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Methylphenidate treatment beyond adolescence maintains increased cocaine self-administration in the spontaneously hypertensive rat model of attention deficit/hyperactivity disorder

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ABSTRACT

Past research with the spontaneously hypertensive rat (SHR) model of attention deficit/hyperactivity disorder showed that adolescent methylphenidate treatment enhanced cocaine abuse risk in SHR during adulthood. The acquisition of cocaine self-administration was faster, and cocaine dose–response functions were shifted upward under fixed-ratio and progressive ratio schedules compared to adult SHR that received adolescent vehicle treatment or to control strains that received adolescent methylphenidate treatment. The current study determined if extending treatment beyond adolescence would ameliorate long-term consequences of adolescent methylphenidate treatment on cocaine abuse risk in adult SHR. Treatments (vehicle or 1.5 mg/kg/day oral methylphenidate) began on postnatal day 28. Groups of male SHR were treated with vehicle during adolescence and adulthood, with methylphenidate during adolescence and vehicle during adulthood, or with methylphenidate during adolescence and adulthood. The group receiving adolescent-only methylphenidate was switched to vehicle on P56. Cocaine self-administration began on postnatal day 77, and groups receiving methylphenidate during adolescence and adulthood were treated either 1-h before or 1-h after daily sessions. At baseline under a fixed-ratio 1 schedule, cocaine self-administration (2 h sessions; 0.3 mg/kg unit dose) did not differ among the four treatment groups. Under a progressive ratio schedule (4.5 h maximum session length; 0.01–1.0 mg/kg unit doses), breakpoints for self-administered cocaine in SHR receiving the adult methylphenidate treatment 1-h pre-session were not different from the vehicle control group. However, compared to the vehicle control group, breakpoints for self-administered cocaine at the 0.3 and 1.0 mg/kg unit doses were greater in adult SHR that received adolescent-only methylphenidate or received methylphenidate that was continued into adulthood and administered 1-h post-session. These findings suggest that extending methylphenidate treatment beyond adolescence does not ameliorate explicitly the long-term consequences of adolescent methylphenidate treatment. Pre-session methylphenidate may mask temporarily the detection of an increase in cocaine self-administration following chronic methylphenidate treatment.

1. Introduction

Methylphenidate is a psychostimulant commonly prescribed for the management of attention deficit/hyperactivity disorder (ADHD) in children and teenagers. Although an early meta-analysis concluded that stimulant medication initiated in childhood is protective against substance use disorders (SUD) later in life (Wilens et al., 2003), the most recent meta-analysis and multimodal treatment study concluded that stimulant treatment for ADHD initiated in childhood neither protects against nor increases risk of later SUD (Humphreys et al., 2013; Molina et al., 2013). Some evidence that ADHD medication initiation (methylphenidate in particular) during adolescence may have different long-term consequences for adult SUD than initiation in childhood is derived from research specifically analyzing age of treatment onset. One study (Mannuzza et al., 2008) excluded participants with conduct disorder and stratified children into age groups (6–7 vs. 8–12 years) for methylphenidate treatment initiation (lasting 2–4 years). Participants developing adult SUD initiated treatment at a later age than those who never developed SUD, although antisocial personality disorder may have influenced this relationship (Mannuzza et al., 2008). In another study, SUD risk in adulthood increased by a factor of 1.5 for every year older that childhood stimulant treatment began (Dalsgaard et al., 2014). A critical gap in the literature exists, however, regarding SUD in adults who began ADHD treatment as teenagers.

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Currently, ~20% of teens with ADHD in the United States receive a first diagnosis between ages 11–17, representing an estimated 700,000 people (National Survey of Children's Health Database, 2011/12). Studying the long-term consequences of adolescent-onset methylphenidate treatment is important because stimulants can change the trajectory of neuronal development during adolescence (Andersen, 2005; Casey and Jones, 2010).

Research using an animal model of ADHD would contribute to understanding the effects of methylphenidate treatment in newly diagnosed teenagers. The spontaneously hypertensive rat (SHR) is the most widely studied and validated animal model of ADHD (Russell, 2011). SHR exhibit frontostriatal neurocognitive deficits during adolescence and adulthood (Gauthier et al., 2014; Harvey et al., 2013; Kantak et al., 2008; Wells et al., 2010) and self-administer greater amounts of cocaine and other drugs of abuse compared to control strains (Chen et al., 2012; dela Pena et al., 2011; Jordan et al., 2014; Marusich et al., 2011; Somkuwar et al., 2013a). These later findings are consistent with epidemiological studies showing that having ADHD carries a 2–3 times greater risk of tobacco, cocaine and marijuana abuse by young adulthood (Lee et al., 2011). Additional preclinical studies demonstrated that adult SHR that had received adolescent methylphenidate treatment acquired cocaine self-administration more rapidly and exhibited upward shifts in cocaine dose–response functions under fixed-ratio (FR) and progressive ratio (PR) schedules compared to adult SHR that had received adolescent vehicle treatment and to control strains that had received adolescent methylphenidate treatment (Harvey et al., 2011). These findings suggest that adolescent methylphenidate treatment further enhanced cocaine abuse risk in adult SHR. In these past studies, methylphenidate treatment was discontinued at the end of adolescence, which was 3 weeks prior to the initiation of cocaine self-administration during adulthood. The current study tested the hypothesis that extending treatment beyond adolescence would ameliorate the long-term consequences of adolescent methylphenidate on cocaine abuse risk in adult SHR. This hypothesis is based on observations that methylphenidate treatment 2 h before sessions does not increase cocaine choice behavior in adult ADHD patients compared to non-ADHD controls (Collins et al., 2006). However, methylphenidate pretreatment reduces cocaine binding at the dopamine transporter (DAT) (Berglund et al., 2013; Volkow et al., 1995), and this may have masked the effects of chronic methylphenidate treatment on cocaine self-administration in the adult ADHD patients. To test this hypothesis, rats receiving chronic methylphenidate from adolescence into adulthood were treated with methylphenidate either 1 h before or 1 h after daily cocaine self-administration sessions, and the number of cocaine infusions was determined.

