman RM, Carelli RM: Subsecond dopamine release promotes cocaine seeking. *Nature* 2003; 422:614–618; correction, 423:461
25. Sutton MA, Beninger RJ: Psychopharmacology of conditioned reward: evidence for a rewarding signal at D1-like dopamine receptors. *Psychopharmacology (Berl)* 1999; 144:95–110
26. Keitz M, Martin-Soelch C, Leenders KL: Reward processing in the brain: a prerequisite for movement preparation? *Neural Plast* 2003; 10:121–128
27. Everitt BJ, Cardinal RN, Parkinson JA, Robbins TW: Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Ann NY Acad Sci* 2003; 985:233–250
28. Georges F, Aston-Jones G: Potent regulation of midbrain dopamine neurons by the bed nucleus of the stria terminalis. *J Neurosci* 2001; 21:RC160
29. McFarland K, Davidge SB, Lapish CC, Kalivas PW: Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* 2004; 24:1551–1560
30. Garavan H, Pankiewicz J, Bloom A, Cho J-K, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA: Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry* 2000; 157:1789–1798
31. Morris JS, Dolan RJ: Involvement of human amygdala and orbitofrontal cortex in hunger-enhanced memory for food stimuli. *J Neurosci* 2001; 21:5304–5310
32. Rilling J, Gutman D, Zeh T, Pagnoni G, Berns G, Kilts C: A neural basis for social cooperation. *Neuron* 2002; 35:395–405
33. Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE: Acute effects of cocaine on human brain activity and emotion. *Neuron* 1997; 19:591–611
34. Berns GS, McClure SM, Pagnoni G, Montague PR: Predictability modulates human brain response to reward. *J Neurosci* 2001; 21:2793–2798
35. Volkow ND, Wang G-J, Ma Y, Fowler JS, Zhu W, Maynard L, Telang R, Vaska P, Ding Y-S, Wong C, Swanson JM: Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. *J Neurosci* 2003; 23:11461–11468
36. Kelley AE: Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neurosci Biobehav Rev* 2004; 27:765–776
37. Bassareo V, Di Chiara G: Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neuroscience* 1999; 89:637–641
38. Sellings LH, Clarke PB: Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. *J Neurosci* 2003; 23:6295–6303
39. Di Ciano P, Everitt BJ: Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology* 2001; 25:341–360
40. Di Ciano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ: Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of Pavlovian approach behavior. *J Neurosci* 2001; 21:9471–9477
41. Ito R, Dalley JW, Howes SR, Robbins TW, Everitt BJ: Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *J Neurosci* 2000; 20:7489–7495
42. Cheng JJ, de Bruin JP, Feenstra MG: Dopamine efflux in nucleus accumbens shell and core in response to appetitive classical conditioning. *Eur J Neurosci* 2003; 18:1306–1314
43. Badre D, Wagner AD: Selection, integration, and conflict monitoring: assessing the nature and generality of prefrontal cognitive control mechanisms. *Neuron* 2004; 41:473–487

44. Shidara M, Richmond BJ: Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* 2002; 296:1709–1711
45. Haber SN: The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat* 2003; 26:317–330
46. Jog MS, Kubota Y, Connolly CI, Hillegaart V, Graybiel AM: Building neural representations of habits. *Science* 1999; 286:1745–1749
47. Pennartz CM, Groenewegen HJ, Lopes da Silva FH: The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioural, electrophysiological and anatomical data. *Prog Neurobiol* 1994; 42:719–761
