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Sex Differences in Learning and Inhibition in Spontaneously Hypertensive Rats

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Abstract

Few studies have addressed potential differences in the nature of cognitive impairment observed in males and females with ADHD. In Experiment 1, we examined sex differences in conditioned inhibitory behaviour in Spontaneously-Hypertensive rats (SHR strain), a purported animal model of ADHD. Rats were presented with two types of trials during each of fifteen conditioning sessions. On some trials an auditory stimulus (a tone) was presented and followed immediately by delivery of food reward. On the remaining trials the tone was preceded by presentation of a visual stimulus and on those trials food was not delivered after the tone was presented. As training progressed, conditioned responding during presentation of the tone increased on reinforced trials and decreased during the non-reinforced trials, indicative of successful discrimination and inhibition. Female SHR rats exhibited less conditioned food cup behaviour overall compared to male rats. In addition, female SHR rats required more training sessions until they responded significantly more during presentation of the tone on reinforced trials versus non-reinforced trials. In contrast, no sex differences were observed in WKY rats (commonly-used control strain) in Experiment 2. Importantly, there were no significant sex differences in baseline activity or motivation during either experiment, indicating that performance differences could not account for the observed results. These results suggest that male and female SHR rats differ in their ability to form conditioned associations and inhibit behavioural responses and may provide a useful model for sex differences in cognitive dysfunction specific to ADHD.

Keywords

Attention-Deficit/Hyperactivity Disorder; associative learning; occasion setting; feature negative discrimination

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is typically more prevalent in boys than girls, with sex ratio estimates typically ranging from 2:1 to 5:1 [8,12,27]. Nonetheless, with prevalence rates of 3–5% for ADHD [1], there are a significant number of girls who are diagnosed with the disorder; yet girls remain a largely understudied population of persons affected by ADHD [9]. The few studies that have investigated potential sex differences in ADHD indicate that girls may exhibit more extreme cognitive symptoms [9,16]. In addition, there is evidence for sex differences in the underlying biological factors contributing to ADHD

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[7,19]. Thus there is currently a significant need for additional research into sex differences in the behavioural and biological characteristics of ADHD [9], as well as animal models to study the nature and basis of these differences.

Among the several animal strains that have been used to model symptoms of ADHD, the Spontaneously Hypertensive Rat (SHR) is the most commonly used and well-studied model [23]. SHR rats exhibit deficits in sustained attention, increased motor activity, shortened delay-of-reinforcement gradients, and altered extinction [11,20,22]. Dopaminergic and noradrenergic systems are hypofunctional in SHR rats, reminiscent of the neurochemical abnormalities observed in ADHD [23]. However, only a few studies have examined sex differences in SHR rats [4,21]. Moreover, there has been no research on potential sex differences in inhibitory behavior in SHR rats. Deficits in inhibitory behaviour are currently thought to be among the core features of ADHD [2,3,14,18,24,25]. These deficits reflect an inability to inhibit behavioural responses, leading to impaired behavioural control and executive functioning in people with ADHD [2,3,15].

In Experiment 1 we examined whether sex differences in inhibition exist in SHR rats using a conditioned inhibition procedure. The task involves learning a serial feature negative discrimination [10] in which rats receive presentations of an auditory stimulus (a tone) followed by food reward on a subset of trials. On the remaining trials the tone is preceded by a visual stimulus (a panel light) and not reinforced. Rats typically begin to discriminate between the two trials after several daily sessions and inhibit responding during presentation of the tone on the non-reinforced trials. It was hypothesized that a sex difference in inhibition would exist between male and female SHR rats and be reflected in a difference in the number of sessions required to learn the discrimination and/or a difference in the magnitude of the discrimination. In a follow up study (Experiment 2), we examined the performance of male and female Wistar-Kyoto (WKY) rats on the conditioned inhibition task. WKY rats are the most commonly used comparison strain for the SHR strain [23] and were included to determine if sex differences in SHR rats were specific to that strain, or simply reflected a more general sex difference in rats. If sex differences were observed in SHR rats and not in WKY rats, this would support the notion that the SHR strain might provide a useful model for studying the basis for sex differences that are specific to ADHD and that do not occur in the normal population.