2. Materials and methods

Male SHR/NCrl rats (25 days old on arrival) were housed individually (08:00 h lights on, 20:00 h lights off) and maintained in accordance with the NIH Guide for Care and Use of Laboratory Animals and the Boston University Institutional Animal Care and Use Committee. Fig. 1 provides a graphical depiction of the experimental timeline and summary of procedures. Rats began treatment with 1.5 mg/kg (±) methylphenidate hydrochloride (Sigma-Aldrich, St. Louis, MO) or water vehicle on postnatal day 28 (P28), the start of adolescence in rats (Spear, 2000). Treatments were administered via oyster crackers on Monday–Friday to mimic the clinical practices of oral dosing and medication-free holidays on weekends for young patients with ADHD (Martins et al., 2004). A 1.5 mg/kg/day dose of oral methylphenidate produces peak plasma concentrations between 9 and 36 ng/ml in rats (Kuczenski and Segal, 2002), which is within peak plasma concentrations (8–40 ng/ml) achieved in pediatric patients (Swanson et al., 1999). This dose of oral methylphenidate also is clinically relevant because it lacks locomotor activating effects (Gerasimov et al., 2000), preferentially increases dopamine and norepinephrine signaling in prefrontal cortex (Berridge et al., 2006), and has procognitive effects in SHR (Harvey et al., 2013; Kantak et al., 2008). The amount of time to consume daily oyster crackers containing methylphenidate or vehicle averaged <3 min. Groups of SHR were treated with vehicle during adolescence and adulthood (VEH/VEH; $n = 10$), with methylphenidate during adolescence and vehicle during adulthood (MPH/VEH; $n = 8$; 20 ± 0 total days of methylphenidate treatment), or with methylphenidate during adolescence and adulthood (MPH/MPH; $n = 15$). The group receiving adolescent-only methylphenidate was switched to vehicle treatment on P56. Rats receiving adolescent and adult methylphenidate were subdivided into two groups and treated with methylphenidate either 1-h before (MPH/MPH 1-h Pre; $n = 8$; 61 ± 3 total days of methylphenidate treatment) or 1-h after (MPH/MPH 1-h Post; $n = 7$; 67 ± 2 total days of methylphenidate treatment) daily self-administration sessions that began on P77 (see below). Rats given vehicle during adulthood received treatment 1-h after daily self-administration sessions.

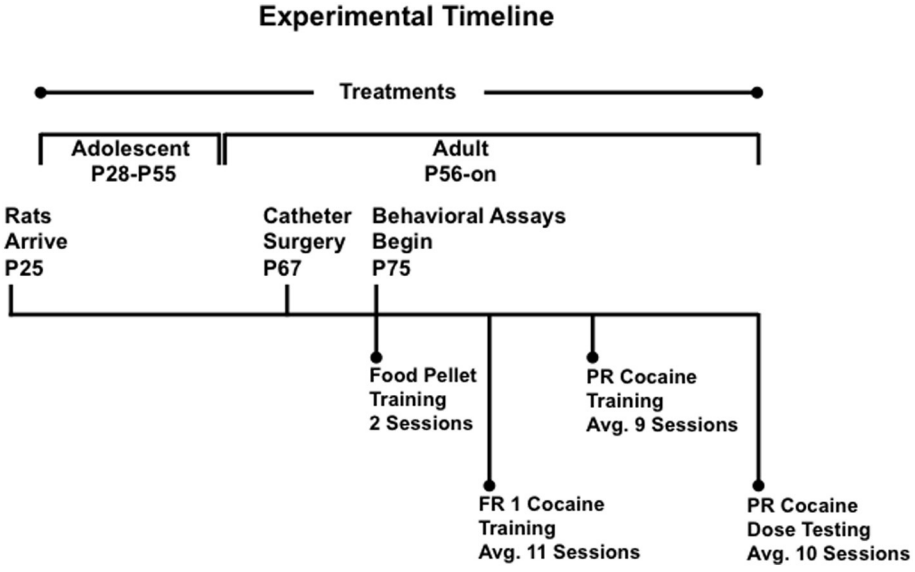

Fig. 1. Graphical depiction of the experimental timeline and summary of procedures Abbreviations: P, postnatal day; FR, fixed-ratio schedule of reinforcement; PR, progressive ratio schedule of reinforcement.