48. Carelli RM, Wondolowski J: Selective encoding of cocaine versus natural rewards by nucleus accumbens neurons is not related to chronic drug exposure. *J Neurosci* 2003; 23:11214–11223
49. 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
50. McGee AW, Bredt DS: Assembly and plasticity of the glutamatergic postsynaptic specialization. *Curr Opin Neurobiol* 2003; 13:111–118
51. Carroll R, Beattie E, von Zastrow M, Malenka R: Role of AMPA receptor endocytosis in synaptic plasticity. *Nat Rev Neurosci* 2001; 2:315–324
52. Scannevin RH, Huganir RL: Postsynaptic organization and regulation of excitatory synapses. *Nat Rev Neurosci* 2000; 1:133–141
53. Capriles N, Rodaros D, Sorge RE, Stewart J: A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)* 2003; 168:66–74
54. McLaughlin J, See RE: Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 2003; 168:57–65
55. McFarland K, Kalivas PW: The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2001; 21:8655–8663
56. Park WK, Bari AA, Jey AR, Anderson SM, Spealman RD, Rowlett JK, Pierce RC: Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. *J Neurosci* 2002; 22:2916–2925
57. Cornish J, Kalivas P: Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neurosci* 2000; 20:RC89
58. McFarland K, Lapish CC, Kalivas PW: Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2003; 23:3531–3537
59. Volkow ND, Wang G-J, Fowler JS, Hitzemann R, Angrist B, Gattley SJ, Logan J, Ding Y-S, Pappas N: Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *Am J Psychiatry* 1999; 156:19–26
60. Wexler BE, Gottschalk CH, Fulbright RK, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC: Functional magnetic resonance imaging of cocaine craving. *Am J Psychiatry* 2001; 158:86–95
61. Rogers RD, Everitt BJ, Baldacchino AM, Blackshaw AJ, Swainson R, Bakera NB, Huntera J, Carthya T, Bookera E, London M, Deakin JFW, Sahakian GJ, Robbins TW: Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 1999; 20:322–339
62. Petry NM: Substance abuse, pathological gambling and impulsiveness. *Drug Alcohol Depend* 2001; 63:29–38
63. Kaufman JN, Ross TJ, Stein EA, Garavan H: Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci* 2003; 23:7839–7843
64. Forman SD, Dougherty GG, Casey BJ, Siegle GJ, Braver TS, Barch DM, Stenger VA, Wick-Hull C, Pizarov LA, Lorensen E: Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol Psychiatry* 2004; 55:531–537
65. Volkow ND, Fowler JS, Wang G-J, Swanson JM: Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry* 2004; 9:557–569
66. Whitelaw RB, Markou A, Robbins TW, Everitt BJ: Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behaviour under a second-order schedule of reinforcement. *Psychopharmacology (Berl)* 1996; 127:213–224
67. Meil WM, See RE: Lesions of the basolateral amygdala abolish the ability of drug associated cues to reinstate responding during withdrawal from self-administered cocaine. *Behav Brain Res* 1997; 87:139–148
68. Kantak KM, Black Y, Valencia E, Green-Jordan K, Eichenbaum HB: Dissociable effects of lidocaine inactivation of the rostral and caudal basolateral amygdala on the maintenance and reinstatement of cocaine-seeking behavior in rats. *J Neurosci* 2002; 22:1126–1136
69. Erb S, Stewart J: A role for the bed nucleus of the stria terminalis, but not the amygdala in the effects of corticotropin-releasing factor on stress-induced reinstatement of cocaine seeking. *J Neurosci* 1999; 19:RC35
70. Shaham Y, Erb S, Stewart J: Stress-induced drug seeking to heroin and cocaine in rats: a review. *Brain Res Rev* 2000; 33:13–33