EXPERIMENT 1

Materials and Methods

Subjects—Twenty-four SHR rats (12 male, 12 female) were obtained from Harlan Laboratories, Indianapolis, IN, USA at 8 weeks of age and maintained on a 14/10-hr light-dark cycle. Rats were housed individually with free access to water and food (Purina standard rat chow; Nestlé Purina, St. Louis, MO, USA) during a seven-day acclimation period. Rats were subsequently handled and weighed daily for three days to establish baseline body weights and then body weights were gradually reduced to 85% of baseline over a seven-day period. Animals were monitored and cared for throughout the experiment in compliance with the principles of laboratory animal care, including the Association for Assessment and Accreditation of Laboratory Animal Care guidelines, the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioural Research, and the Dartmouth College Institutional Animal Care and Use Committee.

Apparatus—The conditioning procedures took place in standard operant conditioning chambers (24 cm × 30.5 cm × 29 cm; Med Associates, St. Albans, VT, USA) constructed of aluminum front and back walls, clear acrylic sides and top, and grid floors. The chambers were enclosed in sound-attenuating cabinets (62 cm × 56 cm × 56 cm) equipped with exhaust fans for air flow and background noise (~68dB). A dimly illuminated food cup was recessed in the

center of one end wall and a 6-W jeweled panel light, which served as the visual conditioned stimulus (CS), was located 5 cm above the opening. A speaker was mounted next to the light and delivered the auditory CS (78dB, 1500 Hz tone). An infrared photobeam was located across the entry of the food cup to monitor placement of the snout into the food cup to retrieve food pellets.

Behavioural Procedures—Rats were first trained to eat from the food cup during a single 64-minute session in which two 45-mg food pellets (Noyes, New Brunswick, NJ) were randomly delivered into the food cup sixteen times. The subsequent fifteen daily conditioning sessions each lasted for approximately 68 minutes and included sixteen trials of two types. Rats received four trials per session consisting of a five-second presentation of the tone followed immediately by delivery of two food pellets. For the other twelve trials, the panel light was presented for five seconds, followed by a five-second empty period, and then the tone was presented for five seconds. No food was delivered after the tone on these trials. The two trial types occurred randomly during the session and the order of trials differed on each day along with the inter-trial intervals (average of 4 minutes).

Analysis of Conditioning Data—Breaks in the infrared photobeam located across the entry of the food cup were monitored by the computer during presentation of the tone as well as during the 5-sec period before the start of a trial (pre-CS responding) and the 5-sec period immediately after food was delivered (post-CS responding). Two measures of conditioned responding (i.e., food cup behaviour) were obtained: 1) the number of times the rat placed its snout into the food cup, and 2) the amount of time spent with the snout inside the food cup. Data for each of these measures were averaged for each trial type and training session. Group differences in conditioned responding were assessed using a repeated measures analysis of variance (ANOVA) with Group as the between-subjects variable and Trial type and Session as the within-subjects variables. In addition, a difference score was calculated by subtracting responding during non-reinforced trials from responding during reinforced trials. This was used to assess the magnitude of the discrimination in each group. All analyses were followed up with appropriate pair-wise comparisons and were conducted using an alpha level of 0.05.

Locomotor Activity—After the final conditioning session locomotor activity was assessed in an open field apparatus. The open field chamber (43.2 × 43.2 cm) was composed of plexiglass walls and was connected to a computer running Open Field Activity Software (Med Associates). The chamber was equipped with 16 photobeams mounted on the sides at two different heights to monitor locomotor activity. On the test day, rats were placed individually in the open field chamber and were allowed to explore the chamber for 15 minutes, during which time the total distance traveled was monitored by the computer. The chamber was cleaned with Quatricide between testing each animal.

