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Research report

Response acquisition with delayed reinforcement in a rodent model of attention-deficit/hyperactivity disorder (ADHD)

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Abstract

The spontaneously hypertensive rat (SHR) has been shown to exhibit behavioral characteristics analogous to those exhibited by humans diagnosed with attention-deficit/hyperactivity disorder (ADHD). The present study was conducted to further evaluate the validity of the SHR model of ADHD by characterizing learning of a novel response under conditions of delayed reinforcement. Seven experimentally naïve SHRs and a control group of seven normotensive Wistar-Kyoto (WKY) rats were exposed to a contingency where one lever press initiated pellet delivery after a 15-s, resetting delay. Rats in both groups acquired lever pressing, and the pattern of acquisition was well described with a three-parameter, sigmoidal equation. Response acquisition was retarded in the SHRs; they took longer to acquire the behavior, exhibited lower response rates and earned fewer reinforcers over the course of the experiment. When reinforcer delivery was made immediate in a subsequent condition, the SHRs exhibited higher response rates than the WKY, suggesting that the lower rates of responding seen in the SHRs were due to the reinforcer delay. The results replicate previous research on response acquisition with delayed reinforcement and provide further validation of the SHR strain as a model of ADHD. Like humans diagnosed with ADHD, the SHRs appear to be hypersensitive to delayed consequences, which in the present context, interfered with learning a novel behavior.

Keywords: Response acquisition; Delayed reinforcement; Spontaneously hypertensive rat; SHR; ADHD; Animal model

1. Introduction

Worldwide, approximately 8% of school-aged children have been diagnosed with ADHD, making it one of the most prevalent childhood disorders [1]. A diagnosis of ADHD is based on behavioral criteria, such as hyperactivity, inattention, impulsivity and learning deficits [1,5]. Research has further shown that children diagnosed with ADHD are more likely to become frustrated when reinforcers are delayed and prefer smaller, more immediate reinforcers over larger, delayed reinforcers, thereby obtaining overall fewer reinforcers [24].

The spontaneously hypertensive rat (SHR) has been proposed as a rodent model of human ADHD presumably because several behavioral characteristics of the rats appear analogous to the behavioral characteristics seen with human ADHD [19,20]. These behavioral characteristics include hyperactivity [12,19], inattention [21], resistance to extinction [10] and hypersensitivity to reinforcer delay [11]. Similarities have also been reported in the time course of the expression of behavior in the SHR. For example, Knardahl and Sagvolden [12] showed that the hyperactivity exhibited by the SHR is not present initially; it instead develops over time and after exposure to the same environment, a finding that is consistent with childhood ADHD.

Related to the hypersensitivity of reinforcer delays, Johansen et al. [11] compared the effects of response-reinforcer delays to water reinforcement on response rates between SHRs and rats belonging to the normotensive parent strain, Wistar-Kyoto (WKY). Rats from both groups were exposed to a schedule that required interresponse times (IRTs) of less than 1 s for reinforcement. This differential-reinforcement-of-high-rate schedule was employed to minimize differences in IRTs between the two strains, as the SHRs had exhibited shorter IRTs in the initial experiment of the study. Resetting response-reinforcer delays of 0, 0.5, 1, 2, 4, 8, 12 and 16 s were imposed across conditions

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(in that order), and each condition was in effect for 14–21 sessions. Typically under such manipulations, response rates are a decreasing, negatively accelerating function of delay [18]; the steepness of this function can be used to index reinforcer delay sensitivity (the steeper the function, the greater the sensitivity). Under the DRH condition, the SHRs had significantly higher response rates at the 0-s delay and, more importantly, had significantly steeper delay-of-reinforcement gradients. Thus, the SHR strain was shown to be more sensitive to response-reinforcer delays under steady-state conditions. A logical step forward in this line of research would be to determine if response-reinforcer delays retard the acquisition of a novel behavior by SHRs.

Lattal and Gleeson [14] reported a series of experiments on rats and pigeons that demonstrated acquisition of a novel response under *resetting* and *nonresetting* delays of reinforcement. In the *nonresetting* delay procedure (technically a tandem fixed-ratio [FR] 1, fixed-time [FT] 30-s schedule of reinforcement), a single lever press initiated a 30-s, unsignaled delay after which a reinforcer was delivered. Responses occurring during the delay had no programmed effect but resulted in shorter delays. Consequently, the delay was not precisely controlled, and subjects experienced variable response-reinforcer delays. In the *resetting* delay procedure (technically a tandem FR 1, differential-reinforcement-of-other-behavior [DRO] 30-s schedule), a single lever press also initiated a 30-s, unsignaled delay, however responses occurring during the delay reset the interval. Thus, each subject always experienced the same 30-s response-reinforcer delay. Using these procedures, Lattal and Gleeson [14] showed that experimentally naïve rats and pigeons acquired a novel response (i.e., pressing levers and pecking translucent discs) when reinforcers were delayed up to 30 s. Subsequent research has validated this procedure and replicated the main finding [4,15,16], however a systematic comparison between various rodent genetic strains is lacking.

