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Cocaine-seeking behavior in a genetic model of attention-deficit/hyperactivity disorder following adolescent methylphenidate or atomoxetine treatments☆

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is often comorbid with cocaine abuse. Controversy exists regarding long-term consequences of ADHD medications on cocaine abuse liability. Whereas childhood methylphenidate treatment may be preventative, methylphenidate in teens appears to further increase later cocaine abuse risk. In rodents, adolescent methylphenidate treatment further increases adult cocaine self-administration in the Spontaneously Hypertensive Rat (SHR) model of ADHD, whereas adolescent atomoxetine treatment does not. Effects of ADHD medications on cocaine cue reactivity, a critical component of addiction, are unknown.

Methods: To investigate this, SHR, Wistar–Kyoto (inbred control) and Wistar (outbred control) rats received therapeutically relevant doses of methylphenidate (1.5 mg/kg, oral) and atomoxetine (0.3 mg/kg, intraperitoneal), or respective vehicles from post-natal day 28–55. Cocaine seeking, reflecting cue reactivity, was measured in adulthood during self-administration maintenance and cue-induced reinstatement tests conducted under a second-order schedule.

Results: Compared to control strains, SHR earned more cocaine infusions, emitted more cocaine-seeking responses during maintenance and reinstatement testing, and required more sessions to reach the extinction criterion. Compared to vehicle, adolescent methylphenidate, but not atomoxetine, further increased cocaine intake during maintenance testing in SHR. Adolescent atomoxetine, but not methylphenidate, decreased cocaine seeking during reinstatement testing in SHR. Neither medication had effects on cocaine intake or cue reactivity in control strains.

Conclusions: The SHR successfully model ADHD and cocaine abuse comorbidity and show differential effects of adolescent ADHD medications on cocaine intake and cue reactivity during adulthood. Thus, SHR have heuristic value for assessing neurobiology underlying the ADHD phenotype and for evaluating pharmacotherapeutics for ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition. Diagnoses have risen 41% over the past decade, with rates escalating fastest in boys aged 14–17 (Visser et al., 2010; Schwarz and Cohen, 2013). ADHD is highly comorbid with substance abuse, including cocaine (van Emmerik-van Oortmerssen et al., 2012). Children with ADHD are 2–3 times more likely to abuse cocaine in adulthood compared to children without an ADHD diagnosis (Lee et al., 2011).

Controversy exists regarding long-term consequences of ADHD medications on cocaine abuse liability. Approximately two-thirds of U.S. children and adolescents diagnosed with ADHD are prescribed a stimulant medication, such as methylphenidate (Schwarz and Cohen, 2013). Methylphenidate, like cocaine, inhibits dopamine and norepinephrine transporters (DAT and NET, respectively). Because adolescence represents a period of elevated plasticity in the mesocorticolimbic dopamine system, stimulant

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exposure during this period may have unique long-term effects on reward responsivity (Andersen, 2005). Whereas childhood methylphenidate treatment is protective against an increase in later cocaine abuse (Wilens et al., 2003; Humphreys et al., 2013), adolescent methylphenidate treatment can increase later abuse of cocaine and other drugs (Lambert and Hartsough, 1998; Mannuzza et al., 2008; Dalsgaard et al., 2014). Although some studies reported protective effects of adolescent stimulant treatment (e.g., Biederman et al., 1999), these studies often fail to distinguish actively medicated participants from those who discontinued treatment at assessment. As cocaine use may be a form of self-medication for untreated ADHD (Gudjonsson et al., 2012), ongoing methylphenidate treatment may compromise detecting increased cocaine abuse, as suggested by animal studies (Schenk and Izenwasser, 2002). Further, many clinical studies employ a limited follow-up period into adulthood. Because cocaine abuse generally develops later than abuse of other substances (Degenhardt et al., 2008), participants evaluated in their late teens and early twenties may not have surpassed the risk period for initiating cocaine use.

Preclinical models can address clinically relevant questions concerning ADHD. Typically used is the Spontaneously Hypertensive Rat (SHR), whose behavioral and cognitive deficits model the ADHD combined subtype and are unrelated to hypertension (Wyss et al., 2003; Sagvolden et al., 2005; Russell et al., 2005; Kantak et al., 2008). Furthermore, SHR exhibit elevated cocaine self-administration compared to Wistar–Kyoto (WKY; inbred progenitor of SHR) or Wistar (WIS; outbred common ancestor to SHR and WKY) control strains (Harvey et al., 2011; Somkuwar et al., 2013b). Using a therapeutically relevant dose (Kuczenski and Segal, 2002), we demonstrated that adolescent treatment with 1.5 mg/kg oral methylphenidate further enhanced the speed to acquire cocaine self-administration and the efficacy and motivating influence of cocaine reinforcement in adult SHR, but not in adult WKY or WIS (Harvey et al., 2011).

Atomoxetine, a non-stimulant ADHD medication, is a viable alternative to methylphenidate for adolescents with ADHD in whom drug abuse is a concern (Kratochvil et al., 2002). At therapeutic doses, atomoxetine selectively inhibits NET to increase extracellular norepinephrine and dopamine in prefrontal cortex (PFC; Bymaster et al., 2002). We recently demonstrated that adolescent treatment with 0.3 mg/kg atomoxetine did not further enhance the speed to acquire cocaine self-administration or the efficacy and motivating influence of cocaine reinforcement in adult SHR or WIS, but did facilitate acquisition of cocaine self-administration in adult WKY (Somkuwar et al., 2013b).

