

# Unmanageable Motivation in Addiction: A Pathology in Prefrontal-Accumbens Glutamate Transmission Minireview

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**Prime diagnostic criteria for drug addiction include uncontrollable urges to obtain drugs and reduced behavioral responding for natural rewards. Cellular adaptations in the glutamate projection from the prefrontal cortex (PFC) to the nucleus accumbens have been discovered in rats withdrawn from cocaine that may underlie these cardinal features of addiction. A hypothesis is articulated that altered G protein signaling in the PFC focuses behavior on drug-associated stimuli, while dysregulated PFC-accumbens synaptic glutamate transmission underlies the unmanageable motivation to seek drugs.**

Drug addiction is characterized by poorly managed motivated behavior, exemplified by an uncontrollable drive to seek drugs and decreased incentive to seek non-drug rewards (Goldstein and Volkow, 2002). The persistence of these characteristics after years of drug abstinence indicates mediation by enduring neuroplasticity in the brain circuitry responsible for processing motivationally relevant stimuli. Research directed toward understanding the cellular mechanisms of neuroplasticity elicited by drugs of abuse has focused on dopamine release in the nucleus accumbens and the subsequent intracellular signaling events. This research has markedly advanced our understanding of the effects of acute drug administration and how drug use may transition from regulated (social) to compulsive (addicted) patterns of drug intake (Nestler et al., 2001). However, the cellular adaptations that underlie unmanageable drug seeking and reduced motivation for natural reward are not as well understood.

In contrast to the bulk of preclinical research, clinical neuroimaging studies have focused on addicts that manifest the diagnostic characteristics of addiction. These clinical investigations use changes in blood flow and metabolism as indicators of brain activity, and they reveal enduring alterations in the prefrontal cortex (PFC) and corticofugal projections to the nucleus accumbens (Goldstein and Volkow, 2002). Thus, basal activity in the PFC is reduced in addicts during withdrawal, and following presentation of drug-associated cues, the PFC and accumbens show large increases in activity that are associated with increased self-reports of “drug craving.” Moreover, presentation of stimuli associated with biological reinforcers, such as sexually evocative cues, also strongly activate the PFC-accumbens projection in normal subjects, but in addicts the increase

is blunted (Garavan et al., 2000). Finally, imaging studies in addicted subjects have shown an association between the abnormalities in PFC and decreased dopaminergic function (as evidence by reductions in dopamine D2 receptors), suggesting an involvement of dopamine in the addiction-related neuroadaptations in PFC. Provoked by the neuroimaging experiments, this minireview articulates an hypothesis that augmented responding for drug-associated stimuli and reduced responding for natural rewards arise from recently discovered cocaine-induced cellular adaptations in the glutamatergic projection from the PFC to the nucleus accumbens.

Initial data leading up to this hypothesis were obtained in vivo using the reinstatement animal model of addiction. In this model, animals are trained to self-administer drug. Responding for the drug (e.g., lever pressing or nose poking) is then extinguished by replacing drug for saline, and responding is subsequently reinstated by various stimuli known to precipitate relapse in addicts, such as stress, drug-associated cues, and acute administration of the drug itself. By combining this model of drug seeking in rats trained to self-administer cocaine with acute inactivation of brain nuclei or intracranial administration of neurotransmitter antagonists it was shown that increased glutamate release in the PFC-accumbens projection is required for the reinstatement of cocaine seeking (McFarland et al., 2004). Moreover, dopamine release and dopamine receptor stimulation in the PFC are also critical antecedents to reinstating drug seeking (Capriles et al., 2003; McFarland et al., 2004). Based on this literature, the simple circuit illustrated in Figure 1 emerges as a substrate required for initiating drug seeking and highlights two sites of neuroadaptation in cell signaling that could underlie the pathophysiology of cocaine addiction: dopamine synapses in the PFC and glutamate synapses in the accumbens. As outlined below, it is proposed that adaptations in PFC dopamine synapses promote behavioral responding by addicts for drug-related stimuli in preference for non-drug stimuli. In contrast, adaptations in glutamate synapses in the accumbens contribute to the uncontrollable drive to engage in drug seeking.

