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Chronic cocaine exposure in adolescence: Effects on spatial discrimination reversal, delay discounting, and performance on fixed-ratio schedules in mice

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ABSTRACT

Adolescence is marked by the continued development of the neural pathways that support choice and decision-making, particularly those involving dopamine signaling. Cocaine exposure during adolescence may interfere with this development and manifest as increased perseveration and delay discounting in adulthood, behavioral processes that are related to drug addiction. Adolescent mice were exposed to 30 mg/kg/day of cocaine (n = 11) or saline vehicle (n = 10) for 14 days and behavior was assessed in adulthood. In Experiment 1, performance on a spatial-discrimination-reversal procedure was evaluated. In the first two sessions following the first reversal, cocaine-exposed mice produced more preservative errors relative to controls. In Experiment 2, cocaine-exposed mice displayed steeper delay discounting than saline-exposed mice, effects that were reversed by acute cocaine administration. Experiment 3 examined responding maintained by a range of fixed-ratio schedules of reinforcement. An analysis based on a theoretical framework called Mathematical Principles of Reinforcement (MPR) was applied to response-rate functions of individual mice. According to MPR, differences in response-rate functions in adulthood were due to a steepening of the delay-of-reinforcement gradient, disrupted motoric capacity (lower maximum response rates), and enhanced reinforcer efficacy for the adolescent cocaine- compared with saline-exposed mice. Overall, these experiments suggest that chronic exposure to cocaine during adolescence may impair different features of 'executive functions' in adulthood, and these may be related to distortions in the impact of reinforcing events.

1. Introduction

In both humans and nonhumans, adolescence is a period marked by the continued development of the neural pathways that support choice and decision-making, particularly the dopamine (DA) neurotransmitter system (Chambers, Taylor, & Potenza, 2003; Johnston, O'Malley, Bachman, & Schulenberg, 2010; Spear, 2000; Wahlstrom, White, & Luciana, 2010). In rodent models, the adolescent period is estimated to begin as early as postnatal day (PND) 21 and last up to PND 59 based on brain development, although the boundaries are not sharply delineated (Laviola, Macrì, Morley-Fletcher, & Adriani, 2003; Marco et al., 2011; Spear, 2000). Adolescent rodents have increased DA synthesis in the prefrontal cortex (Andersen, Dumont, & Teicher, 1997) and greater DA-receptor expression in the striatum and nucleus accumbens relative to adult controls (Brenhouse, Sonntag, & Andersen, 2008; Tarazi & Baldessarini, 2000; Teicher, Andersen, & Hostetter, 1995). Adolescent-onset fluctuations in DA signaling co-occur with the expression of behavior that is implicated in substance abuse, such as perseveration and impulsive choice (De Wit, 2009; Ersche, Roiser, Robbins, & Sahakian, 2008; Shen, Pope, Hutsell, & Newland, 2015). Specifically, adolescent mice prefer smaller-sooner reinforcers over larger-later ones (i.e., choose more impulsively) in a delay-discounting procedure more than adults (Pinkston & Lamb, 2011). These reports indicate that DA signaling and DA-mediated behavior during adolescence is in a transitional state and is potentially malleable. Therefore, pharmacological insult, such as cocaine exposure, could produce permanent neurobehavioral alterations.

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In rodent models, cocaine exposure that occurs during adolescence results in a number of neurobiological and behavioral alterations that persist into adulthood. Adolescent cocaine exposure increases behavioral sensitivity to cocaine (and other stimulants) as well as self-administration of cocaine in early adulthood in rodents (Brandon & Marinelli, 2001; Laviola, Wood, Kuhn, Francis, & Spear, 1995; Marin, Cruz, & Planeta, 2008; Valzachi, Teodorov, Marcourakis, Bailey, & Camarini, 2013). Adaptations in DA and glutamate neurotransmission in the adult nucleus accumbens and medial prefrontal cortex underlie behavioral alterations that result from adolescent cocaine exposure in rodents (Black et al., 2006; Marin et al., 2008), but whether these altered neurobiological responses to cocaine manifest themselves in increased perseverative and impulsive behavior is not as well established. Cocaine self-administration during adolescence increases perseverative errors (Kantak, Barlow, Tassin, Brisotti, & Jordan, 2014) and methylphenidate administration during adolescence increases preference for larger-later reinforcers in rats (Adriani, Canese, Podo, & Laviola, 2007), suggesting a role for DA agonists in these processes. The role of a repeated dosing regimen of cocaine during the rodent adolescent period on perseveration and impulsive choice is unclear, however, as are the possible behavioral mechanisms for the effects of adolescent cocaine exposure. For example, adolescent cocaine exposure may alter reinforcer efficacy, resulting in perseverative errors in a spatial discrimination reversal task, or it may steepen the delay-of-reinforcement gradient, resulting in preference for smaller-immediate reinforcers. Characterizing the behavioral mechanism(s) involved in adolescent cocaine exposure will provide a more complete description of any alterations in resultant preservative and impulsive behavior.