Environmental cues associated with cocaine use play a major role in compulsive drug seeking and relapse, and are linked to changes in dopamine-mediated neurotransmission in cortical sites such as medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) (Ciccocioppo et al., 2001; Di Pietro et al., 2008). DAT function in mPFC and OFC also is affected by adolescent ADHD medications (Somkuwar et al., 2013a,b). Unknown is whether ADHD influences reactivity to cocaine-related cues, and if medications prescribed for teens with ADHD alter cue reactivity in adulthood after treatment discontinuation. Cocaine cue reactivity is a fundamentally different issue than those addressed in our previous studies, which focused instead on the efficacy and motivating influence of cocaine reinforcement through the use of fixed-ratio (FR) and progressive-ratio (PR) schedules of cocaine delivery (Harvey et al., 2011; Somkuwar et al., 2013b). To address these new clinically relevant questions, we assessed strain differences in cocaine cue reactivity among SHR, WKY and WIS rats, and determined whether adolescent methylphenidate or atomoxetine influenced cocaine cue reactivity during adulthood after adolescent treatment was discontinued. A second-order schedule of cocaine delivery and cue presentation was used so that cocaine seeking, reflecting cue reactivity, could be measured when cocaine was (maintenance) and was not (reinstatement) available for self-administration (Kantak et al., 2002).

2. Materials and methods

2.1. Subjects

Male WKY/Cr, WIS/Cr, and SHR/Cr rats (Charles River Laboratories, USA) arrived on postnatal day 25 (P25). Rats had free access to water. Food was restricted to ~90% of a growth-adjusted free-feeding body weight until P55 to mimic conditions of past comparator studies (Harvey et al., 2011, 2013; Somkuwar et al., 2013a,b). Rats in Experiment 1 were utilized previously to measure strategy set shifting performance during adolescence (Harvey et al., 2013), whereas rats in Experiment 2 were experimentally naïve to behavioral testing. Procedures were approved by the Institutional Animal Care and Use Committee at Boston University and performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

To mimic clinical practice of medication-free holidays on weekends (Martins et al., 2004), (±)-methylphenidate hydrochloride (Sigma–Aldrich; St. Louis, MO) and atomoxetine hydrochloride (Tocris Biosciences; Ellisville, MO) treatments were administered during the light phase Monday-Friday from P28-P55, constituting the rat adolescent period (Spear, 2000). The chosen dose (1.5 mg/kg) and oral route of methylphenidate administration produces therapeutically relevant plasma drug levels that mimic clinical oral dosing (Kuczenski and Segal, 2002). The chosen dose (0.3 mg/kg) and intraperitoneal (i.p.) route of atomoxetine administration selectively increases extracellular norepinephrine and dopamine in PFC (Bymaster et al., 2002). Atomoxetine was injected i.p. due to poor oral bioavailability in rats (Mattiuz et al., 2003). Methylphenidate was dissolved in water (1.5 mg/ml). To attain a dose of 1.5 mg/kg, 1 ml/kg was injected into an oyster cracker for oral consumption. Oyster crackers injected with water (1 ml/kg) were used for vehicle control. Atomoxetine was dissolved in 0.9% sterile saline (0.15 mg/ml) and injected intraperitoneally (i.p.) in a volume of 2 ml/kg to attain a dose of 0.3 mg/kg. Injections of 0.9% sterile saline (2 ml/kg) were used for vehicle control. Cocaine hydrochloride (NIDA, Bethesda, MD) was mixed in 0.9% sterile saline containing 3 IU of heparin/ml and was self-administered at a dose of 0.3 mg/kg via catheters implanted into the right femoral vein on P67. A 0.8 mg/ml solution of cocaine was infused at a rate of 1.8 ml/min. The infusion duration was adjusted for each animal's daily body weight (1.2 s/100 g) to attain a dose of 0.3 mg/kg. Details for surgery and the testing environment are described in Supplementary Materials.[1] The number of animals that survived surgery and completed all phases of testing with intact catheters is indicated below.

2.3. Experiment 1: Effects of adolescent methylphenidate on adult behavior

2.3.1. Maintenance testing. On P77, vehicle- and methylphenidate-treated WKY (n = 10 and 7, respectively), vehicle- and methylphenidate-treated WIS (n = 10 and 10, respectively), and vehicle- and methylphenidate-treated SHR (n = 9 and 7, respectively) began cocaine self-administration training for delivery of 0.3 mg/kg cocaine under an FR 1 schedule. Testing was conducted during the light phase at the same time each day throughout all phases of the experiments. Illumination of the house light signaled the onset of each session. Drug delivery coincided with onset of the cue light and accompanying pump sound. Infusions were followed by a 20-s timeout for which the cue light remained illuminated while the house light was extinguished. The house light was re-illuminated following the 20-s timeout period. Rats were trained incrementally to a terminal fixed-interval (FI)-based second-order schedule designated FI 5-min [FR5:S]. The cue light (S) was presented under an FR 5 contingency and was illuminated for 2-s upon completion of each FR 5 during the FI 5-min. The house light was not extinguished during 2-s cue light presentations. After the FI elapsed, cocaine was delivered upon completion of an FR 5, and coincided with 20-s cue light presentation and termination of the house light. After the 20-s timeout, the house light was re-illuminated and the FI component was again in effect. Self-administration sessions were conducted once daily, Monday-Friday during the light phase for 2-h. Training continued until rats achieved stable levels of responding (≤15% variation in active lever responding, and ≤33% of total responses on the inactive lever) for a minimum of 5 sessions, designated as the maintenance baseline. A dose of 0.3 mg/kg cocaine was selected because it produces the highest rate of responding under an FI 5-min [FR5:S] schedule of cocaine delivery in rats (Kantak et al., 2009).

2.3.2. Extinction training. Following maintenance testing, rats underwent response extinction training. Sessions were conducted once daily, Monday-Friday, for 2-h durations. Rats received a minimum of 10 extinction sessions; criterion was defined

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2014.04.020.

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