71. Kilts CD, Gross RE, Ely TD, Drexler KPG: The neural correlates of cue-induced craving in cocaine-dependent women. *Am J Psychiatry* 2004; 161:233–241
72. Di Ciano P, Everitt BJ: Contribution of the ventral tegmental area to cocaine-seeking maintained by a drug-paired conditioned stimulus in rats. *Eur J Neurosci* 2004; 19:1661–1667
73. See RE, Kruzich PJ, Grimm JW: Dopamine, but not glutamate, receptor blockade in the basolateral amygdala attenuates conditioned reward in a rat model of relapse to cocaine-seeking behavior. *Psychopharmacology (Berl)* 2001; 154:301–310
74. Volkow ND, Wang G-J, Fowler JS, Logan J, Gattley SJ, Hitzemann R, Chen AD, Pappas N: Decreased striatal responsiveness in detoxified cocaine abusers. *Nature* 1997; 386:830–833
75. Graybiel AM, Moratalla R, Robertson HA: Amphetamine and cocaine induce drug-specific activation of the c-fos gene in striosome-matrix and limbic subdivisions of the striatum. *Proc Natl Acad Sci USA* 1990; 87:6912–6916
76. Nestler EJ: Molecular basis of long-term plasticity underlying addiction. *Nat Rev Neurosci* 2001; 2:119–128; correction, 2: 215
77. Lanahan A, Worley P: Immediate-early genes and synaptic function. *Neurobiol Learn Mem* 1998; 70:37–43
78. Nye HE, Hope BT, Kelz MB, Iadarola M, Nestler EJ: Pharmacological studies of the regulation of chronic FOS-related antigen induction by cocaine in the striatum and nucleus accumbens. *J Pharmacol Exp Ther* 1995; 275:1671–1680
79. Nestler EJ, Barrot M, Self DW: DeltaFosB: a sustained molecular switch for addiction. *Proc Natl Acad Sci USA* 2001; 98:11042–11046
80. Bibb JA, Chen J, Taylor JR, Svenningsson P, Nishi A, Snyder GL, Yan Z, Sagawa ZK, Ouimet CC, Nairn AC, Nestler EJ, Greengard P: Effects of chronic exposure to cocaine are regulated by the neuronal protein Cdk5. *Nature* 2001; 410:376–380

81. McClung CA, Nestler EJ: Regulation of gene expression and cocaine reward by CREB and DeltaFosB. *Nat Neurosci* 2003; 6: 1208–1215
82. Carlezon WA Jr, Nestler EJ: Elevated levels of GluR1 in the mid-brain: a trigger for sensitization to drugs of abuse? *Trends Neurosci* 2002; 25:610–615
83. Nestler EJ, Aghajanian GK: Molecular and cellular basis of addiction. *Science* 1997; 278:58–63
84. Rahman Z, Schwarz J, Gold SJ, Zachariou V, Wein MN, Choi KH, Kovoov A, Chen CK, DiLeone RJ, Schwarz SC, Selley DE, Sim-Selley LJ, Barrot M, Luedtke RR, Self D, Neve RL, Lester HA, Simon MI, Nestler EJ: RGS9 modulates dopamine signaling in the basal ganglia. *Neuron* 2003; 38:941–952
85. Neisewander JL, O'Dell LE, Tran-Nguyen LTL, Castaneda E, Fuchs RA: Dopamine overflow in the nucleus accumbens during extinction and reinstatement of cocaine self-administration behavior. *Neuropsychopharmacology* 1996; 15:506–514
86. Grimm JW, Hope BT, Wise RA, Shaham Y: Neuroadaptation: incubation of cocaine craving after withdrawal. *Nature* 2001; 412:141–142
87. Bowers MS, McFarland K, Lake RW, Peterson YK, Lapish CC, Gregory ML, Lanier SM, Kalivas PW: Activator of G-protein signaling 3: a gatekeeper of cocaine sensitization and drug-seeking. *Neuron* 2004; 42:269–281
88. Grimm JW, Lu L, Hayashi T, Hope BT, Su TP, Shaham Y: Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. *J Neurosci* 2003; 23:742–747
89. Swanson C, Baker D, Carson D, Worley P, Kalivas P: Repeated cocaine administration attenuates group I metabotropic glutamate receptor-mediated glutamate release and behavioral activation: a potential role for Homer 1b/c. *J Neurosci* 2001; 21: 9043–9052
90. Robinson TE, Gorny G, Mitton E, Kolb B: Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. *Synapse* 2001; 39:257–266