## *Dopamine in the Prefrontal Cortex*

Dopamine transmission in the PFC is critical for the reinstatement of cocaine seeking. Thus, intra-PFC microinjections of dopamine receptor antagonists prevent while agonists induce reinstatement, and increased release of dopamine in the PFC occurs during reinstatement (Capriles et al., 2003; McFarland et al., 2004; McFarland and Kalivas, 2001; Park et al., 2002). One cellular adaptation particularly important for cocaine-induced alterations in PFC pyramidal cell responses to dopamine is an increase in the content of activator of G protein signaling 3 (AGS3), which sequesters  $G_{i\alpha}$  and thereby limits signaling via  $G_{i\alpha}$ -coupled receptors (Bowers et al., 2004; Notochin et al., 2000). Dopamine D2 receptors are coupled to  $G_{i\alpha}$ , while D1 receptors signal via  $G_{s\alpha}$ , and corresponding to the elevation in

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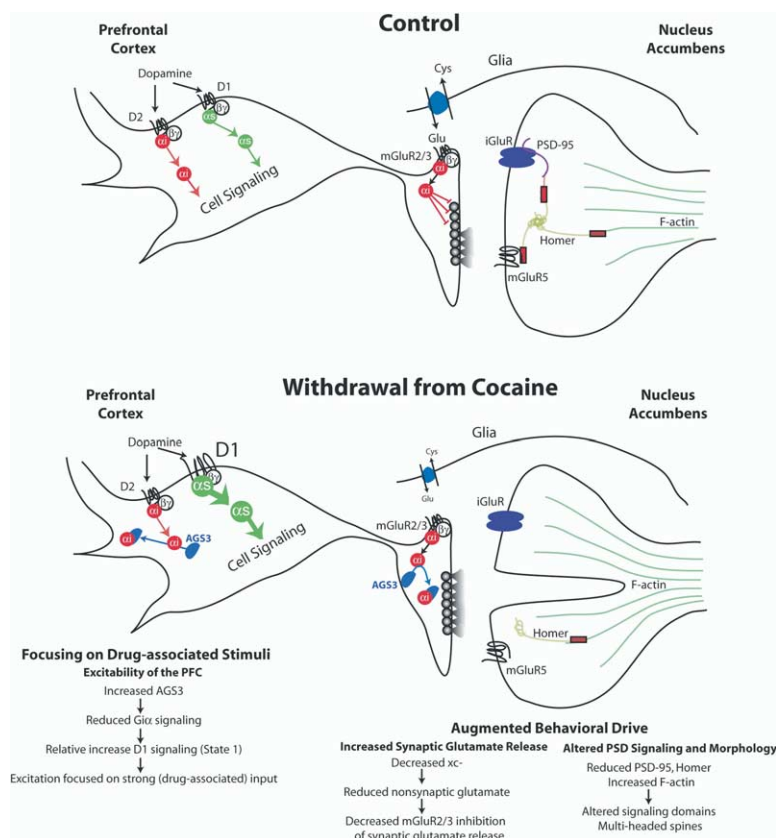


Figure 1. Cellular Adaptations in the PFC-Accumbens Projection that May Underlie the Cardinal Characteristics of Addiction

Cell signaling, changes induced by dopamine receptor signaling in ion channel conductances regulating cell excitability (see [Seamans and Yang, 2004](#), for detailed description); iGluR, ionotropic glutamate receptor; mGluR, metabotropic glutamate receptor. The size of symbols or lettering connotes increases or decreases following withdrawal from cocaine.

AGS3, G protein coupling to D2 receptors is reduced in the PFC following cocaine withdrawal ([Bowers et al., 2004](#)). Importantly, if AGS3 levels in the PFC of rats trained to self-administer cocaine are restored to normal using an antisense oligonucleotide strategy, the reinstatement of cocaine seeking is abolished. Conversely, if AGS3 sequestration of cells with the AGS3-Giα binding domain, animals show sensitized cocaine-induced behavioral responses and increased release of glutamate in the accumbens ([Bowers et al., 2004](#)).

