Behavioural Brain Research 286 (2015) 85–92

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Comparison of the validity of the use of the spontaneously hypertensive rat as a model of attention deficit hyperactivity disorder in males and females

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HIGHLIGHTS

- Female spontaneously hypertensive rats (SHR) have been much less studied than males.
- SHR rats are used to model symptoms of attention deficit hyperactivity disorder.
- We report that levels of impulsivity and hyperactivity are elevated in both sexes.
- However, only SHR males exhibit attentional deficits compared to same-sex controls.

ARTICLE INFO

Article history:
Received 20 October 2014
Received in revised form 18 January 2015
Accepted 16 February 2015
Available online 24 February 2015

Keywords:
Spontaneously hypertensive rat (SHR)
Attention deficit hyperactivity disorder (ADHD)
Attention
5-choice serial reaction time task (5-CSRTT)
Sex difference

ABSTRACT

The spontaneously hypertensive rat (SHR) is a commonly used and well-studied rodent model of attention deficit hyperactivity disorder (ADHD). Sex differences in the cognitive symptoms of ADHD are reported. However, the female SHR rat is much less studied than its male counterpart. The goal of the current study was to assess the validity of the SHR rodent model of ADHD by examining attentional performance, inhibitory control, and hyperactivity in both male and female SHR rats. Adult SHR and control Wistar–Kyoto rats were trained on the 5-choice serial reaction time task, a self-paced test of attention and inhibitory control. This task requires animals to identify the location of a brief light stimulus among five possible locations under several challenging conditions. Analyses of percent correct revealed that attentional performance in SHR females was not significantly different from control females, whereas attentional performance in SHR males was significantly different from control males. Analyses of the number of premature responses revealed that SHR rats made more inhibitory control errors than did control rats and that this decrease in inhibitory control was present in both SHR males and females. Analyses of activity in the open field revealed that SHR rats were more hyperactive than were control rats and that this increased hyperactivity was present in both SHR males and females. The current findings have implications for the study of sex differences in ADHD and for the use of SHR rats as a model of ADHD in females.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is more frequently diagnosed in boys than it is in girls, with estimates typically ranging from 2:1 to 5:1 [1–3]. In 40–60% of children with ADHD, the disorder persists into adulthood [4], with a male:female ratio closer to 2:1 [5]. ADHD has a strong genetic basis [6] and is characterized by three core symptoms: attention deficits, pathological impulsivity, and extreme hyperactivity [7]. Studies investigating sex differences in ADHD indicate that females display greater attentional deficits and are more frequently diagnosed with the inattentive subtype of ADHD than are males [1,3], whereas males display greater inhibitory control deficits and are more frequently diagnosed with the hyperactive-impulsive and combined subtypes of ADHD than are females [8,9]. These findings suggest that males and females may differ in the way that they process attentional information [10]. Previous research using rodents supports this

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http://dx.doi.org/10.1016/j.bbr.2015.02.029
0166-4328/

interpretation [11]. We have reported that female rats make more attentional errors than do males during challenging behavioral conditions and that male rats make more impulsive actions than do females when a delayed response is required [12]. In addition, male rats make more impulsive choices than do females for an immediate small food reward over a delayed large food reward [13].

ADHD affects 3–5% of the population [7], meaning that even with the sex bias in diagnosis, a significant number of females are diagnosed with ADHD. However, females are largely understudied with respect to preclinical research using animal models of ADHD [8]. Furthermore, the disparity in the diagnosis of ADHD and its subtypes between the sexes suggests that each sex expresses the disorder differently. Therefore, a greater understanding of the sex differences in ADHD can lead to novel insights into the etiology of the disorder. The spontaneously hypertensive rat (SHR) is one of the most commonly used and well-studied rodent models of ADHD [14]. However, the majority of studies conducted to validate the SHR model of ADHD have used only male animals [15–21]. SHR male rats exhibit deficits in attention, impulsivity, and hyperactivity, the three core symptoms of ADHD [14,22]. In addition, dopaminergic and noradrenergic neurotransmitter systems are hypofunctional in SHR male rats, similar to the neurochemical abnormalities observed in ADHD [14,16]. The few behavioral studies examining female SHR rats have focused on associative learning and conditioned inhibitory behavior [23–25]. These studies report that female SHR rats exhibit increased distractibility, less conditioned responding, and require more training sessions to learn an inhibitory response discrimination than do male SHR rats. Furthermore, gonadal hormone levels influence these sex differences in conditioned behavior. These studies were primarily designed to examine sex differences in SHR rats and not necessarily to validate the SHR model of ADHD in females through direct comparison to same-sex controls in a similar approach as the validation studies conducted using male animals. Furthermore, to our knowledge, no studies have investigated female SHR performance during tasks designed specifically to measure attentional performance.