91. Segal M: Changing views of Cajal's neuron: the case of the dendritic spine. *Prog Brain Res* 2002; 136:101–107
92. Xi ZX, Ramamoorthy S, Baker DA, Shen H, Samuvel DJ, Kalivas PW: Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. *J Pharmacol Exp Ther* 2002; 303: 608–615
93. Nestler EJ, Terwilliger RZ, Walker JR, Sevarino KA, Duman RS: Chronic cocaine treatment decreases levels of the G protein subunits Gi alpha and Go alpha in discrete regions of rat brain. *J Neurochem* 1990; 55:1079–1082
94. Kelley AE, Schiltz CA: Accessories to addiction: G protein regulators play a key role in cocaine seeking and neuroplasticity. *Neuron* 2004; 42:181–187
95. Peterson JD, Wolf ME, White FJ: Altered responsiveness of medial prefrontal cortex neurons to glutamate and dopamine after withdrawal from repeated amphetamine treatment. *Synapse* 2000; 36:342–344
96. Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, Kalivas PW: Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003; 6:743–749
97. Bowers MS, Kalivas PW: Forebrain astroglial plasticity is induced following withdrawal from repeated cocaine administration. *Eur J Neurosci* 2003; 17:1273–1278
98. Kozell B, Meshul K: Alterations in nerve terminal glutamate immunoreactivity in the nucleus accumbens and ventral tegmental area following single and repeated doses of cocaine. *Psychopharmacology (Berl)* 2003; 165:337–345
99. Gnegy ME: Ca²⁺/calmodulin signaling in NMDA-induced synaptic plasticity. *Crit Rev Neurobiol* 2000; 14:91–129
100. Pierce RC, Quick EA, Reeder DC, Morgan ZR, Kalivas PW: Calcium-mediated second messengers modulate the expression of behavioral sensitization to cocaine. *J Pharmacol Exp Ther* 1999; 286:1171–1176
101. Shih AY, Murphy TH: xCt cystine transporter expression in HEK293 cells: pharmacology and localization. *Biochem Biophys Res Commun* 2001; 282:1132–1137
102. Baker DA, Xi ZX, Shen H, Swanson CJ, Kalivas PW: The origin and neuronal function of in vivo nonsynaptic glutamate. *J Neurosci* 2002; 22:9134–9141
103. Moran M, McFarland K, Melendez RI, Kalivas PW, Seamans J: Cystine-glutamate exchange regulates synaptic transmission. *J Neurosci* (in press)
104. Yao WD, Gainetdinov RR, Arbuckle MI, Sotnikova TD, Cyr M, Beaulieu JM, Torres GE, Grant SG, Caron MG: Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron* 2004; 41:625–638
105. Ghasemzadeh MB, Permenter LK, Lake R, Worley PF, Kalivas PW: Homer1 proteins and AMPA receptors modulate cocaine-induced behavioural plasticity. *Eur J Neurosci* 2003; 18:1645–1651
106. Szumlinski KK, Dehoff MH, Kang SH, Frys KA, Lominac KD, Klugmann M, Rohrer J, Griffin W III, Toda S, Champiaux NP, Berry T, Tu JC, Shealy SE, During MJ, Middaugh LD, Worley PF, Kalivas PW: Homer proteins regulate sensitivity to cocaine. *Neuron* 2004; 43:401–413
107. Griffith OW: Biologic and pharmacologic regulation of mammalian glutathione synthesis. *Free Radic Biol Med* 1999; 27: 922–935
108. Baptista MA, Martin-Fardon R, Weiss F: Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: comparison between cocaine and a potent conventional reinforcer. *J Neurosci* 2004; 24:4723–4727
109. Chiamulera C, Epping-Jordan M, Zocchi A, Marcon C, Cottiny C, Tacconi S, Corsi M, Orzi F, Conquet F: Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat Neurosci* 2001; 4:873–874
110. Paterson NE, Semenova S, Gasparini F, Markou A: The mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice. *Psychopharmacology (Berl)* 2003; 167:257–264