Behavioural Brain Research 312 (2016) 333–340

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Nicotine-induced behavioral sensitization in an adult rat model of attention deficit/hyperactivity disorder (ADHD)

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HIGHLIGHTS

- Baseline rotational activity is similar in SHR (ADHD model) and WKY (control) rats.
- SHR displays weaker nicotine-induced suppression of rotational activity than WKY.
- Nicotine sensitizes rotational activity in both strains.
- Nicotine effects on SHR performance are dependent of cholinergic receptors.
- SHR may model an ADHD-related reduction in nicotine aversion that promotes smoking.

ARTICLE INFO

Article history:
Received 13 March 2016
Received in revised form 23 June 2016
Accepted 26 June 2016
Available online 27 June 2016

Keywords:
Nicotine
Sensitization
Suppression
Spontaneously hypertensive rat
Wistar Kyoto
ADHD

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is associated with increased risk of tobacco dependence. Nicotine, the main psychoactive component of tobacco, appears to be implicated in ADHD-related tobacco dependence. However, the behavioral responsiveness to nicotine of the prevalent animal model of ADHD, the spontaneously hypertensive rat (SHR), is currently underinvestigated. The present study examined the activational effects of acute and chronic nicotine on the behavior of adult male SHRs, relative to Wistar Kyoto (WKY) controls. Experiment 1 verified baseline strain differences in open-field locomotor activity. Experiment 2 tested for baseline strain differences in rotational behavior using a Rotorat apparatus. Adult SHR and WKY rats were then exposed to a 7-day regimen of 0.6 mg/kg/d s.c. nicotine, or saline, prior to each assessment. A separate group of SHRs underwent similar training, but was pre-treated with mecamylamine, a cholinergic antagonist. Nicotine sensitization, context conditioning, and mecamylamine effects were then tested. Baseline strain differences were observed in open-field performance and in the number of full rotations in the Rotorat apparatus, but not in the number of 90° rotations or direction changes. In these latter measures, SHRs displayed weaker nicotine-induced rotational suppression than WKYs. Both strains expressed nicotine-induced sensitization of rotational activity, but evidence for strain differences in sensitization was ambiguous; context conditioning was not observed. Mecamylamine reversed the effects of nicotine on SHR performance. These findings are consistent with the hypothesis that a reduced aversion to nicotine (expressed in rats as robust locomotion) may facilitate smoking among adults with ADHD.

1. Introduction

Attention deficit-hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity [1] that often persist into adulthood [2–4]. ADHD is a risk factor for smoking and tobacco dependence [5–7]. Adolescents with ADHD begin experimenting with tobacco and progress to regular use at a younger age than their non-diagnosed peers, and are more likely to continue smoking as adults [8–10]. Prevalence of smoking among adolescents and adults with ADHD is double that of the general population [8,10]. In addition, smokers with ADHD consume more cigarettes per day and

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http://dx.doi.org/10.1016/j.bbr.2016.06.050
0166-4328/

are measurably more dependent on tobacco than smokers without ADHD [11,12]. Once dependent, smokers with ADHD report more frequent but less successful quit attempts than smokers without ADHD, and exhibit more severe withdrawal symptoms [6,13–15].

Smokers with ADHD report that smoking is reinforcing, induces wakefulness, enhances cognition, decreases irritability, and improves mood [16,17]. Although smokers without ADHD also report these effects [18], smokers with ADHD report stronger effects [16,17] and report that cigarette puffs are more satisfying and better "liked" [17]. Nicotine, the primary psychoactive component of tobacco [19], appears to mediate the impact of smoking on cognition and affect [18,20–23]. Collectively, these findings suggest a strong, potentially nicotine-mediated impact of tobacco use on the behavior and cognition of smokers with ADHD.

The physiological mechanisms underlying the heightened responsiveness to tobacco in individuals with ADHD are yet unknown. To test candidate mechanisms, including those involving nicotinic-receptor function, animal models may be employed. Behavioral responsiveness to nicotine is expressed in adult rat models as locomotor suppression (initially) and sensitization (after repeated exposures). Tolerance to the suppression of locomotion induced by acute nicotine administration develops rapidly over a few exposures [24–27]. Nicotine-induced locomotor suppression appears to reflect the aversive properties of acute nicotine in adult rats. For instance, nicotine pre-exposure reduces nicotine-induced locomotor suppression [28] and taste aversion [29], but facilitates nicotine-induced place preference [30]. These effects suggest that tolerance to the aversive effects of nicotine develops during pre-exposure, and may be expressed as attenuated nicotine-induced locomotor suppression.

