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The Brain on Drugs: From Reward to Addiction

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Advances in neuroscience identified addiction as a chronic brain disease with strong genetic, neurodevelopmental, and sociocultural components. We here discuss the circuit- and cell-level mechanisms of this condition and its co-option of pathways regulating reward, self-control, and affect. Drugs of abuse exert their initial reinforcing effects by triggering supraphysiologic surges of dopamine in the nucleus accumbens that activate the direct striatal pathway via D1 receptors and inhibit the indirect striato-cortical pathway via D2 receptors. Repeated drug administration triggers neuroplastic changes in glutamatergic inputs to the striatum and midbrain dopamine neurons, enhancing the brain's reactivity to drug cues, reducing the sensitivity to non-drug rewards, weakening self-regulation, and increasing the sensitivity to stressful stimuli and dysphoria. Drug-induced impairments are long lasting; thus, interventions designed to mitigate or even reverse them would be beneficial for the treatment of addiction.

The nature of addiction is frequently debated as either a personal "lifestyle choice" or a "biological vulnerability." Current evidence shows that most drugs of abuse exert their initial reinforcing effects by activating reward circuits in the brain and that, while initial drug experimentation is largely a voluntary behavior, continued drug use impairs brain function by interfering with the capacity to exert self-control over drug-taking behaviors and rendering the brain more sensitive to stress and negative moods. Indeed, individuals with genetic vulnerabilities, exposed to chronic stress, or suffering from comorbid psychiatric conditions, as well as those who abused drugs during early adolescence, are at greater risk of transitioning into the automatic and compulsive behaviors that characterize addiction.

Drugs modulate the expression of genes involved in neuroplasticity through epigenetic and possibly RNA modifications, ultimately perturbing intracellular signaling cascades and the neuronal circuits whose dysfunction have been implicated in the long-lasting changes associated with addiction. Here, we highlight some of the most significant and recent findings in drug reward and addiction, describing the circuit, behavioral, and synaptic mechanisms underlying this process. Space limitations do not allow us to review the intracellular signaling cascades and epigenetic modifications associated with addiction; thus, we refer readers to recent reviews on these topics (Heller et al., 2014; Nestler, 2012; Pascoli et al., 2014a).

Drug Reward Signaling in Brain

Dopamine (DA) neurons located in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) play a key role in the processing of reward-related stimuli, including those associated with drugs of abuse (Wise, 2008). Drugs of abuse, through their different pharmacological effects, increase the release of DA in the shell subregion of the NAc (Di Chiara, 2002), mimicking the phasic DA neuronal firing that leads to very fast DA increases (Owesson-White et al., 2009) and thus the mechanism through which the brain signals reward (Box 1). The large DA increases triggered by phasic DA cell firing are necessary to stimulate D1 receptors (D1R) in the NAc.

DA neurons in the VTA fire in either a tonic (1–8 Hz) or a transient (<500 ms) high-frequency phasic mode (>15 Hz), with the phasic mode resulting in larger DA increases than the tonic mode. Though it was initially believed that DA signaling in the brain encoded for reward, more recent findings have revealed that it encodes for a reward prediction signal. Specifically, these studies have shown that phasic DA firing is time locked to unexpected or novel reward but is also triggered by cues that predict reward. Moreover, the firing frequency of DA neurons triggered by cues is associated with the expected reward value and its probability of delivery, but if the expected reward does not materialize, DA cell firing is inhibited (Schultz, 2002). Changes in the response patterns of DA cell firing are modulated by more distinct projections for tonic than for phasic firing (Box 1). Changes in phasic DA firing patterns modify the strength of cortico-striatal glutamatergic synapses, thus altering signaling in D1R- and D2R-expressing GABAergic medium spiny neurons (MSNs) (Paladini and Roeper, 2014). This is distinct from DA signaling in the NAc driven by release from tonic DA neuron firing, which results in lower DA increases than from phasic firing but that are sufficient to stimulate D2R signaling and have been mostly associated with motivational drive (Dreyer et al., 2010; Trifilieff et al., 2013). Though most studies link drug-induced neuroplasticity with the fast and large transient DA changes triggered by drugs, the contribution from

Box 1. Modulation of VTA DA Neuronal Firing

Recent pseudorabies virus-based methods for monosynaptic network tracing have shown that neurons from many brain areas synapse on distinct VTA DA neuron subpopulations (Lammel et al., 2014) and that neurons from the dorsal raphe (DR) provide the majority of monosynaptic inputs (Ogawa et al., 2014). Studies of the influence of these projections on DA neurons have been limited to a few brain structures (Paladini and Roeper, 2014). For instance, the control of tonic firing of VTA DA neurons involves the stria terminals and the ventral pallidum (Georges and Aston-Jones, 2001; Mahler et al., 2014), whereas the control of phasic firing of VTA DA neurons involves the pedunculo pontine tegmentum (PPT), the subthalamic nucleus (STN), and the laterodorsal tegmentum (Floresco et al., 2003; Lodge and Grace, 2006). VTA DA neurons receive GABAergic innervation from local GABAegic neurons, the NAc, globus pallidus, and rostromedial tegmental nucleus, among others. These GABAergic projections are implicated in the control of burst timing (Paladini and Roeper, 2014). It is likely that phasic and tonic changes in DA neuronal firing triggered by repeated drug administration, reflect neuroplastic changes in these regions and on inputs that relay to them. For example, the lateral habenula (LHb) indirectly inhibits VTA DA neurons via its inputs to GABA neurons in rostromedial tegmental nucleus (Ji and Shepard, 2007), eliciting aversion (Lammel et al., 2012), and these inputs are modified by repeated cocaine administration (Meye et al., 2015). Thus, future studies will be able to assess their contribution to the dysphoria and enhanced stress reactivity in addiction.

