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RESEARCH HIGHLIGHT

D-amphetamine maintenance treatment goes a long way: lasting therapeutic effects on cocaine behavioral effects and cocaine potency at the dopamine transporter

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Decades of research have demonstrated that exposure to cocaine engenders adaptations to dopamine systems that result in aberrant dopamine neurotransmission in the striatum. For many years, studies have focused on the dopamine transporter (DAT) as a key participant in altered dopamine neurotransmission following cocaine exposure, with patterns of cocaine intake dictating whether DAT sensitivity to cocaine is enhanced or decreased following exposure [1, 2]. Despite this evidence, there are still no approved pharmacotherapies for the treatment of cocaine abuse, resulting in the need for continued examination of potential treatments.

One promising therapeutic avenue for treating cocaine abuse involves the use of D-amphetamine, as it is thought to interfere with the activity of cocaine at the DAT [3]. In support of this therapeutic approach, previous studies demonstrated that exposure to D-amphetamine, particularly at high doses [4], decreases cocaine use in humans as well as motivation to self-administer cocaine in nonhumans [5, 6]. In fact, treatment with D-amphetamine has recently been shown to reduce cocaine self-administration and attenuate tolerance to cocaine at the DAT following a long access self-administration procedure [7].

In this issue of *Neuropsychopharmacology*, Allain et al. [8] examined to what extent chronic D-amphetamine treatment (via Alzet osmotic minipumps) concurrent with cocaine self-administration attenuates behavioral and dopaminergic sensitization to cocaine. The investigators employed an intermittent access self-administration procedure, which mirrors the intermittent and spiking patterns of cocaine intake seen clinically in humans. The authors demonstrated that this pattern of cocaine intake elicited psychomotor sensitization to cocaine during self-administration and that concurrent treatment with D-amphetamine reduced this sensitization. Despite this attenuated psychomotor response, D-amphetamine did not affect the pattern or magnitude of intake during intermittent access to cocaine, indicating that reductions in psychomotor sensitization cannot be attributed to changes in cocaine intake during treatment.

While concurrent D-amphetamine treatment did not affect cocaine self-administration during intermittent cocaine access, it nevertheless produced lasting effects on motivation for cocaine that extended beyond cessation of treatment. Using a progressive ratio schedule of reinforcement following the intermittent access and D-amphetamine treatment period, Allain et al. demonstrated that D-amphetamine reduced motivation for cocaine. Following the progressive ratio testing, the investigators went on to examine reinstatement of cocaine seeking, demonstrating that the earlier D-amphetamine treatment also attenuated cocaine-primed reinstatement. These findings suggest that D-amphetamine leads to a lasting reduction of the incentive value of cocaine or cocaine-associated cues, which are posited to drive cocaine seeking and taking.

To examine if changes in dopamine neurotransmission underlie the behavioral effects of D-amphetamine, the investigators used fast-scan cyclic voltammetry to assess electrically stimulated dopamine release and uptake in brain slices from the nucleus accumbens. Similar to previous observations [2], intermittent access to cocaine self-administration induced a robust increase in cocaine potency at the DAT. As predicted, chronic D-amphetamine treatment prevented this increase in cocaine potency, thus normalizing the ability of cocaine to inhibit the DAT. This reduced potency of cocaine is consistent with the current behavioral findings, in which D-amphetamine decreased motivation for cocaine and reinstatement of cocaine seeking. Given the extensive evidence that motivation for cocaine is dependent on drug dose [9], it follows that preventing enhanced cocaine potency with D-amphetamine effectively decreased responding for cocaine.

The observation that D-amphetamine prevented enhanced cocaine potency provides a persuasive explanation for why amphetamine-treated rats display decreased progressive ratio responding and cocaine-primed reinstatement. However, in the current studies D-amphetamine was also shown to decrease extinction responding, a behavior during which there is no cocaine present. Thus, unlike what was observed with the progressive ratio and reinstatement experiments, the behavioral changes in extinction responding cannot be directly attributed to changes in cocaine potency. The investigators wisely note that a separate mechanism must underlie the reduction in extinction responding. Indeed, one possible explanation could lie with generally altered dopamine neurotransmission in cocaine-free states. Recent evidence indicates that intermittent access to cocaine not only enhances cocaine potency, but also increases dopamine release and uptake efficiency independent of cocaine effects [2]. When considered in the context of the present study, these prior observations suggest the presence of an aberrant state of dopamine neurotransmission during the extinction tests, which is expected to influence dopamine responses to cocaine-associated cues and influence how readily rats extinguish cocaine-seeking behavior. Future experiments can focus on the extent to which basal changes in dopamine neurotransmission affect cue-induced cocaine seeking.

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Allain et al. provide a notable addition to the literature concerning cocaine use and treatment. In particular, this study makes a compelling argument for the utility of chronic D-amphetamine treatment in attenuating behavioral and dopaminergic sensitization to cocaine. As the effects of D-amphetamine have previously been demonstrated in the realm of tolerance to cocaine, these findings contribute to the ongoing discussion of tolerance and sensitization to drugs of abuse. These findings are also important from a translational perspective as they suggest that the beneficial effects of D-amphetamine can last well beyond the discontinuation of treatment. This is particularly important as the effectiveness of chronic D-amphetamine following treatment cessation has not been comprehensively studied in the clinic, especially within the context of relapse to cocaine use. The present data will no doubt inspire future preclinical and clinical studies geared toward understanding chronic D-amphetamine maintenance as a treatment strategy for cocaine use.

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AUTHOR CONTRIBUTIONS

EMB and RAE wrote the paper.

ADDITIONAL INFORMATION

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