Analysis of Activity Data—The total distance traveled was divided into fifteen 60-sec epochs. Locomotor activity was analyzed using a repeated measures ANOVA with Group as the between-subjects variable and Epoch as the within-subjects variable. Correlations between locomotor activity in the open field and the measures of conditioned responding during the tone were assessed by calculating Pearson correlation coefficients. An alpha level of 0.05 was used for all analyses.

Results

Serial Feature Negative Discrimination

Conditioned responding during presentation of the tone on reinforced and non-reinforced trials is presented in Figure 1. The two measures of conditioned responding (number of nose-pokes

and time in food cup) yielded highly similar patterns of results and illustrate a sex difference in learning the conditioned inhibition task. An analysis of the number of nose-pokes into the food cup (Figure 1A) revealed a significant difference between male and female rats [main effect of Group, $F(1,22)=10.8$, $p<0.003$; Group $\times$ Trial type interaction, $F(1,22)=5.2$, $p<0.03$]. Pair-wise comparisons revealed that male rats responded more than female rats during presentation of the tone on both reinforced ($p<0.004$) and non-reinforced trials ($p<0.01$). In addition, male rats learned the discrimination in fewer sessions than females rats [Group $\times$ Trial type $\times$ Session interaction, $F(14,308)=2.5$, $p<0.003$]. Males rats began exhibiting significantly more nose-poke behaviour on reinforced versus non-reinforced trials in Session 5 ($p<0.04$) while female rats required 7 sessions to respond more on reinforced trials ($p<0.001$). The magnitude of the discrimination, as assessed by the difference in responding on reinforced and non-reinforced trials, was not significantly different between male and female SHR rats [main effect of Group, $F(1,22)=0.2$, $p>0.6$; Group $\times$ Session interaction, $F(14,308)=0.8$, $p>0.6$].

An analysis of the amount of time spent with the snout inside the food cup (Figure 1B) revealed a significant Group $\times$ Trial type $\times$ Session interaction [$F(14,308)=1.9$, $p<0.03$]. The main effect of Group and the Group $\times$ Trial type interaction did not reach statistical significance (p 's=0.1) likely due to greater variability in the time-in-food-cup data compared to the number of nose-poke data (compare Figures 1A and 1B). Using the time measurement, the number of sessions needed until rats successfully discriminated between the two trial types was the same as that obtained with the number of nose-pokes; males spent significantly more time in the food cup on reinforced trials versus non-reinforced trials beginning on Day 5 ($p<0.04$) while female SHR rats did not begin discriminating between the two trial types until Day 7 ($p<0.04$). There was no significant difference in the magnitude of the discrimination between males and females using the time measurement [main effect of Group, $F(1,22)=0.1$, $p>0.7$; Group $\times$ Session interaction, $F(14,308)=1.1$, $p>0.4$].

The amount of food-cup behaviour exhibited just prior to the start of a trial (i.e., pre-CS behaviour) was very low and did not differ between male and female rats using either measure of responding (time or nose-pokes). The mean number of nose-pokes recorded during the pre-CS period was 0.6 ± 0.1 and 0.5 ± 0.1 ($p>0.7$) and the mean amount of time spent with the snout in the food cup during the pre-CS period was 0.3 ± 0.1 sec and 0.3 ± 0.1 sec ($p>0.9$) for males and females, respectively. Responding immediately after the tone was turned off and food was delivered was also comparable between the groups. The mean number of nose-pokes exhibited during the post-CS period was 1.7 ± 0.1 and 1.7 ± 0.1 ($p>0.7$) and the time spent in the food cup during the post-CS period was 3 ± 0.1 sec and 2.7 ± 0.1 sec ($p>0.1$) for males and females, respectively.