One of the most commonly used tests of attentional performance and inhibitory control in rodents is the 5-choice serial reaction time task (5-CSRTT), which was developed from the continuous performance task used to quantify attentional deficits in humans [26]. During the 5-CSRTT, rats must identify the location of a brief light stimulus presented randomly across five possible locations over a large number of independent trials [27]. The 5-CSRTT has been shown to be dependent upon the prefrontal cortex [26] and assesses both attentional performance, the ability to continuously allocate attentional resources across many trials, and inhibitory control, the ability to refrain from making an inappropriate or premature response [28]. Only two studies to date have examined performance of male SHR rats on the 5-CSRTT. These studies provide inconsistent findings, reporting decreased attentional performance in male SHR rats as compared to controls [21], and reporting similar levels of attentional performance in SHR rats and controls [15]. To date, no study has examined the performance of female SHR rats on the 5-CSRTT.

The goal of the current study was to compare the validity of the SHR rodent model of ADHD in males and females by examining the three core symptoms of ADHD, attentional deficits, impulsivity, and hyperactivity, in SHR and same-sex control rats. In the current study as has been utilized in other SHR studies [18–20], we used the strain from which SHR rats were bred, Wistar-Kyoto (WKY) rats, as our control animals [29]. Attentional performance and inhibitory control in male and female SHR and control WKY rats were assessed on the 5-CSRTT under baseline conditions and under behavioral challenge conditions during which task difficulty was increased. Behavioral challenge conditions included shortening the stimulus duration, shortening the time before the onset of the stimulus, lengthening the time before the onset of the stimulus, and presenting a distracting noise. Following testing on the 5-CSRTT, activity levels were measured using the open field arena.

2. Materials and methods

2.1. Subjects

Eight male and eight female young adult SHR rats and eight male and eight female young adult control WKY rats, approximately 2 months of age, were purchased from Harlan Sprague Dawley Inc. (Indianapolis, IN). Animal care was in accordance with the guidelines set by the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*, and all procedures were approved by the Institutional Animal Care and Use Committee of Tulane University. Animals were pair-housed under a 12-h light/dark cycle and tested during the light phase of the cycle. All animals were weighed daily following behavioral training and food was provided in their home cages to maintain their weights at 85% of their free-feeding weights while allowing for growth of approximately 2% of their body weight each week.

2.2. Testing on the 5-choice serial reaction time task

2.2.1. Apparatus

Animals were trained and tested in one of four separate 25 × 25 cm aluminum chambers (Lafayette Instrument Co., Lafayette, IN). The rear wall of each chamber was convexly curved and contained five light apertures, each 2.5 cm square, 4 cm deep, and set 2 cm above floor level. Each light aperture could be illuminated by a 3 W light bulb located at the rear of the hole, and each hole had an infrared photocell beam monitoring the entrance. The four conditioning chambers were individually housed in sound attenuating cabinets. Each chamber was illuminated by a 3 W house light and equipped with a speaker that could deliver bursts of white noise. The front wall could be opened to place in and remove the animal from the chamber. On the front wall, 25 cm from each nose-poke hole, there was a food magazine where 45 mg food pellets (Test Diet, Richmond, IN) could be automatically dispensed. Each animal received one session of training per day throughout the experiment. House lights were on unless stated otherwise.

2.2.2. Behavioral training

First, animals were successively shaped to retrieve food rewards from the food tray and to poke any of the holes to receive food rewards. Then each animal was trained daily for 30 min on the 5-CSRTT by passing through several training stages of increasing difficulty. Each session terminated after 100 trials had been completed or 30 min had expired, whichever occurred first. An animal was moved to the next training stage once it performed at >80% correct and <20% omissions for two consecutive days. Percent correct reflects the percentage of correct responses, whereas omissions reflect the failure to respond to the light stimulus. Each rat was always trained in the same conditioning chamber. Females were always trained in the same two chambers while males were always trained at the same time as the females in the other two chambers. Animals were trained at approximately the same time of the light phase each day.

For the initial training stage, animals were placed in the chamber and initiated the first trial by retrieving a single food pellet from the food tray. After a fixed 5 s intertrial interval (ITI), one of the five horizontal lights was illuminated for a maximum of 60 s (cue duration) or until a response had been made. From the time the light first turned on, the animal had 60 s (limited hold period) to respond by making a nose-poke into the previously lit aperture. Correct responses were immediately rewarded with delivery