Repeated nicotine exposure leads to an escalation in nicotine-induced locomotion [31,32]. Behavioral sensitization induced by nicotine and other drugs reflects neural adaptations in the dopaminergic mesolimbic pathway that are associated with drug dependence [33–35]. Therefore, nicotine-induced behavioral sensitization is a potential measure of vulnerability to nicotine dependence; it complements other measures that involve more complex learning mechanisms, such as nicotine self-administration [36].

This study investigated whether the most widely used animal model of ADHD, the spontaneously hypertensive rat (SHR) [37,38], displays the pattern of nicotine-induced locomotor suppression and sensitization that may reflect the heightened vulnerability to tobacco dependence in humans with ADHD. Prior studies suggest that, relative to its progenitor and most commonly used control strain, the inbred Wistar Kyoto rat (WKY) [39–43], SHR is more responsive to nicotine. In particular, young SHR self-administers intravenous nicotine at a higher rate [44], and appears to display more robust nicotine-induced conditioned place preference [45] than WKY. These effects, however, may reflect differential learning deficits and interference by non-learning factors across strains [46,47]. Watterson and colleagues [45] also reported heightened dose-dependent nicotine-induced locomotion in adolescent SHR relative to WKY, but did not explicitly test for sensitization or at other ages.

One disadvantage of the SHR model—for the purpose of this study—is that it exhibits elevated baseline levels of locomotor activity relative to WKY [39,42,43,69]. Preexisting strain differences confound potential differences in nicotine-induced locomotor effects between strains. To circumvent this obstacle, the present study sought to assess strain differences in nicotine-induced sensitization of a behavior that (a) does not differ between strains at baseline, (b) involves mesolimbic dopamine activity, and thus (c) displays a pattern of suppression and sensitization over repeated exposure that is potentially indicative of vulnerability to dependence. This study tested various rotational behavior measures as potential target behaviors [48,49].

Experiment 1 verified differences in baseline levels of locomotor activity between strains in the open field arena. Experiment 2 evaluated differences in baseline levels of various rotational behaviors in the Rotorat apparatus. Measures of rotational behavior that did not differ significantly between strains served as dependent measures to evaluate nicotine-induced behavioral suppression and sensitization. Experiment 2 tested the hypothesis that, to the extent that the SHR strain models ADHD-related responsiveness to nicotine, SHR rats display reduced nicotine-induced suppression or enhanced nicotine-induced sensitization of baseline-equated rotational behavior, relative to WKY rats.

2. Material and methods

2.1. Animals

Adult male rats of two inbred strains, spontaneously hypertensive rats (SHR/NCrl; Charles River Laboratories) and Wistar Kyoto (WKY/NHsd; Harlan Laboratories), served as subjects. Strains and breeders were selected to model the ADHD combined subtype [41]. All rats had previous experimental history with a variable-interval (VI) schedule of food reinforcement, procured by lever pressing, and during which access to food was restricted to 1 h/d. Training and food regimens were identical for both strains. Food restriction was discontinued for at least 3 days prior to the present experiments; food and water were provided ad libitum in the home cage throughout experimentation. All subjects were pair-housed in a colony room with a 12:12-h light-dark cycle, with lights on at 1900 h and experiments conducted during the dark phase. All experimental protocols were conducted in accordance with the guidelines provided by the National Institute of Health and approved by the Arizona State University Institutional Animal Care and Use Committee.

2.2. Apparatus

Horizontal locomotion and rotational behavior were assessed using an open field arena (experiment 1) and a Rotorat apparatus (experiment 2), respectively. The open field arena consisted of a black plastic box with an open top measuring $90 \times 90 \times 40$ cm, located in a dimly lit room. A single shielded white light bulb was suspended 90 cm above the center of the arena to illuminate it. The arena was divided into two zones of interest: the center zone, defined as a 54×54 cm square in the center of the arena, and the perimeter, defined as the remaining area of the arena; no stimulus demarcated the boundary between center and perimeter. Video tracking software (EthoVision XT 8.1, Noldus Information Technology, Wageningen, Netherlands) recorded the position of the animal and horizontal distance traveled, sampling at 5 Hz.

The Rotorat apparatus consisted of a stainless steel bowl (40.6 cm diameter $\times$ 25.4 cm height; model ENV-500, Med Associates, St. Albans, VT) surrounded by clear Plexiglas walls. A spring tether was secured to the top of the apparatus by a rotational sensor that recorded rotational activity. A zip-tie collar was placed loosely around the neck of the rat and connected to the spring tether via a stainless steel alligator clip.

2.3. Drugs

Nicotine hydrochloride tartrate (NIC; Sigma, St. Louis, MO, USA) and mecamylamine hydrochloride (MEC; Sigma, St. Louis, MO, USA) were dissolved in saline (0.9% NaCl). MEC is a non-selective nicotinic receptor antagonist; it served as a pre-treatment to verify the cholinergic dependency of NIC-induced rotational behavior in SHR