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Cocaine withdrawal alters the reward omission effect and enhances traits of negative urgency in rats across multiple days of testing

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ABSTRACT

Background: The personality trait of negative urgency, characterized as behaving rashly when emotionally perturbed, is gaining attention as an indicator for susceptibility to problematic substance use. How this trait is influenced by exposure to drugs of abuse is still unclear. Using an animal model of binge cocaine consumption, we tested this relationship in a reward-omission task across multiple days.

Methods: Adult, male, Sprague-Dawley rats received seven daily (ip) injections of saline, cocaine (10–20 mg/kg), or cocaine (20–40 mg/kg). Cocaine doses increased linearly each day from the lower to the higher dose. A separate group received RTI-113 (3.0 mg/kg), a selective dopamine transporter inhibitor, for 7 days. Fifteen days after their final injection, rats were trained on a reward-omission task with an operant component to earn further rewards.

Results: Previous exposure to cocaine resulted in dose-dependent increases in negative urgency in separate behavioral variables across days of testing. The lower dose range increased negative urgency on the dimension of decreased reaction time to press a lever, while the higher dose range increased the rate of increase in lever presses made per trial. Rats receiving RTI-113 did not resemble either cocaine group and instead showed a decrease in lever pressing across days.

Conclusions: Our results indicate that previous binge cocaine consumption enhances behavioral markers of negative urgency in a dose-dependent, time-sensitive manner on discrete behavioral dimensions. The results with RTI-113 suggest the relationship between cocaine exposure and negative urgency is unlikely to be explained solely by inhibition of dopamine reuptake.

1. Introduction

Personality variables have long been associated with individual risk of substance abuse (Whiteside and Lynam, 2003). The trait of impulsiveness, once thought to be a well-defined construct, can be sub-factored into the traits of disinhibition, sensation seeking, and urgency (Whiteside and Lynam, 2001). Each of these sub-factors interacts differentially with drug-consumption tendencies, with urgency showing the strongest relationship to developing problematic substance use (Bardo et al., 2007; Ersche et al., 2012; Gunn et al., 2013). An individual high in urgency is characterized as one who scores low in the personality trait of conscientiousness, high in impulsivity, and high in disagreeableness (Bardo et al., 2007; Ersche et al., 2012; Gunn et al., 2013). Urgency is distinct from general impulsivity by the inclusion of an emotional response component that goes beyond lack of behavioral inhibition or forethought (Settles et al., 2012); individuals with high degrees of urgency tend to behave impulsively when in emotionally elevated states, but are not otherwise volatile. Negative urgency is the tendency to make poor choices when in an emotionally distressed state, such as drinking to ameliorate stress (Settles et al., 2012; Whiteside and Lynam, 2001). This form of urgency is particularly interesting because it serves as a predictor of problem drinking and smoking in children as young as fifth grade (Settles et al., 2012), and is associated with cocaine dependence (Albein-Urios et al., 2012; Verdejo-Garcia et al., 2008; Whiteside and Lynam, 2003). The neural mechanisms underlying negative urgency are purported to involve an imbalance of functional connectivity between cortical, striatal, and limbic areas (Cyders and Smith, 2008; Gipson et al., 2012; Judice-Daher and Bueno, 2013; Judice-Daher et al., 2012; Tavares et al., 2014). Repeated cocaine use impairs global functioning of frontal cortex, which manifests as hypofrontality, but also causes damage locally in orbito-frontal cortex, resulting in impairments in judgment and cognitive flexibility, as well as in increased impulsivity

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(Albein-Urios et al., 2013; Stalnaker et al., 2007a, 2007b, 2007c; Zuo et al., 2011). Imaging of cocaine addicts revealed an increase in urgency in patients with comorbid personality disorders, and was accompanied by a decrease of temporal gray matter, indicating further possible involvement of the limbic forebrain (Albein-Urios et al., 2013).

Considering the association of human cocaine abuse with negative urgency, we adopted a dosing schedule to mimic the binge consumption and dosage escalation common to human addicts (Ahmed and Koob, 1998; Ahmed et al., 2002, 2003). Each day for seven consecutive days of cocaine administration, the dosage was increased in a linear fashion so that the dose on the final day was twice the dose of the initial day. A similar dosage escalation is also seen in rats self-administering cocaine, and demonstrates the maintenance of a particular desired subjective state that requires an increasing amount of drug (Ahmed and Koob, 1998; Ahmed et al., 2002, 2003; Fischer et al., 2013; Knackstedt and Kalivas, 2007). After withdrawal, craving for the drug increases (Conrad et al., 2008; Grimm et al., 2001), marked by enhanced drug-seeking behavior, but also manifests at the cellular level as structural and functional changes largely in the pre-frontal cortex (PFC) and nucleus accumbens (NAcc) (Conrad et al., 2008; Fischer et al., 2013; Grimm et al., 2001; Sun and Rebec, 2006). The role of these mechanisms in re-establishing drug-seeking behavior and a subsequent loss of cognitive flexibility is well established. Here, we assessed the effects of binge cocaine withdrawal on negative urgency as manifested in a reward-omission task. Because cocaine inhibits dopamine reuptake, we also examined the effects of withdrawal from RTI-113, a highly-selective dopamine transporter (DAT) inhibitor (Carroll et al., 2004; Kuhar et al., 1999).

