Commentary

Biological Psychiatry

Unexpected Results on the Role of Nucleus Accumbens Dopamine in Stress-Induced Relapse

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In this issue of *Biological Psychiatry*, Twining *et al.* (1) reported that an aversive stimulus (quinine solution) reduces tonic dopamine signal in nucleus accumbens (NAc) shell and reinstates cocaine seeking after extinction of drug-reinforced responding in rats. They also reported that injections of a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist into the ventral tegmental area (VTA) reverse the effect of quinine on the tonic dopamine levels and prevent quinine-induced reinstatement of cocaine seeking. We first summarize these data and then discuss their implications for the role of mesocorticolimbic dopamine in stress-induced relapse to drug seeking and for the dopamine depletion hypothesis of drug addiction.

Summary of Study

The authors of this excellent study first used fast-scan cyclic voltammetry to monitor dopamine fluctuations in NAc shell during a session in which brief intraoral delivery of an aversive taste stimulus, a quinine solution, was passively delivered to freely moving drug-naïve rats. Quinine infusions induced characteristic aversive taste reactivity responses that were associated with time-locked (millisecond scale) reductions in phasic dopamine signaling in NAc. Intraoral quinine delivery also reduced NAc time-averaged dopamine concentrations that were evident at baseline and during the period after quinine delivery; this decrease was due to reduced dopamine transient frequency but not amplitude. The authors interpreted these data to indicate that quinine delivery caused a long-lasting (minute scale) decrease in tonic dopamine levels in NAc. Next, the authors used the reinstatement model to demonstrate that under identical quinine delivery parameters, the aversive taste stimulus reinstates drug seeking after extinction of drug-reinforced responding in rats with a history of intravenous cocaine self-administration. They also showed that blockade of CRF type 1 receptors in VTA of drug-naïve rats prevents quinine's effect on the reduction in tonic (but not phasic) dopamine concentrations in NAc and that the same manipulation in cocaine-experienced rats prevents quinine-induced reinstatement of cocaine seeking.

Implications for the Role of Mesocorticolimbic Dopamine in Stress-Induced Relapse

The present data are elegant and internally consistent, but they are highly unexpected based on the previous literature. In particular, since the early to mid 1980s, many studies using the reinstatement model indicate that reinstatement induced by aversive (intermittent footshock stress) and appetitive (drug cues or priming) stimuli is mediated by activation rather than inhibition of the mesocorticolimbic dopamine system (2). Additionally, the effect of intermittent footshock (a stressor that increases tonic dopamine concentrations in NAc) on reinstatement of cocaine seeking is prevented by blockade of CRF receptors in VTA (3,4).

What might account for the seemingly contradictory results from the study by Twining *et al.*? One possibility is that tonic dopamine concentrations measured in fast-scan cyclic voltammetry are different from the tonic dopamine that is measured by in vivo microdialysis. We believe it is unlikely that the two methods would yield opposite changes in dopamine concentrations under the same experimental conditions because consistent with the finding by Twining *et al.* of reduced NAc dopamine by an aversive tastant is evidence from an early microdialysis study that taste aversion is associated with a rapid decrease in NAc dopamine concentrations (5). However, one issue to consider in interpreting the data of Twining *et al.* (1) is that, as mentioned earlier, the effect of quinine on NAc dopamine concentrations was determined in drug-naïve rats, whereas the effect of quinine on reinstatement of drug seeking was determined in cocaine-experienced rats. Particularly in reference to stress or aversive stimuli effects on mesocorticolimbic dopamine transmission, this difference may be critical. Wang *et al.* (3) reported that in cocaine-experienced (but not drug-naïve) rats, footshock stress increases CRF levels in VTA, leading to increased local glutamate release, which causes activation of the mesocorticolimbic dopamine system that leads to reinstatement of cocaine seeking.

Based on these findings, it remains an open question whether the aversive quinine taste would decrease NAc dopamine tone in drug-experienced rats in the presence of cocaine-associated contexts and cues and whether quinine-induced changes in tonic dopamine can directly drive cocaine seeking in these rats. Figure 1 illustrates the opposite effects that footshock and quinine stressors have on NAc dopamine concentrations, despite both changes being associated with increased cocaine seeking, and further illustrates the surprising conclusion from the study by Twining *et al.* and the above-described studies that CRF antagonism in the VTA regulates reinstatement induced by both stressors.

Implications for the Dopamine Depletion Hypothesis

The 1985 dopamine depletion hypothesis posits that cocaine addiction results from a withdrawal-induced dysphoric state in which the depletion of synaptic dopamine drives cocaine

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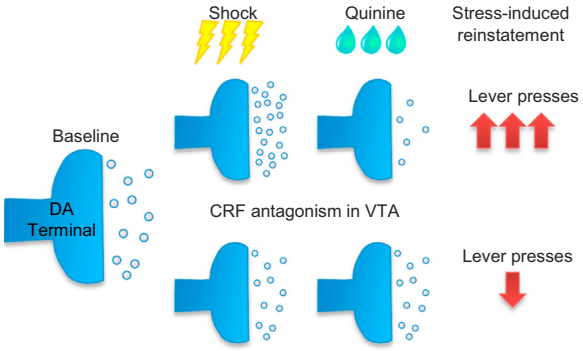

Figure 1. The effects of intermittent footshock stress and aversive quinine solution on extracellular dopamine concentrations in nucleus accumbens and on reinstatement of cocaine seeking. The two aversive stimuli cause reinstatement of cocaine seeking but have opposite effects on dopamine release from the mesolimbic dopamine system (the ventral tegmental area dopamine neurons that project to the nucleus accumbens). Unexpectedly, blockade of corticotropin-releasing factor receptors in the ventral tegmental area blocks the effect of stressors on reinstatement of cocaine seeking and activation (footshock) or inhibition (quinine) of this dopamine system. Data summarize results from the study by Twining *et al.* (1) and previous published reports (3,4). CRF, corticotropin-releasing factor; DA, dopamine; VTA, ventral tegmental area.

seeking to return dopamine to normal, drug-naïve levels (6). A series of in vivo microdialysis and electrical intracranial self-stimulation (a dopamine-dependent phenomenon) studies during the early 1990s provided a physiological basis for this hypothesis by demonstrating that during early withdrawal from different drugs of abuse the threshold for intracranial self-stimulation is increased (reflecting decreased brain stimulation reward) and extracellular dopamine levels in NAc are decreased (7,8). However, with one potential recent exception (9), over the years investigators were unable to demonstrate in animal models of drug addiction that a NAc dopamine-depleted withdrawal state can motivate drug-taking behavior. For example, a study using the reinstatement model showed that naloxone-precipitated heroin withdrawal decreases NAc dopamine levels (assessed by in vivo microdialysis) but does not reinstate heroin seeking in opiate-dependent rats. In contrast, a spontaneous withdrawal condition, which does not decrease NAc dopamine levels, reinstates heroin seeking in the same rats (10).

In conclusion, from the perspective of the dopamine depletion hypothesis, the results of Twining *et al.* (1) are highly significant because they potentially provide the first evidence that a decrease in NAc dopamine tone, which has long been associated with the emergence of early drug withdrawal symptoms, can provoke relapse to drug seeking during abstinence. Although the authors' results are in line with the dopamine depletion hypothesis, it is surprising that such a finding has come from a study in which rats were trained under limited daily drug access conditions (2 hours/day) that do not lead to dependence-related symptoms in animal models of drug addiction, such as escalation of drug self-administration and decreases in brain stimulation reward (7).

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