Locomotor Activity

The distance traveled by male and female SHR rats in the open field is illustrated in Figure 2. A repeated measures ANOVA revealed a main effect of Epoch [$F(14,308)=19.3$, $p<0.0001$] indicating that locomotor activity habituated over the course of the 15 min test session. Although there was no significant Group difference in activity [main effect of Group, $F(1,22)=2.1$, $p>0.2$], there was a significant Group $\times$ Epoch interaction [$F(14,308)=2.2$, $p<0.01$] reflecting greater activity in female rats during epochs 2 and 11. There were no significant correlations between locomotor activity measured in the open field test and any measure of conditioned responding during the tone (r 's <0.1 , p 's >0.5).

Discussion

Experiment 1 examined the ability of male and female SHR rats to learn a serial feature negative discrimination, a form of conditioned inhibition. Female SHR rats exhibited less conditioned responding than male rats on both types of trials. In addition, male rats learned the

discrimination in fewer training sessions than females. The magnitude of the discrimination, however, was comparable in male and female rats. These results suggest that male and female SHR rats differ in their ability to form conditioned associations and that females SHR rats are slower in learning to inhibit a conditioned response.

Female SHR rats exhibited slightly more locomotor activity than male rats when allowed to explore an open field apparatus after the discrimination task was completed. This is consistent with a previous report that female SHR rats were more active than males on a lever-pressing task [4]. It is possible that female rats were more distracted and less likely to focus on task-related stimuli than male rats. This could have led to less conditioned responding in females compared to males as well as impaired acquisition of the conditioned discrimination. However, responding prior to the start of a trial (pre-CS behaviour) was infrequent and comparable between males and females. We have argued previously that pre-CS behaviour may be a more task-relevant measure of potential group differences in baseline activity than locomotor activity in an open field [6]. Regardless, there were no significant correlations between locomotor activity and any measure of conditioned responding. Together with the pre-CS data, this suggests that the observed differences in conditioned responding during the tone were not merely due to differences in baseline activity. Likewise, responding after food reward was delivered (post-CS behaviour) was comparably high in both sexes, suggesting that there were no motivational differences between males and females that could explain the sex differences in learning the discrimination or responding to the tone.

The few studies that have investigated potential sex differences in ADHD indicate that girls may exhibit more extreme cognitive symptoms [9,16,19]. One study that is particularly relevant to the present data revealed that girls diagnosed with the inattentive subtype of ADHD exhibited deficits in inhibition whereas boys were unimpaired [16]. In light of that study, the present findings in female SHR rats are encouraging insofar as female rats exhibited greater difficulty in acquiring the conditional discrimination. However, if this paradigm is to serve as a useful model for characterizing and studying the biological basis of sex differences in ADHD, it is important to determine how the performance of SHR rats compares to normo-active control rats. Thus, Experiment 2 was designed to follow up these data by testing male and female WKY rats in the serial feature negative discrimination task. SHR rats were originally derived from the WKY strain, which does not exhibit hyperactivity and is considered by some to be the most appropriate comparison strain for SHR rats [23].

EXPERIMENT 2

Materials and Methods

Twenty-four WKY rats (12 male, 12 female) were obtained from Harlan Laboratories, Indianapolis, IN, USA at 8 weeks of age and maintained exactly as described in Experiment 1. Likewise, the *Apparatus*, *Procedures*, and *Analyses* were identical to those used in Experiment 1.

Results

Serial Feature Negative Discrimination—Conditioned responding in male and female WKY rats during presentation of the tone on reinforced and non-reinforced trials is presented in Figure 3. A repeated measures ANOVA of the number of nose-pokes (panel A) did not reveal any significant differences between male and female WKY rats [main effect of Group, $F(1,22)=0.4$, $p>0.6$; Group $\times$ Trial interaction, $F(1,22)=0.4$, $p>0.5$; Group $\times$ Trial $\times$ Session interaction, $F(14,308)=0.8$, $p>0.6$]. Likewise, there was no significant difference in the magnitude of the discrimination between WKY males and females using the nose-poke

measurement [main effect of Group, $F(1,22)=0.4$, $p>0.5$; Group $\times$ Session interaction, $F(14,308)=0.8$, $p>0.7$].