Given the importance of dopamine transmission in the PFC in regulating cocaine seeking, it is possible that the reduction in D2 relative to D1 signaling may mediate the ability of AGS3 in the PFC to regulate PFC-accumbens glutamate transmission and cocaine seeking. A recent synthesis and modeling of the molecular mechanisms underlying the modulatory role of dopamine on PFC pyramidal cells is consistent with this possibility ([Seamans and Yang, 2004](#)). Thus, dopamine promotes two distinct states in PFC networks depending upon which dopamine receptor subtype is more potently regulating cell signaling ([Seamans and Yang, 2004](#)). State 1 predominates under D2 receptor stimulation and consists of reduced inhibition, which promotes the access of multiple excitatory inputs to drive PFC output to the accumbens. In contrast, state 2 predominates under increased D1 tone and is a relatively inhibited state that allows only particularly strong inputs to regulate PFC output. Thus, in state 1, multiple inputs

result in behavior that is regulated by competing motivationally relevant stimuli, while state 2 promotes more focused behavioral responding regulated by relatively few motivational stimuli. The inhibition of D2 signaling elicited by the cocaine withdrawal-induced increase in AGS3 will promote state 2, which may cause behavior to be oriented by particularly strong stimuli ([Figure 1](#)). In addicts, drug-associated stimuli would provide particularly strong activation of the prefrontal cortex due to the fact that the administration of drugs of abuse promotes dopamine release, and the pairing of drug-induced dopamine release with an environmental stimulus is thought to strengthen the encoding and motivational salience of that stimulus ([Schultz, 2002](#)). Thus, in addicts, only the potentiated drug-associated inputs would be of sufficient strength to overcome the inhibitory conditions produced by the AGS3-induced D1 predominance in state 2. Moreover, due to the elevated AGS3 and reduced D2 signaling caused by cocaine withdrawal, the release of dopamine in the PFC that is elicited by stimuli that initiate cocaine seeking (e.g., stress or cocaine) would preferentially act via D1 receptors to push PFC networks further into a state 2 dynamic, thereby further focusing behavior toward drug-associated stimuli.

#### Glutamate in the Nucleus Accumbens

Behavioral studies demonstrate that blocking AMPA/kainate glutamate receptors in the accumbens prevents the reinstatement of drug seeking ([Cornish and Kalivas, 2000](#); [Di Ciano and Everitt, 2001](#); [Park et al.,](#)

2002). Also, microdialysis estimates of extracellular glutamate reveal that increased release of glutamate from the PFC-accumbens pathway is associated with drug seeking, in particular the projection from the prelimbic cortex to the core compartment of the accumbens (McFarland et al., 2004). Cellular adaptations that alter the probability of glutamate release and glutamate signaling in the postsynaptic density (PSD) in pre- and postsynaptic glutamate transmission have been identified in the accumbens. Based on the data outlined below, it is proposed that cocaine-induced cellular adaptations in glutamate synapses reduce homeostatic regulation of glutamate transmission, thereby promoting synaptic glutamate release and compromising postsynaptic plasticity.

#### **Presynaptic Glutamate Transmission**

A primary cocaine withdrawal-induced adaptation in the accumbens impacting the probability of glutamate release is reduced levels of extracellular glutamate (Baker et al., 2003). Most of the basal extracellular glutamate in the accumbens is derived from the  $\text{Na}^+$ -independent exchange of one intracellular glutamate for one extracellular cystine molecule via cystine-glutamate exchange (system  $x_c^-$ ), and system  $x_c^-$  is down-regulated after withdrawal from repeated cocaine (Baker et al., 2003). Importantly, system  $x_c^-$  is substrate, not energy, dependent, and adding cystine to the extracellular space increases  $x_c^-$  activity (McBean, 2002). Thus, increasing  $x_c^-$  by systemic administration of procysteine drugs such as N-acetylcysteine restores extracellular glutamate and blocks cocaine-primed drug seeking and the associated increase in synaptic glutamate release (Baker et al., 2003). Figure 1 illustrates the proposed mechanism by which system  $x_c^-$  mediated elevation in nonsynaptic glutamate decreases synaptic glutamate release and thereby prevents the reinstatement of cocaine seeking. Glutamate derived from system  $x_c^-$  stimulates extrasynaptic group II metabotropic glutamate autoreceptors (mGluR2/3), which are known to regulate the probability of synaptic glutamate release (Dietrich et al., 2002). Electrophysiological studies in accumbens slices support this mechanism (Moran et al., 2003), as well as the fact that directly stimulating mGluR2/3 receptors inhibits the reinstatement of cocaine seeking (Baptista et al., 2004). In addition to reduced system  $x_c^-$ , an increased probability of synaptic glutamate release could also arise from cocaine withdrawal-induced reduction in mGluR2/3 signaling through  $\text{Gi}\alpha$  (potentially a result of elevated AGS3 produced in the accumbens by withdrawal from cocaine; Bowers et al., 2004).

