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Disparate cocaine-induced locomotion as a predictor of choice behavior in rats trained in a delay-discounting task

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Abstract

Heightened impulsivity and differential sensitivity to a drug's behavioral effects are traits that, individually, have been associated with chronic drug use and dependence. Here, we used an animal model to test whether individual differences in cocaine-induced activity are predictive of impulsive choice behavior. Adult, male Sprague-Dawley rats were given cocaine (10 mg/kg, i.p.) and classified into low or high cocaine responders (LCRs or HCRs, respectively) based on their locomotor response in an open-field arena. Rats were then trained in a delay-discounting task that offers a choice between immediately delivered, but smaller reinforcements, or larger reinforcements that are delivered after a delay. We also examined the effects of amphetamine (AMPH; 0.3–1.0 mg/kg) and the 5-HT_{1A} agonist 8-OH-DPAT (0.3–1.0 mg/kg) on delay-discounting. Lastly, all rats were retested in the open-field to determine if phenotypes were stable. We observed baseline differences in choice behavior between the groups, with HCRs behaving more impulsively (i.e., choosing the small reinforcement) compared to LCRs. AMPH decreased choice of the large reinforcement in LCRs, but did not alter choice in HCRs. Impulsive choice was increased in both phenotypes following 8-OH-DPAT, with LCRs exhibiting changes across a wider range of delays. When cocaine-induced open-field behavior was retested, responses in LCRs were similar whereas HCRs showed evidence of tolerance. Our results suggest that differential sensitivity to cocaine-induced locomotion is predictive of impulsivity and the potential neurobiological differences in LCRs and HCRs may provide insight into mechanisms contributing to vulnerability for chronic drug use and/or dependence.

Keywords: Cocaine; Individual differences; Delay-discounting; Locomotor activity; 8-OH-DPAT; Amphetamine; Rat

1. Introduction

Impulsivity is a complex, multifaceted trait that is broadly defined by a lack of behavioral inhibition, which includes premature and poorly controlled actions, and impulsive choice, where decisions are poorly conceived and sensitive to delayed rewards (see Evenden, 1999; Winstanley et al., 2006a for more detailed accounts). Individuals who abuse drugs tend to exhibit heightened levels of these traits, particularly with regards to impulsive decision-making (Bornovalova et al., 2005; Coffey et al., 2003; Heil et al., 2006; Kirby and Petry, 2004; Lejuez et al., 2007; Moeller et al., 2002; Verdejo-Garcia et al., 2007). It has been suggested that a high level of impulsivity develops as a result of repeated exposure to abused drugs, and this in turn facilitates the development and/or maintenance of addiction (Jentsch and Taylor, 1999). Evidence supporting this hypothesis comes in part from studies using animal models, where repeated exposure to cocaine in rats leads to an increase in impulsive choice behavior relative to that observed in saline-treated controls (Paine et al., 2003; Roesch et al., 2007; Simon et al., 2007), and from clinical studies, where individuals who have been chronically exposed to cocaine show increases in impulsive choice relative to non-drug users or drug abstainers (for review, see Bickel and Marsch, 2001 and Reynolds, 2006).

An alternative and not necessarily mutually exclusive hypothesis is that a high level of impulsivity is a pre-existing trait whose multidimensional components overlap with other traits or behaviors that also confer enhanced vulnerability to chronic drug use and/or dependence (Bechara, 2005; Dalley et al., 2007a,b; Kreek et al., 2005). An example of one such candidate trait is differential sensitivity to a drug's behavioral effects. In humans, for example, differences in initial sensitivity to cocaine are

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predictive of long-term use and dependence (Davidson et al., 1993; Haertzen et al., 1983; Schafer and Brown, 1991) and a recent study has indicated that individuals who reported a high degree of "liking" or "wanting" on their initial use of cocaine had a significantly increased risk of cocaine abuse (Lambert et al., 2006). In rodents, a reliable indicator of initial sensitivity to psychostimulants is drug-induced locomotor activity in an open-field arena. Cocaine, in particular (Briegleb et al., 2004) has variable stimulant effects on behavior, such that outbred rats can readily be classified as low or high cocaine responders (LCRs or HCRs, respectively) based on their response to a single treatment with cocaine (Sabeti et al., 2002; Gulley et al., 2003; Gulley, 2007). Interestingly, these individual differences are related to differences in the function of dopamine transporters (DATs) in the dorsal striatum and nucleus accumbens (Sabeti et al., 2002, 2003) and not to pharmacokinetic factors (Gulley et al., 2003). Subsequent studies have shown that the LCR/HCR phenotype can be used to predict behavior in a food-reinforced operant task (Gulley, 2007), as well as conditioned place preference for cocaine (Allen et al., 2007).