The amount of time spent with the snout inside the food cup during presentation of the tone on each of the two types of trials is presented in Figure 3B. A repeated measures ANOVA failed to reveal a significant main effect of Group ($p>0.1$) or a Group $\times$ Trial type interaction ($p>0.2$). However, there was a significant Group $\times$ Trial type $\times$ Session interaction [$F(1,14)=2$, $p<0.02$], indicating that female WKY rats exhibited more conditioned responding than male WKY rats during the last few training sessions. In addition, female WKY rats began spending significantly more time in the food cup on reinforced versus non-reinforced trials on Session 6 ($p<0.05$) while male rats required 7 sessions to respond more on reinforced trials ($p<0.003$). The magnitude of the discrimination, as assessed by the percent-difference in nose-pokes emitted during reinforced and non-reinforced trials, was not significantly different between male and female WKY rats [main effect of Group, $F(1,22)=1.3$, $p>0.3$]. Yet the Group $\times$ Session interaction was significant [$F(14,308)=2$, $p<0.02$], indicating that during the later sessions female WKY rats exhibited a more robust discrimination than males.

The amount of food-cup behaviour exhibited just prior to the start of a trial (i.e., pre-CS behaviour) was very low and did not differ between WKY male and female rats using either measure of responding (time or nose-pokes). The mean number of nose-pokes recorded during the pre-CS period was 0.7 ± 0.1 and 0.9 ± 0.1 ($p>0.2$) and the amount of time spent with the snout in the food cup was 0.4 ± 0.1 sec and 0.6 ± 0.1 sec ($p>0.3$) for males and females, respectively. Responding immediately after the tone was turned off and food was delivered was also comparable between the groups. The mean number of nose-pokes exhibited during the post-CS period was 1.8 ± 0.1 and 2.1 ± 0.1 ($p>0.4$) and the amount of time spent in the food cup during the post-CS period was 3.2 ± 0.2 sec and 3.4 ± 0.1 sec ($p>0.6$) for males and females, respectively.

Locomotor Activity—The distance traveled by male and female WKY rats in the open field was comparable, as illustrated in Figure 4. A repeated measures ANOVA revealed a main effect of Epoch [$F(14,308)=8.1$, $p<0.0001$] indicating that locomotor activity habituated over the course of the 15 min test session. There was no main effect of Group [$F(1,22)=0.5$, $p>0.5$] and no significant Group $\times$ Epoch interaction [$F(14,308)=1.4$, $p>0.1$].

Comparisons between SHR and WKY Rats—Although the SHR and WKY rats were tested in separate experiments, we conducted a post-hoc analysis to compare the performance of males and females in each strain in the conditioned inhibition task. Analyses were carried out on the average amount of time spent in the food cup during presentation of the tone on each trial type. A repeated measures ANOVA revealed a main effect of Strain [$F(1,44)=13.7$, $p<0.001$], indicating that WKY rats exhibited more conditioned responding overall compared to SHR rats. The Strain by Sex interaction was also significant [$F(1,44)=5$, $p<0.03$], reflecting a significant difference between female SHR and female WKY rats ($p<0.001$).

General Discussion

The present study examined the ability of male and female SHR and WKY rats to learn and perform a conditional discrimination. The serial feature negative discrimination task used in this experiment is well established in the learning theory literature and has been used previously to examine the involvement of different brain regions in inhibitory behaviour [5,10]. During presentations of the tone alone, rats learned to approach the food cup in anticipation of receiving food reward. When the tone was preceded by presentation of the light (stop signal), rats learned that no food would be delivered and refrained from approaching the food cup. In Experiment 1, female SHR rats exhibited less conditioned responding than male rats on both types of trials.

In addition, male SHR rats learned the discrimination in fewer training sessions than SHR females. This sex difference was not observed in WKY rats in Experiment 2. In fact, there was some evidence of the opposite pattern of effects (i.e., females outperforming males). Taken together, the results of these experiments suggest that male and female SHR rats differ in their ability to form conditioned associations and learn a conditional discrimination. Moreover, this female disadvantage in conditioned inhibition is not present in normo-active control strains. Lastly, post-hoc comparisons between the two experiments indicated that SHR rats exhibit impaired performance on the conditioned inhibition task compared to WKY rats.