The current experiments were designed to assess the effects of repeated cocaine exposure during adolescence on perseverative and impulsive behavior in mice using a spatial-discrimination-reversal (SDR) and delay-discounting procedure, respectively. Sensitivity to acute cocaine injections was assessed in the delay-discounting procedure to uncover neurobiological adaptations that may have persisted into adulthood. To uncover a possible behavioral mechanism that may underlie adolescent cocaine exposure, we examined responding on a series of fixed-ratio schedules of reinforcement using a theoretically-driven mathematical model, Mathematical Principles of Reinforcement (Killeen, 1994; Killeen & Sitomer, 2003), to quantify changes in reinforcer efficacy, motor ability, and the slope of the delay-of-reinforcement gradient simultaneously.

2. Experiment 1: Spatial discrimination reversal

Experiment 1 was designed to assess the effects of repeated injections of cocaine during the murine adolescent period on behavioral flexibility and perseverative responding in adulthood using a spatial-discrimination-reversal (SDR) task. In our implementation, each trial is response-initiated and responding on a lever designated as "correct" is reinforced until an accuracy criterion is met, at which point responding on the opposite lever is reinforced and responding on the original lever is placed on extinction. We hypothesized that mice exposed to cocaine during adolescence would make more perseverative errors (i.e., responses on the non-reinforced lever) immediately following the first reversal compared to mice exposed to saline, but the groups would perform similarly on the original discrimination.

2.1. Methods

2.1.1. Subjects and cocaine exposure

Three-week-old male C57Bl/6 mice ($n = 21$) were purchased from Harlan Laboratories (Indianapolis, Indiana) and were pair-housed in an AAALAC-accredited facility in clear OptiMICE® cages (Animal Care Systems Inc., Centennial, CO). The vivarium was temperature- and humidity-controlled (minimum 21 °C) under a 12-h light-dark cycle (lights on 0600). Experimental sessions were conducted during the light period. All animals had free access to food and water upon arrival until they reached their adult body weight around PND 70, which was maintained at approximately 26 g with mild food restriction.

Beginning on PND 30, mice were administered an i.p. injection of saline ($n = 10$) or 30 mg/kg/day cocaine hydrochloride (Sigma–Aldrich, St. Louis, MO, USA; $n = 11$) in a 4 ml/kg injection volume dissolved in saline. Injections occurred once daily for 14 consecutive days. All procedures were approved by the Auburn University Institutional Animal Care and Use Committee.

2.1.2. Apparatus

Experimental sessions were conducted in eleven operant conditioning chambers (12.0″ L × 9.5″ W × 11.5″ H) manufactured by Med Associates (Med Associates Inc., St. Albans, VT) enclosed in sound-attenuating cabinets and modified to accommodate mice. The rear wall in each chamber was equipped with a non-retractable response lever and two Sonalert® tone generators located at the top of the chamber equidistant from a centrally located houselight. The front wall of each chamber was equipped with two retractable response levers. For reinforcement, a liquid dipper system for mice delivered 0.1-cc presentations of a 3:1 solution of water to sweetened condensed milk for 3 s. A computer with Med Associates® IV programming and interface system in an adjacent room controlled experimental events and collected data with a temporal resolution of 0.01 s.

2.1.3. Autoshaping and chain training

At approximately PND 70, mice were trained on an autoshaping procedure previously described (see Paletz, Day, Craig-Schmidt, & Newland, 2007). Briefly, autoshaping for mice of each group was conducted independently for left and right front levers and the back lever, respectively. Responding on the two front levers was autoshaped first for all mice, but which front lever (left or right) was autoshaped first was counterbalanced within and across groups, followed by autoshaping of back lever responding. Once mice made 40 reinforced responses (according to a fixed-ratio, FR, 1 schedule of reinforcement) for each lever (i.e., left, right, and back), subjects then began chain training for the SDR procedure. During chain training, mice acquired a two-response chain comprising a trial-initiation response on the back lever followed by a choice response on one of two front levers. Each trial began with the presentation of a pulsating tone combination and illumination of the houselight. A trial-initiation response on the back lever within 15 s caused one of two front levers to extend for 15 s (left or right, counterbalanced across subjects). A response on the extended front lever within 15 s produced reinforcement (3-s access to sweetened condensed milk), followed by a 10-s inter-trial interval (ITI). A failure to initiate a trial on the back lever or to make a response on the extended front lever during the either of the 15-s limited holds ended the trial and began the ITI. Sessions consisted of 60 trials, and chain training continued for each mouse until 50 correct chains were executed within a single session for three consecutive sessions.

2.1.4. SDR procedure

Sessions comprised 60 trials separated by a 20-s ITI. For the original discrimination (OD) phase, a trial-initiation response on the back lever following the ITI caused the two front levers to be extended into the chamber. A response on the front lever designated "correct" for a mouse (e.g. left, but counterbalanced within groups) resulted in 3-s access to milk reinforcement followed by