We recently showed abundant glutamatergic projections from the DR to VTA DA neurons that innervate the NAc, whose activation induced DA release in NAc and evoked reward (Qi et al., 2014). The DR is best known as a serotonergic structure that regulates emotional behaviors. However, findings on the role of DR serotonergic neurons in reward have been inconsistent (Cohen et al., 2015; Fonseca et al., 2015; Liu et al., 2014; McDevitt et al., 2014; Miyazaki et al., 2014), which is likely to reflect, in part, the functional diversity of these neurons. In this regard, cellular recordings from DR serotonergic neurons in behaving mice have revealed that they convey reward information through tonic as well as phasic firing and that they signal reward and punishment on multiple timescales (Cohen et al., 2015). The DR also has glutamatergic and GABAergic neurons, some of which co-release serotonin, and thus future studies are necessary to tease apart the specific targets of the diverse serotonergic neurons and of their neighboring GABAergic and glutamatergic neurons (Liu et al., 2014; McDevitt et al., 2014; Qi et al., 2014). In this regard, we recently showed that, within the VTA, DR neurons expressing the vesicular glutamate transport (VGluT3) preferentially establish synapses on DA neurons (Qi et al., 2014). These DR-VGluT3 neurons provide a major glutamatergic input to VTA DA neurons, including those that innervate the NAc. Selective activation of these DR-VGluT3 fibers results in VTA glutamate release, NAc DA release, and reward (Qi et al., 2014). Notably, these DR VGluT3-glutamatergic neurons (some of which may co-release serotonin) are highly interactive with the serotonergic system (Commons, 2009). Thus, a better understanding of the function and connections of the diverse DR neurons will help us determine whether they serve as a link between reward and mood regulation and whether they contribute to the high co-morbidity between drug use and depression.

the longer-lasting stimulation of D2R (also D3R and D4R) has been much less investigated.

VTA DA neurons project predominantly to the NAc, where DA interacts with D1R, D2R, and D3R, which are mainly expressed in MSNs. Stimulatory striatal MSNs that express D1R (D1R-MSNs) signal through the direct striatal pathway, whereas those that express D2R (D2R-MSNs) signal through the striatal indirect pathway and act in an inhibitory manner. D3R mostly co-localize with D1R-MSNs, with which they heteromerize, potentiating their function (Marcellino et al., 2008). The ventral striatal direct and indirect pathways have distinct roles in modulating reward and motivation. The direct pathway is associated with reward, whereas the indirect one is associated with punishment (Hikida et al., 2010; Kravitz et al., 2012). Thus, DA receptor stimulation of the direct pathway directly mediates reward, whereas DA-receptor-mediated inhibition of the indirect pathway opposes aversive responses. This could explain why maximal drug reward is obtained when DA binds to both D1R and D2R. However, in contrast to the situation in the dorsal striatum, where the direct and indirect pathways are fully segregated, in the NAc, both D1R- and D2R-expressing MSNs project into the ventral globus pallidum (Smith et al., 2013b). To be reinforcing, drug-induced DA increases need to be fast and sufficiently large to stimulate low-affinity D1R in addition to D2R, leading to the activation of the direct pathway and the inhibition of the indirect pathway. D1R stimulation in the NAc by itself is sufficient to produce drug reward (Caine et al., 2007), whereas D2R stimulation is not (Caine et al., 2002; Durieux et al., 2009; Norman et al., 2011), and maximal reward occurs when both D1R and D2R are activated (Steinberg et al., 2014; Welter et al., 2007). Indeed, brain imaging studies in humans have documented that fast DA increases triggered by drugs are associated with the "high" associated with drug abuses, whereas stable DA increases are not (Volkow et al., 2008). Specifically, when large DA increases triggered by stimulant drugs were achieved over a short time period (<10 min), they were associated with reward, whereas DA increases achieved over 60 min were not. The rate dependency for a drug's rewarding effects might explain why the time course of the subjective "high" is much shorter than the longer-lasting DA increases triggered by drugs such as cocaine and more notable methylphenidate (Figure 1). Presumably, stimulation of D1 and D2R only occurs when drugs achieve fast peak concentrations, whereas as the concentration of DA starts to decrease, D2R are predominantly stimulated (Luo et al., 2011). This may also explain why routes of administration that achieve faster and higher drug levels in the brain, such as smoking and intravenous injection, are more rewarding and addictive than routes of administration that result in slow brain uptake, like oral administration.

DA increases that are sufficiently large to activate D1R, such as those induced by drugs in the NAc, can induce associative learning, also referred to as conditioning (Zweifel et al., 2009). Stimuli (including contextual or environmental) associated with the drug become conditioned and, with repeated co-exposure, will trigger phasic DA neuronal firing in the VTA, resulting in fast, large, and short-lasting DA increases in the NAc. The DA increases triggered by these conditioned stimuli (CS) are believed to reflect the expectation of receiving a reward. Glutamatergic projections into D1R-expressing MSNs coming from the amygdala (involved in emotional reactivity), hippocampus (involved in memory), and ventral PFC (involved in salience attribution) mediate these conditioned responses. The increased dopaminergic signaling that follows exposure to the CS ensures that