Unlike most studies involving appetitive conditioning procedures, we chose to analyze two different measures of conditioned responding: time in food cup and number of nose-pokes into the food cup. The pattern of responding is usually similar in most rat strains, and indeed, most studies typically measure just one or the other. However, given the hyperactive phenotype of SHR rats, it seemed possible that the two measures could result in different patterns of behaviour. For example, SHR rats might exhibit abnormally high rates of nose-poke behaviour that could lower the accumulated amount of time spent in the food cup. The results of Experiment 1 indicate that this was not the case, as the analysis of both measures of conditioned responding in SHR rats produced similar results. The complementary findings with both measures of responding add strength to the observed differences in male and female SHR rats in this study. Moreover, these data are consistent with our previous studies with Long-Evans rats using the same serial feature negative discrimination task [13]. Interestingly, the two measures did not yield similar results with WKY rats in Experiment 2. Although the time-in-food-cup measure indicated that males and females learned the discrimination, analysis of the nose-poke data did not. WKY rats are the most commonly used comparison strain for SHR rats, and these data suggest that caution needs to be exercised in choosing between different measures of responding. Indeed, if only nose-poke data were analyzed in the present study, the results would indicate that SHR rats but not WKY rats were able to learn the conditional discrimination.

The present study is the only one thus far to examine sex differences in inhibitory-related behaviour in SHR rats; only two other published studies have examined sex differences in behaviour in SHR rats. Using an operant discrimination task, Sagvolden and Berger reported that male SHR rats exhibited shorter delay-of-reinforcement gradients while female SHR rats exhibited deficits more consistent with inattention [4,21]. Consistent with the current findings, female SHR rats exhibited deficits in the ability to discriminate, leading to fewer reinforcers being obtained by females compared to males [21]. The present findings provide additional insight into the differences between male and female SHR rats indicating that females may be less able to form conditional associations. This has been observed previously in another study involving simple conditioning to a visual stimulus [17]. Together, these findings provide new insight into the potential use of SHR rats to model sex differences in ADHD in humans.

Although some studies have investigated sex differences in the cognitive and motor symptoms in persons with ADHD, there has not yet been a definitive characterization published in the literature or a consensus as to the nature of the differences in deficits between boys and girls. One study revealed that girls diagnosed with ADHD exhibited deficits in inhibition whereas boys were unimpaired [16], consistent with the sex differences in conditioned inhibition in SHR rats observed in the present study. Moreover, the task used in our study shares many procedural similarities with go/no-go tasks that are commonly used to assess inhibition in persons with ADHD [26]. However, additional studies in both humans and rat models of ADHD need to be carried out to fully address the utility of the SHR strain to model sex differences in ADHD. Indeed, the importance of establishing a useful laboratory animal model is supported by evidence of sex differences in the underlying biological factors contributing to ADHD [7,19].

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Figure 1A

Figure 1B

Figure 1.

Mean number of food cup entries (A) and time spent in the food cup (B) exhibited by male and female SHR rats during presentation of the tone on each trial type across training days in Experiment 1. Data are means $\pm$ SEM (R=reinforced trials, NR=non-reinforced trials).

Figure 2.

Locomotor activity exhibited by male and female SHR rats during a 15-min exploration of an open field. Data are mean $\pm$ SEM.

Figure 3A

Figure 3B

Figure 3.

Mean number of food cup entries (A) and time spent in the food cup (B) exhibited male and female WKY rats during presentation of the tone on each trial type across training days in Experiment 2. Data are means $\pm$ SEM (R=reinforced trials, NR=non-reinforced trials).

Figure 4. Locomotor activity exhibited by male and female WKY rats during a 15-min exploration of an open field. Data are mean $\pm$ SEM.