#### **Postsynaptic Glutamate Transmission**

Proteins in the PSD regulate experimentally induced synaptic plasticity, such as long-term synaptic potentiation (LTP) (Malenka and Bear, 2004; Yao et al., 2004). Adaptations have been identified in PSD proteins following withdrawal from repeated cocaine that contribute to cocaine-induced behavioral plasticity. Figure 1 illustrates three of these proteins, including Homer, PSD-95, and filamentous (F)-actin. Homer, PSD-95, and actin are important for trafficking glutamate receptors and creating signaling microdomains in the PSD (Chandler, 2003). Homer1 content is reduced in the accumbens following withdrawal from cocaine, and deletion

of the Homer1 or Homer2 genes causes a behavioral and neurochemical phenotype remarkably similar to that produced by withdrawal from repeated cocaine, including the aforementioned alterations in AGS3,  $x_c^-$ , and extracellular glutamate (Szumlinski et al., 2004). Moreover, when Homer is rescued in the accumbens of Homer2 knockout mice using a viral transfection strategy, the increased release of glutamate and enhanced behavioral sensitivity to cocaine is eliminated (Szumlinski et al., 2004). PSD-95 is also decreased by withdrawal from chronic cocaine administration, and reducing PSD-95 by either cocaine withdrawal or gene deletion enhances LTP at PFC-accumbens glutamate synapses and produces sensitized behavioral responding to acute cocaine administration (Yao et al., 2004). F-actin is elevated in the accumbens by withdrawal from cocaine as a result of decreased levels of Lim kinase-1 (LIMK) (S. Toda et al., 2004, Soc. Neurosci., abstract). LIMK regulates cycling between monomeric and F-actin, and both actin cycling and LIMK are required for the extrusion and retraction of dendritic spines (Lee-Hoeflich et al., 2004). Thus, elevated F-actin and reduced LIMK may contribute to the increase in spine density and multiheaded spines produced by chronic cocaine (Robinson and Kolb, 1999). Importantly, inhibition of actin cycling and lowering F-actin levels by intraccumbens injection of latrunculin A prevents the expression of behavioral sensitization in cocaine-withdrawn animals (S. Toda et al., 2004, Soc. Neurosci., abstract). Taken together, the changes in PSD proteins elicited by withdrawal from cocaine may limit the formation and efficiency of signaling microdomains, as well as induce the dendritic dysmorphisms associated with chronic administration of psychostimulants and opioids.

#### **Conclusions**

Figure 1 illustrates sites of cellular plasticity in the PFC-accumbens glutamate projection that may account for the cardinal features of addiction. These molecular adaptations can be framed in concert with current clinical perspectives on cocaine addiction. First, AGS3-mediated predominance of D1 signaling in the PFC results in relative inhibition of PFC output, which can be characterized as hypofrontality and reduced motivation to respond to non-drug-related stimuli. However, strong motivational stimuli (e.g., drug-associated stimuli in addicts) will be more potent in activating PFC networks and initiating behavior directed toward this limited set of stimuli. Stimulated PFC pyramidal cells will encounter homeostatic deficits in glutamate synapses in the accumbens that will strengthen the behavior, making it more compulsive and difficult to disrupt. Thus, glutamate release at PFC-accumbens synapses is augmented due to reduced system  $x_c^-$  regulation of mGluR2/3 inhibitory autoreceptors, and the ability of the PSD to adaptively regulate postsynaptic responses to pathologically augmented glutamate release is compromised due to alterations in scaffolding and structural proteins. Taken together, these adaptations in addicts result in the compulsive focusing of behavior on drug-associated stimuli and reduced responding to non-drug stimuli.

