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Ventral tegmental glutamate: A role in stress-, cue-, and cocaine-induced reinstatement of cocaine-seeking

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Abstract

Ventral tegmental dopamine neurons are activated by primary rewards and, when such rewards are predictabale, by reward-predicting stimuli. Glutamatergic input to the ventral tegmental area contributes to this activation: in animals trained to self-administer cocaine, cocaine predictive cues trigger ventral tegmental glutamate release and dopaminergic activation. Mild footshock stress similarly causes glutamate release and dopaminergic activation in cocaine-trained but not cocaine-naïve animals. The ability of cocaine-predictive and stress-associated cues to activate the dopamine system and to trigger cocaine craving appears to be related to changes in the ability of glutamate to activate dopaminergic neurons, changes known to be caused by experience with stress or with drugs of abuse.

The habit-forming and habit-sustaining effects of cocaine are linked to the drug's ability to elevate dopamine levels in the terminal fields of the mesocorticolimbic dopamine system (Wise, 2004). While it is difficult to train animals to self-administer cocaine into this region (Carlezon et al., 1995; Goeders and Smith, 1983; Ikemoto, 2003), the nucleus accumbens figures strongly in most accounts (Pettit et al., 1984; Pettit and Justice, 1989; Roberts et al., 1977; Wise et al., 1995). Nucleus accumbens also figures strongly in theories dealing with the motivation for trained animals to initiate cocaine self-administration, even after the response habit has undergone substantial extinction (Kalivas, 2004). Inasmuch as trained animals will initiate responding even when the dopamine system pharmacologically blocked (de Wit and Wise, 1977; Yokel and Wise, 1975), it is the glutamatergic rather than the dopaminergic input to nucleus accumbens that is seen to be primarily responsible for instigation of responding (Kalivas, 2004).

While glutamatergic input to nucleus accumbens is sufficient to reinstate responding in animals that have undergone extinction of their cocaine-trained habit, cocaine-seeking can also be induced by glutamatergic input to the ventral tegmental dopamine system itself (You et al., 2007). Interest in this possibility was prompted in part by evidence that the medial prefrontal cortex innervates the ventral tegmental area as well as the nucleus accumbens (Sesack and Pickel, 1992). Inhibition of prefrontal cortex decreases stratal dopamine release, and disinhibition of prefrontal cortex increases it (Karreman et al., 1995). Electrical stimulation of the medial prefrontal cortex causes glutamate release in the ventral tegmental area (Rossetti et al., 1998) and activates the early immediate gene *c-fos* in ventral tegmental neurons (Rossetti et al., 1998); this effect of glutamate release is blocked by ionotropic glutamate receptor blockade in the ventral tegmental area (Taber et al., 1995; You et al., 1998). Stimulation of prefrontal cortex also elevates nucleus accumbens dopamine release, an effect that is also blocked by ionotropic glutamate receptor blockade in the ventral tegmental area. Thus the

prefrontal cortex appears to cause striatal dopamine release by activating dopaminergic neurons at the level of their cell bodies.

These facts and the fact that reward-conditioned stimuli are known to activate the dopamine system (Schultz et al., 1997) led to our interest in the possibility that ventral tegmental glutamate release contributes to the rewarding and response-initiating effects of cocaine. Indeed, we found that ionotropic glutamate antagonists infused into the ventral tegmental area appear to reduce the rewarding effects of intravenous cocaine injections, as reflected in compensatory increases in drug-taking (You et al., 2007). Interestingly, the role of glutamate was not tied to cocaine reward itself, but rather appeared due to the added value provided by cocaine-associated environmental stimuli; this conclusion was drawn in part from the fact that ventral tegmental infusion of ionotropic glutamate antagonists blocked almost completely the normal ability (Davis and Smith, 1976) of cocaine-conditioned stimuli to maintain prolonged responding during extinction testing (You et al., 2007).

