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RESEARCH HIGHLIGHT

Rate matters: rapid cocaine delivery promotes incubation of cocaine craving

Ida Fredriksson[1] and Xuan Li[2]

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Cocaine, as a powerful psychostimulant, has high abuse potentials. Cocaine addiction, usually developing after repeated cocaine use, can lead to declined health and inability to perform in daily lives. According to the 2014 National Survey on Drug Use and Health, nearly 1 million Americans were diagnosed with cocaine dependence within the past year. A major challenge in treating cocaine addiction is relapse during abstinence, which is commonly triggered by exposure to cues and other stimuli previously associated with cocaine use [1]. In both rats and humans, cue-induced cocaine seeking progressively increases after withdrawal, a phenomenon termed "incubation of cocaine craving" [2].

Among people who have experienced cocaine, not everyone develops addiction. A key factor that contributes to the abuse liability is the temporal profile of cocaine use, which includes the intermittency (e.g., binge-taking sessions with long-intervals in between) and the rate of cocaine delivery [3]. Clinical observations have shown that rapid routes of cocaine administration (e.g., smoking and intravenous injection), which leads to high plasma concentration of cocaine within 2–5 min, facilitates the transition from controlled drug use to compulsive drug-taking behavior, a major characteristic of drug addiction [4]. Preclinical studies using rats have also demonstrated that rapid cocaine delivery promotes cocaine-induced behavioral effects, including locomotor sensitization, incentive motivation, escalation of cocaine intake, and cocaine-primed reinstatement of cocaine seeking [3, 5]. However, a key question remained unanswered: does rapid cocaine injection promote incubation of cocaine craving?

In this issue of Neuropsychopharmacology, Gueye et al. [6] answered exactly this question. By delivering cocaine injection at different rates (over 5 s versus over 90 s) in combination with an intermittent-access self-administration procedure, they examined in rats the effect of rapid versus prolonged cocaine injections on incubation of cocaine craving. They showed that cocaine seeking, assessed by extinction responding, of rats that previously self-administered cocaine with an infusion duration of 5 s, but not 90 s, significantly increased on withdrawal day 45 compared with day 1. These data indicate that incubation of cocaine craving occurred only after rapid cocaine delivery. Next, the authors assessed cue- or cocaine-induced reinstatement of cocaine seeking. They found that cues- or cocaine-priming injections only reinstated cocaine seeking above extinction levels in 5-s rats, but not 90-s rats, on both withdrawal day 1 and day 45. Lastly, the authors found a time-dependent increase of brain-derived neurotrophic factor (BDNF) protein expression in prelimbic cortex (PrL), nucleus accumbens (NAc) core and ventral tegmental area (VTA) in 5-s rats, but not 90-s rats, after cue-induced, but not cocaine-priming-induced reinstatement.

The behavioral findings in the study, which extend previous work by the Samaha and Robinson groups on the role of rapid cocaine injection in locomotor sensitization, cocaine self-administration, and relapse [3, 5], provide new evidence that rapid cocaine injection promotes incubation of cocaine craving and cue-induced reinstatement of cocaine seeking. The findings on cocaine-primed reinstatement are consistent with a previous study by Robinson group [5]. It is also of note that both 5-s rats and 90-s rats exhibit similar cumulative cocaine intake and cocaine-taking pattern. Therefore, the effects on relapse are not due to differences in drug intake during cocaine self-administration training. Together, these findings support the notion that the rate of cocaine delivery plays a critical role in contributing to relapse susceptibility during abstinence. Moreover, while clinical data suggest that rapid route of administration contributes to the development of cocaine addiction, whether this holds true for relapse susceptibility is unknown. Therefore, this preclinical study raises an important question for clinical researchers, which is to examine whether the rate of cocaine delivery is directly associated with cocaine craving and relapse during abstinence in cocaine-dependent individuals.

The study demonstrates that incubation of cocaine craving occurs after an intermittent-access self-administration procedure, during which rats have access to cocaine for 6 min, followed by a 26-min timeout period during the 6-h daily session. This is distinct from previous "incubation" studies, in which cocaine is available through the entire self-administration session (continuous-access). It is believed that the intermittent procedure can better mimic the binging of cocaine use in humans [3]. Indeed, recent studies showed that intermittent-access self-administration increases incentive motivation for cocaine as assessed by the economic-demand procedures [7], and a new study demonstrated that intermittent-access procedure potentiated incubation of cocaine craving [8], when directly compared with the continuous-access procedure. These evidences point out that intermittency of cocaine intake is another key factor that promotes relapse during abstinence. Therefore, an interesting question for authors in the future is to determine the distinct roles of intermittency versus rate of drug delivery in cocaine relapse.

Why does rapid versus slow cocaine injection lead to distinct relapse behavior? The answers lie largely in the neurobiological changes induced by varied rates of cocaine delivery. Gueye et al. [6] did an initial exploration by focusing on BDNF, a neurotrophic factor

[1]Behavioral Neuroscience Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD, USA and [2]Department of Psychology, University of Maryland College Park, College Park, MD, USA
Correspondence: Xuan Li (annali@umd.edu)

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that plays a complex role in synaptic plasticity and cocaine self-administration and relapse [9]. They found that BDNF protein expression in NAc, PrL, and VTA exhibits a time-dependent increase after cue-induced reinstatement tests performed after 1 or 45 withdrawal days. However, the current study did not examine whether this increase is associated with withdrawal alone, cue presentation alone, or withdrawal plus cue presentation. Additionally, BDNF protein level showed no time-dependent changes after cocaine-primed reinstatement, suggesting that the role of BDNF is specific to cue-induced cocaine relapse. Overall, these findings are consistent with previous incubation studies using a continuous-access procedure [9], and highlight BDNF and its signaling pathways as candidate neural substrates through which rapid cocaine delivery promotes cue-induced cocaine relapse. An important question for future studies is whether BDNF plays a causal role in cocaine seeking after rapid cocaine injections. Another question is what upstream mechanisms lead to changes in brain BDNF after rapid cocaine injection. One potential candidate is enhanced glutamate transmission, previously implicated in contributing to increased BDNF in NAc during incubation of cocaine craving [9].

Collectively, Gueye et al. [6] demonstrated that rapid cocaine injection promotes incubation of cocaine craving and reinstatement of cocaine seeking after an intermittent-access cocaine self-administration procedure. Rapid cocaine injection also leads to long-term effects at the neurobiological level by increasing BDNF protein expression in different brain regions after cue-induced relapse during abstinence. These findings highlight the rate of cocaine delivery as a key contributor to relapse susceptibility during abstinence, and will hopefully inspire future preclinical and clinical studies to incorporate the temporal profile of cocaine administration into studies designed to determine relapse susceptibility and its underlying neural mechanisms.

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ADDITIONAL INFORMATION

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