2. Methods

2.1. Subjects

Adult, male, Sprague-Dawley rats, weighing approximately 300 g provided by Harlan Industries (Indianapolis, IN), were single-housed in clear plastic cages. Water was provided *ad libitum* throughout the course of study. During periods of training and testing, food intake was restricted to maintain 85% of free-feeding weight. Prior to training, during drug administration days and during the drug withdrawal portion of the experiment, food and water were available *ad libitum*. The rats were housed on a 12:12 light cycle, with all testing and drug administration conducted during the lights-on portion of the day. All housing and animal-use procedures followed NIH guidelines and were approved by the Indiana University Institutional Animal Care and Use Committee.

2.2. Drugs

The rats were divided into four treatment groups for injections, which occurred once daily for seven consecutive days: Saline, Cocaine (10–20 mg/kg), Cocaine (20–40 mg/kg), and because cocaine binds rather indiscriminately to monoamine transporters, we also assessed the behavioral effects produced by 2β-carbophenoxy-3β-(4-chlorophenyl) tropane (RTI-113), an ultra-selective dopamine transporter inhibitor with similar behavioral effects to cocaine to help identify the relative contribution of dopamine uptake inhibition (Carroll et al., 2004; Kuhar et al., 1999). Rats in the RTI-113 group received 3.0 mg/kg, which is based on DAT binding affinities such that an equal saturation of DAT would occur with RTI-113 as in the Cocaine (20–40 mg/kg) group (Dworkin et al., 1998). USP grade cocaine HCl and RTI-113 provided by Research Triangle Institute, were dissolved in USP saline at a concentration that maintained a constant injection volume of 1.0 mL/kg. To simulate the escalating dosage schedule observed in human cocaine dependence, cocaine doses escalated each day in a linear fashion such that on the final day of injections the dose had doubled. Due to lack of safety data on high doses of RTI-113, this escalation of dose was limited to the two cocaine groups (see below for further discussion). Injections (ip) were administered once daily for seven days. After injection, subjects were returned to their home-cage for monitoring before returning to the colony room. Following the final day of injections, subjects remained in their home cages in the colony room with food and water available *ad libitum* for 15 days.

2.3. Apparatus

For training and data collection operant chambers were used. They were operated by a Med-PC SG-6510D controller using MED-PC IV (ver. 4.0.1.47) software from Med Associates, Inc. (St. Albans, VT). The boxes measure 31.75 cm $W \times 31.75$ cm $D \times 41.9$ cm H, and are equipped with a central food hopper with a lever and cue-light positioned to either side. Opposite the food-hopper is a house light and an embedded speaker. The food-hopper is attached to an external pellet dispenser that dispenses 48 mg TestDiet Sucrose Pellets (Richmond, Indiana).

2.4. Reward omission training

After their final day of injections, rats remained in their home cages for a 15-day withdrawal period before they began training on a reward omission test. Training consisted of three phases prior to data collection.

2.4.1. Phase I. Subjects are conditioned to anticipate a free-food pellet delivered immediately following the presentation of a cue light and tone. The session begins with illumination of the house light for 60 s. When the house light turns off, one of the two cue lights is illuminated on a randomly determined counterbalance for each light. The light is illuminated for 5 s, and is accompanied by a 400 Hz, 50 dB, 0.5 s tone along with the release of a single sucrose pellet into the food hopper. A 2 s dark period ensues followed by

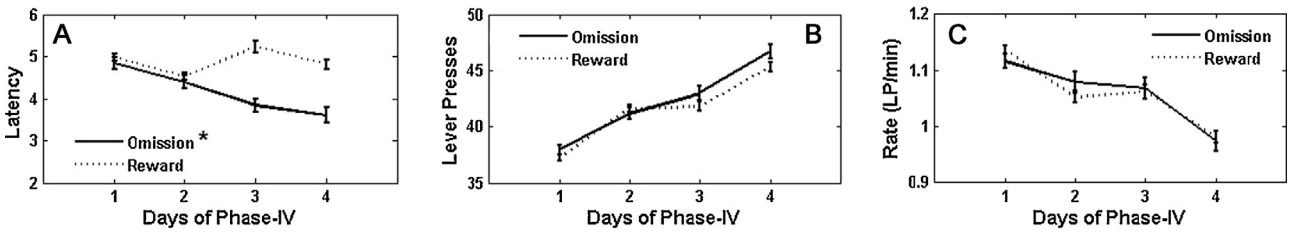

Fig. 1. (A) Mean (±SEM) latency for reaction time on the lever after presentation with all groups represented together. A clear strong trend of increasingly shorter reaction times on omission trials confirms the presence of a test-wide negative urgency effect. (B) Mean (±SEM) lever presses per trial after lever presentation. While a main effect of trial-type was observed, there was no interaction of trial-type-by-day as was observed with latency. This demonstrates latency as a greater marker of negative urgency in our particular task. (C) Mean (±SEM) rate of lever pressing (LP). $^{*}p < 0.05$, compared to reward trials.