Our conclusion that glutamate mediates the motivational effects of cocaine-associated conditioned stimuli was also based on our finding that ventral tegmental glutamate release was not caused only by cocaine reward itself, but also by the stimuli and conditions that predicted cocaine reward (You et al., 2007). Thus glutamate was released in the ventral tegmental area of cocaine-trained rats when they earned the expected cocaine but also when their lever-pressing earned unexpected saline injections. After several days of extinction training, when the animals had repeatedly earned saline rather than cocaine, the saline injections lost the ability to cause glutamate release. If unearned cocaine injections were given to animals that had been trained to self-administer the drug, the injections caused glutamate release. However, if given to cocaine-naïve animals, or if given to animals that had received unpredictable cocaine injections in the past, unearned cocaine injections failed to cause significant ventral tegmental glutamate release (You et al., 2007). Thus it was not cocaine but rather the expectancy of cocaine that triggered ventral tegmental glutamate release. This finding fit well with the finding of Schultz that dopaminergic neurons become responsive to environmental stimuli as those stimuli come to reliably predict reward (Schultz, 1998). It also fit with earlier data of Duffy and Kalivas that intraperitoneal cocaine causes ventral tegmental glutamate release in animals that have received such injections in the past but not in animals that have received repeated saline injections in the past (Kalivas and Duffy, 1998).

The finding that cocaine experience alters both the ability of cocaine itself and also the ability of cocaine-associated stimuli to cause glutamate release and dopaminergic activation raises the question of what neuroadaptations occur in this circuitry as a result of cocaine self-administration experience. This is a question also raised by our findings with reinstatement of cocaine-seeking by stress. We have found that mild footshock stress causes ventral tegmental glutamate release, ventral tegmental dopamine release, and relapse to drug-seeking in animals previously trained to self-administer cocaine; however, it does not cause ventral tegmental glutamate or dopamine release (or significant lever-pressing) in animals without such training (Wang et al., 2005). Here we have traced the sequence of events in some detail. The footshock stress causes ventral tegmental release of the stress-associated neurohormone corticotropin-releasing factor (CRF). It does so equally in cocaine-trained and cocaine-naive animals. Ventral tegmental infusion of CRF antagonists blocks the effects of footshock on local glutamate and dopamine release and blocks the ability of footshock to reinstate cocaine-seeking. Footshock stress or infusion of CRF into the ventral tegmental area causes ventral tegmental glutamate and dopamine release in cocaine-trained but not cocaine-naïve animals (Wang et al., 2005). Local blockade of ionotropic glutamate receptors blocks the evoked—dendritic—dopamine release (Wang et al., 2005) that is a correlate of dopaminergic neuronal activation (Legault et al., 2000; Legault and Wise, 1999, 2001). Here again, cocaine experience causes neuroadaptations that alter the glutamatergic activation of the dopamine system.

It is not yet clear exactly *how* cocaine experience alters the ability of footshock stress to activate the glutamate input to the dopamine system. On the one hand, there are clear parallels to work of the Bonci group on the long-term potentiation of glutamatergic input to dopamine neurons in an in vitro slice preparation. They have found that prior stress or prior experience with cocaine, morphine, nicotine or ethanol increases the ability of glutamate to activate dopamine neurons (Saal et al., 2003; Ungless et al., 2001). Similar long-term potentiation of glutamatergic activation of ventral tegmental dopamine neurons can be induced by local application of CRF (Ungless et al., 2003). CRF-induced long-term potentiation of glutamatergic signaling (Ungless et al., 2003) and CRF-induced glutamate release and reinstatement of drug-seeking (Wang et al., 2007) are similarly blocked by local infusion of CRF receptor-R1 (CRF-R1) but not CRF-R2 antagonists or by local infusion of $CRF_{6–33}$, a CRF fragment that does not bind to either CRF receptor but binds to CRF-binding protein (Chan et al., 2000), a protein that can bind CRF and alter CRF function in multiple ways (Seasholtz et al., 2002). The similarity of pharmacological profile suggests a common neuroadaptation underlying CRF-induced long-term potentiation of ventral tegmental glutamate signaling and of CRF-induced reinstatement of drug-seeking.

