Methamphetamine Induces Chronic Corticostriatal Depression: Too Much of a Bad Thing

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Leading theories of drug addiction propose that repeated drug exposure produces a long-lasting homeostatic dysregulation in brain reward processing that is normalized by drug readministration. In this issue of *Neuron*, Bamford and colleagues describe a novel neurobiological substrate that may contribute to this effect.

Drug addiction is a persistent, relapsing brain disorder characterized by a progressive increase in drug taking over which the addict maintains little control. Although the majority of research into the cellular underpinnings of addiction has typically focused on plasticity in brain regions such as the nucleus accumbens (NAc) and ventral tegmental area (VTA) (Kauer and Malenka, 2007), emerging evidence suggests that "habit" circuitry within the dorsal striatum also plays a heavy role in the maintenance of compulsive drug seeking evident during the latter stages of addiction (Everitt and Robbins, 2005; Porrino et al., 2004). Thus, AMPA or dopamine receptor antagonism in the dorsal (but not ventral) striatum produces decreases in compulsive drug seeking, indicating that glutamate and dopamine neurotransmission is critical for the expression of habitual drug-related behaviors (Vanderschuren et al., 2005).

The striatum is comprised of functionally distinct subregions defined in part by their differential input from discrete cortical areas. At the level of the ventral striatum, cortical information arrives largely from the prefrontal cortex, whereas glutamatergic inputs to the dorsolateral and dorsomedial striatum arise primarily from sensorimotor and prefrontal/cingulate cortices, respectively (Voorn et al., 2004). Glutamate terminals rest opposite the dendritic spines of GABAergic medium spiny neurons (MSNs), whereas dopamine axons from the midbrain and local acetylcholine interneurons form synapses on the necks of MSN spines (Surmeier et al., 2007). This arrangement places dopamine and acetylcholine terminals in a position to modulate neurotransmitter release and induce a number of plastic changes. Under normal conditions, it has been proposed that dopamine acts as a low-pass filter at less active corticostriatal terminals, reducing glutamate release via the dopamine D2 receptor (Bamford et al., 2004). Conversely, acetylcholine controls neurotransmitter release at dopamine and glutamate terminals by acting at presynaptic nicotinic receptors (nAchRs) (Wang and Sun, 2005; Zhang and Sulzer, 2004). However, relatively little is known about how repeated drug experience alters neurotransmission at these synapses or how this may contribute to the compulsive or habitual nature of drug seeking.

In this issue of *Neuron*, Bamford et al. (2008) begin to address this issue by investigating whether repeated exposure to the dopamine-releasing psychostimulant methamphetamine alters neurotransmission at corticostriatal synapses. Imaging of vesicular glutamate exocytosis in the dorsolateral striatum of mouse brain slices was accomplished using state-of-the-art optical techniques (Bamford et al., 2004). Briefly, the fluorescent dye FM1-43 was loaded into presynaptic corticostriatal terminals, and florescence levels were analyzed during electrical stimulation of the motor cortex designed to evoke glutamate exocytosis. The rate at which terminal florescence decreased as a result of stimulation (typically captured by the destaining half-time) provided an index of overall glutamate release from individual cortical terminals.

To investigate whether repeated drug exposure produced changes in corticostriatal neurotransmission, mice were treated with either saline or methamphetamine for 10 consecutive days. In comparison to saline-treated animals, mice repeatedly exposed to methamphetamine exhibited a significant increase in destaining half-times (i.e., slower glutamate release), indicative of a presynaptic depression at corticostriatal terminals. This finding was corroborated using electrophysiological techniques, as evidenced by a reduction in the frequency of spontaneous and miniature excitatory postsynaptic currents in MSNs from methamphetamine-treated animals. Importantly, this drug-induced depression (termed chronic presynaptic depression, or CPD, by the authors) was incredibly long lasting, as it was evident for up to 140 days following methamphetamine withdrawal. Additional experiments suggested that corticostriatal CPD was produced in part through a drug-related decline in tonic acetylcholine levels and a corresponding decrease in excitatory signaling at nicotinic acetylcholine receptors located on corticostriatal terminals.

Homeostatic models of drug addiction posit that recurring drug exposure produces long-lasting dysregulation in the neural systems evolved to mediate reward processing and that drug relapse may partially or temporarily return this system to a normal state (Ahmed and Koob, 1998). With this in mind, Bamford et al. delivered a challenge dose of methamphetamine to both drug-experienced (but withdrawn) and control animals. As

previously reported (Bamford et al., 2004), the induction of dopamine release in control animals acted as a low-pass filter, producing frequency-dependent decreases in glutamate release at less active terminals. In stark contrast, animals with a drug history exhibited accelerated and renormalized glutamate release from the most active corticostriatal terminals following drug readministration, thereby disrupting normal filtering mechanisms. However, this alteration was not produced by a change in drug-induced dopamine release, which remained normal following repeated methamphetamine exposure. Rather, this "paradoxical presynaptic potentiation," or PPP, occurred via stimulation of both dopamine D1 receptors and nAchRs, as it was blocked by either D1 or nAchR receptor antagonism and could be mimicked by both D1 and nAchR receptor agonists.

Collectively, these findings demonstrate that repeated psychostimulant administration produces a robust and long-lasting decrease in corticostriatal glutamate release that is reversed by re-exposure to methamphetamine. These results are largely consistent with reports that drug experience produces decreases in glutamate levels and long-term depression at MSNs within the ventral striatum (McFarland et al., 2003; Thomas et al., 2001). Thus, drug-induced corticostriatal depression may not be unique to the dorsolateral striatum. However, a number of separate mechanisms for plasticity have been observed at corticostriatal synapses (Kauer and Malenka, 2007). It is not clear whether CPD and PPP influence this plasticity or how these alterations may work together to produce intractable and compulsive behaviors characteristic of drug addiction. Indeed, as this report only examined corticostriatal exocytosis following experimenter-administered methamphetamine, precisely how drug-induced corticostriatal depression emerges and interacts with learning-related alterations during drug self-administration (Carelli and Wightman, 2004; Phillips et al., 2003) is a question for open discussion and research. One possibility is that CPD and PPP disrupt normal filtering mechanisms of corticostriatal information flow critical for learning, leading to aberrant reward processing and action selection. If so, the discovery of methods to reverse this plasticity may be a promising avenue for addiction treatment.

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A Remarkable Facilitating Effect of Parietal Damage

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When distracters conflict with our instructions, our reactions normally get slower. However, Coulthard and colleagues in this issue of *Neuron* show that damage to the right parietal lobe reverses this effect, paradoxically *facilitating* responses. This surprising result may shed light on the functional role of parietal cortex within a larger cortical circuit for voluntary behavior.

Functional interpretation of the posterior parietal cortex (PPC) has been notoriously challenging. Despite decades of research using a variety of approaches including single-unit recording, functional imaging, lesion studies, and transcranial magnetic stimulation (TMS), a unified view of PPC function has not yet emerged. PPC is clearly involved in many kinds of spatial attention (Colby and Goldberg, 1999; Rushworth et al., 1997), but it has also been implicated in sensorimotor control