### Selected Reading

- Baker, D.A., McFarland, K., Lake, R.W., Shen, H., Tang, X.C., Toda, S., and Kalivas, P.W. (2003). *Nat. Neurosci.* 6, 743–749.
- Baptista, M.A., Martin-Fardon, R., and Weiss, F. (2004). *J. Neurosci.* 24, 4723–4727.
- Bowers, M.S., McFarland, K., Lake, R.W., Peterson, Y.K., Lapish, C.C., Gregory, M.L., Lanier, S.M., and Kalivas, P.W. (2004). *Neuron* 42, 269–281.
- Capriles, N., Rodaros, D., Sorge, R.E., and Stewart, J. (2003). *Psychopharmacology* 168, 66–74.
- Chandler, L.J. (2003). *Pharmacol. Ther.* 99, 311–326.
- Cornish, J., and Kalivas, P. (2000). *J. Neurosci.* 20, 81–85.
- Di Ciano, P., and Everitt, B.J. (2001). *Neuropsychopharmacology* 25, 341–360.
- Dietrich, D., Kral, T., Clusmann, H., Friedl, M., and Schramm, J. (2002). *Neuropharmacology* 42, 297–305.
- Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.K., Sperry, L., Ross, T.J., Salmeron, B.J., Risinger, R., Kelley, D., and Stein, E.A. (2000). *Am. J. Psychiatry* 157, 1789–1798.
- Goldstein, R.A., and Volkow, N.D. (2002). *Am. J. Psychiatry* 159, 1642–1652.
- Lee-Hoeflich, S., Causing, C., Podkowa, M., Zhao, X., Wrana, J., and Attisano, L. (2004). *EMBO J.* 23, 4792–4801.
- Malenka, R., and Bear, M. (2004). *Neuron* 44, 5–21.
- McBean, G.J. (2002). *Trends Pharmacol. Sci.* 23, 299–302.
- McFarland, K., and Kalivas, P.W. (2001). *J. Neurosci.* 21, 8655–8663.
- McFarland, K., Davidge, S.B., Lapish, C.C., and Kalivas, P.W. (2004). *J. Neurosci.* 24, 1551–1560.
- Moran, M., Melendez, R., Baker, D., Kalivas, P., and Seamans, J. (2003). *Ann. N Y Acad. Sci.* 1003, 445–447.
- Natochin, M., Lester, B., Peterson, Y.K., Bernard, M.L., Lanier, S.M., and Artemyev, N.O. (2000). *J. Biol. Chem.* 275, 40981–40985.
- Nestler, E.J., Barrot, M., and Self, D.W. (2001). *Proc. Natl. Acad. Sci. USA* 98, 11042–11046.
- Park, W.K., Bari, A.A., Jey, A.R., Anderson, S.M., Spealman, R.D., Rowlett, J.K., and Pierce, R.C. (2002). *J. Neurosci.* 22, 2916–2925.
- Robinson, T.E., and Kolb, B. (1999). *Eur. J. Neurosci.* 11, 1598–1604.
- Schultz, W. (2002). *Neuron* 36, 241–263.
- Seamans, J.K., and Yang, C.R. (2004). *Prog. Neurobiol.* 74, 1–57.
- Szumliński, K.K., Dehoff, M.H., Kang, S.H., Frys, K.A., Lominac, K.D., Klugman, M., Rohrer, J., Toda, S., Griffin, W.C., Champtiaux, N.P., et al. (2004). *Neuron* 43, 401–413.
- Yao, W.D., Gainetdinov, R.R., Arbuckle, M.I., Sotnikova, T.D., Cyr, M., Beaulieu, J.M., Torres, G.E., Grant, S.G., and Caron, M.G. (2004). *Neuron* 41, 625–638.