In the current study, we used rats to examine if differential sensitivity to the locomotor activating effects of cocaine were predictive of one component of impulsivity, impulsive choice behavior. Rats were first characterized as LCRs and HCRs based on their response to 10 mg/kg cocaine in an open-field arena. They were then trained in a delay-discounting task that offered a choice between immediately delivered, but smaller reinforcements, or larger reinforcements that were delivered after a delay of up to 60 s. After 34 daily training sessions, we performed a series of drug challenges in order to determine if impulsive choice could be altered in a differential manner between LCRs and HCRs. First, rats were given amphetamine (AMPH; 0.3–1.0 mg/kg) or saline prior to the start of daily delay-discounting sessions. AMPH has been shown previously to increase or decrease delay-discounting behavior (Cardinal et al., 2000; Evenden and Ryan, 1996, 1999; van Gaalen et al., 2006) and it has been suggested that an individual's baseline level of impulsive choice behavior influences this response (Barbelivien et al., 2008; Winstanley et al., 2003). Rats were then challenged with the 5-HT_{1A} agonist 8-OH-DPAT (0.3–1.0 mg/kg) or saline prior to their daily session. 8-OH-DPAT has been shown to increase impulsive choice (Winstanley et al., 2005; but see Evenden and Ryan, 1999; Poulos et al., 1996) and it is not clear if this effect depends on the baseline level of impulsive choice. Lastly, all rats were retested in the open-field for their response to cocaine in order to assess if the phenotypic differences in cocaine response that were established initially remained stable following the ~3 months time period that elapsed during the course of the study.

2. Methods

2.1. Animals

Male Sprague-Dawley rats ($n = 16$), bred in our animal facility from stock rats obtained from Harlan (Indianapolis, IN), were housed individually starting at ~2 months of age and were 3–3.5 months old (300–490 g) at the start of experiments. They were maintained on a 12:12 h light:dark cycle (lights on at 0800) with experimental sessions conducted between 0900 and 1800 h. Rats were handled five times for 15 min intervals prior to being used in experiments. With the exception of periods when rats were undergoing operant training and testing, food was available *ad libitum*. Water was always available *ad libitum*. All experimental procedures were approved by the IACUC at the University of Illinois, Urbana-Champaign and were consistent with the *Principles of Laboratory Animal Care* (NIH Publication no. 85–23).

2.2. Apparatus

Locomotor activity was measured in an open-field chamber that consisted of a transparent, Plexiglas box (40.6 cm × 40.6 cm × 40.6 cm) surrounded by photobeams (Coulbourn Instruments; Allentown, PA). Each apparatus was connected to a computer operating software (TruScan, v. 2.01; Coulbourn Instruments) that recorded all horizontal and vertical beam breaks (100 ms sampling rate). The horizontal beam breaks, or coordinate changes, were converted into distance traveled (cm). The chambers were individually contained inside sound-attenuating cubicles (76 cm × 80 cm × 63 cm). Each cubicle contained a speaker (76 mm diameter) fixed to one wall, two ceiling-mounted white lights (4 W) for dim illumination, and a ceiling-mounted camera between the two lights. White nose (70 dB) was played continuously through the speakers when rats were in the testing room.

Operant behavior was monitored in standard operant chambers (Coulbourn Instruments). One wall of the chamber contained two retractable levers that were positioned on either side of a centrally located food trough. Infrared detectors were used to monitor head entries into the food trough. White cue lights were located above each lever. A white houselight was located near the top of the chamber on the opposite wall.

2.2.1. Initial behavioral characterization: locomotor activity in the open-field. After a 30 min acclimation period in the testing room, rats were placed in the open-field chambers for 90 min. They were then removed from the chamber, injected (i.p.) with (−) cocaine HCl (10 mg/kg) and placed back into the chamber for an additional 60 min. This dose was chosen based on previous studies (Sabeti et al., 2002; Gulley et al., 2003) showing that it is optimal for inducing the widest range of behavioral responses in male Sprague-Dawley rats. After the testing session, rats were returned to the colony room and their access to food was restricted so that they were reduced to 85% of their free-feeding weight over the course of several days. Rats were maintained at 85–90% of free-feeding weight for the duration of operant training and testing.

2.2.2. Delay-discounting behavior. Seven days after the open-field test, rats were trained in overnight sessions (2100–0900 h) to respond on either of two available levers for a food pellet (45 mg; Bio-Serv F0021 or F0042) on a fixed ratio schedule (FR1) of reinforcement. After they displayed approximately equal responding on both levers, rats were moved to the next training phase (1 h sessions, between 0900 and 1700 h). Trials began with levers retracted, and the food trough illuminated by a cue light. A nosepoke into the trough resulted in the extension of one randomly selected lever, with a subsequent lever press response reinforced by delivery of a food pellet. After 3–4 days of training at this stage, rats began the final stage of training.

Training in the delay-discounting task was done in daily, 100 min sessions that consisted of five blocks of 12 trials. Each trial lasted 100 s and began with the illumination of the house light and cue light located in the food trough. Rats were required to nosepoke into the trough within 10 s, whereupon a single lever would be presented randomly and a response was reinforced with food pellet delivery. The amount of food delivered was pre-assigned to a lever, such that responses on one (e.g., left side lever) resulted in a larger, delayed reward of four pellets and responses on the other (e.g., right side lever) resulted in a small, immediate reward of one pellet. Assignment of reward magnitude to levers was counterbalanced across groups, but remained consistent for each rat. After a lever response, the house light turned off, the levers retracted, and the cue light above the lever was illuminated until food was delivered. If the rat either failed to nosepoke within 10 s or respond on the presented lever, the trial was recorded as an omission. On omission trials, the levers remained retracted and the chamber was returned to an intertrial interval (ITI) state until the beginning of the next trial. After completing or omitting the first two forced-choice