However, several findings fail to fit will with our initial working model. Our data suggest that footshock stress causes ventral tegmental release of CRF, that the CRF causes local glutamate release, and that the glutamate release is responsible for activation of the dopamine system (as reflected in dendritic dopamine release) (Wang et al., 2005). However, the primary effect reported by Ungless et al. is a post-synaptic change in the ratio of NMDA to AMPA signaling (Ungless et al., 2001), where our effect appears to be a presynaptic change in a glutamate release mechanism (Wang et al., 2007). The Bonci group is currently looking for signs of presynaptic modifications (personal communication) that might cause or contribute to their post-synaptic changes. In addition, while Ungless et al. were able to detect signs of mRNA for the CRF-R2 in dopaminergic neurons using PCR, this mRNA is not expressed strongly enough for detection by *in situ* hybridization (Van Pett et al., 2000). Selective antibodies for CRF-R2 are not available, so it is not known if CRF-R2 is expressed in ventral tegmental terminals of glutamatergic projections. While no known anatomical findings support the view that CRF-containing fibers synapse on glutamatergic terminals in the ventral tegmental area, there is evidence that CRF is co-expressed in glutamate-containing fibers making direct excitatory synapses on dopaminergic neurons (Tagliaferro and Morales, 2008), neurons that express mRNA for both CRF-R1 (Tagliaferro et al., 2007) and for the CRF binding protein (Wang and Morales, 2008). Thus while our pharmacological data suggest that CRF acts at CRF-R2 receptors to activate dopaminergic neurons indirectly, through an action on glutamatergic neurons, the anatomical evidence to date suggest that CRF and glutamate are co-released directly onto dopaminergic neurons that express CRF-R1. Further work on the interaction of CRF and glutamate with ventral tegmental neurons is in progress.

Our initial hypothesis was that CRF interacted at presynaptic glutamatergic terminals originating perhaps in the medial prefrontal cortex or the laterodorsal or pedunculopontine tegmental nucleus. Recently, however, it has become clear that the glutamatergic projection from the prefrontal cortex to the ventral tegmental area is a weak one (Omelchenko and Sesack, 2007), that there are many subcortical glutamatergic inputs to the ventral tegmental area (Geisler et al., 2007), and that there are even ventral tegmental glutamatergic neurons (Yamaguchi et al., 2007) that synapse with their dopaminergic neighbors (Dobi and Morales, 2007). Thus there are multiple sources of glutamate input to the ventral tegmental area, and it is not clear which of them is the source of the CRF-mediated glutamate input. The pedunculopontine tegmental nucleus seems a likely candidate for the cue-induced glutamate input (Pan and Hyland, 2005).

Whatever the details, it is clear that glutamatergic afferents carry conditioned motivational signals to the dopamine system and that prior experience with cocaine causes neuroadaptations in this pathway. While this pathway does not carry instructions about where in the environment the relevant reward can be found, it appears to carry information about the availability of reward, information that comprises part of an arousal signal with potential importance both for reward function and motivational function.

This system is then positioned to interact with the more information-laden glutamatergic input to the striatum. The dopamine system projects to the shafts of the spines of striatal output neurons, spines which receive the glutamatergic input from prefrontal cortex (Sesack and Pickel, 1992), medial thalamus (Pinto et al., 2003), amygdala (Johnson et al., 1994), and hippocampus (Totterdell and Smith, 1989). These structures presumably carry epicritic information about the motivationally significant stimuli that, in parallel, provide protopathic information to the ventral tegmental area. Presumably, the glutamatergic input to the ventral tegmental dopamine neurons acts in concert with glutamatergic input to the output neurons of the stratum (Kalivas, 2004), modulating the glutamatergic input to the striatal output neurons involved in initiation and reinstatement of cocaine-seeking.

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