The purpose of the present study was to examine how delayed reinforcement affects the acquisition of lever pressing in the SHR strain compared to its normotensive parent strain, WKY. Given the finding that the SHRs have steeper delay-of-reinforcement gradients [11], it is expected that the acquisition of lever pressing in SHRs will be retarded relative to the WKY rats. That is, the SHRs should take longer to learn a novel behavior, exhibit lower response rates and earn fewer reinforcers than the WKY rats. Such an investigation has the potential to: (1) extend the generality of response acquisition of delayed reinforcement to different strains of rats, (2) provide an approach that emphasizes acquisition rather than steady-state performances that could be useful in evaluating other animal models and (3) further validate the SHR model of ADHD.

2. Method

2.1. Subjects

Fourteen (seven WKY and seven SHR), experimentally naïve rats purchased from Charles River Laboratories (Wilmington, MA) served as subjects. The rats were five weeks old at the time of delivery. They were housed individually in wire cages with free access to food and water. Their weights stabilized after approximately seven weeks, at which time they were reduced to 85% of their free-feeding weights. Post-session feedings were provided to maintain their 85% weight throughout the experiment. Rats were 14 weeks old at the beginning of the study. The lights in the colony room were programmed according to a 12-h reverse day:night cycle (on at 8:00 p.m.).

2.2. Apparatus

All sessions were completed in four equally equipped Med-Associates (Med-Associates, Georgia, VT) operant chambers which were enclosed in sound-attenuating boxes with exhaust fans that provided masking noise. The chambers measured 27 cm wide × 22 cm deep × 20 cm high and had side walls and ceilings of Plexiglas, front and rear walls of aluminum, and floors constructed from stainless steel rods. The front panel of each chamber was equipped with two levers, each 4.5 cm wide, 7.5 cm above the floor, and 8 cm from the midline of the panel on center. Levers required a force of 25 g to register a response. Above each lever was a 28-V dc light bulb recessed behind a translucent plastic cover. Located between the two levers was a recessed pellet tray measuring 5 cm wide, 4 cm tall, and 3 cm above the floor into which 45-mg Bio-Serv® Dustless Precision Pellets (Product #F0021) were delivered. A 28-V dc house light located 20 cm above the floor on the rear panel provided general illumination. An IBM®-compatible computer running Microsoft Windows XP® and Med-PC IV® software provided environmental control and recorded data.

2.3. Procedure

2.3.1. Magazine training

Before the experiment proper began all rats were exposed to two sessions of magazine training over two days. During these 30-m magazine training sessions, the levers were removed, the lever stimulus lights were off, and the house light was illuminated. Thirty pellets were delivered according to a variable-time (VT) 60-s schedule; the values of the VT were generated using a constant probability algorithm [2]. The removal of levers during magazine training has been shown to decrease the latency to an initial response when the lever is returned to the chamber [9].

2.3.2. Experimental procedure

Each of the 30 experimental sessions lasted 30 min and began with a 30-s acclimation period with the chamber darkened, after which both the house light and the stimulus light over the left lever were illuminated. From this point, pressing the left lever was reinforced according to a tandem FR 1, DRO 15-s schedule. In other words, one lever press initiated a 15-s unsignaled, resetting delay after which a food pellet was delivered. Responses during the delay interval reset it such that each delivery of food was always delayed by exactly 15 s from a response. Right lever presses were recorded but had no programmed consequences. The presence of an inoperative lever is often used as a control procedure to better assess the effects of the contingency [25]; it essentially makes this task a simultaneous discrimination

procedure in which the left lever is associated with food and the right lever is not. After 30 sessions, all rats were exposed to an FR 1 schedule of reinforcement for two sessions to assess response rates in the presence of immediate reinforcement.

3. Results

3.1. Response rates

Fig. 1 shows average response rates for each group across the 30 sessions. The SHR responded at a lower rate than the WKY starting with the third session and continuing throughout the experiment. A mixed-model ANOVA conducted on the response rate data revealed a main effect of strain that approached significance [$F(1, 12) = 3.57$, $p = .08$] and a significant main effect of session [$F(29, 348) = 5.73$, $p > .001$]. The session by strain interaction was also significant [$F(29, 348) = 1.58$, $p = .03$], indicating that the course of acquisition was different depending on strain. Analysis of simple main effects revealed that the effect of session was significant for both SHR [$F(29, 174) = 6.00$, $p < .001$] and WKY [$F(29, 174) = 3.12$, $p < .001$], indicating that both strains showed significant changes in response rate across sessions.

The first FR 1 session of immediate reinforcement was excluded from analysis as the response rates were still in transition. Under the second session of FR 1, the average response rates of the SHR rats were slightly higher than the WKY rats; .29 and .25 responses/min, respectively. A one-way ANOVA showed that this difference was significant [$F(1, 13) = 7.80$, $p = .02$].

3.1.1. Quantitative modeling of response rates

In order to facilitate group comparison, a model of response acquisition was developed (see Eq. (1)). In modeling acquisition, four parameters are needed; operant level before conditioning (O_L), asymptotic response rate after learning (O_{max}), the rate of acquisition (λ) and the number of sessions to reach half of the asymptotic rate (k):

$$B = O_L + \frac{O_{max} - O_L}{1^{k-x/h}} \quad (1)$$

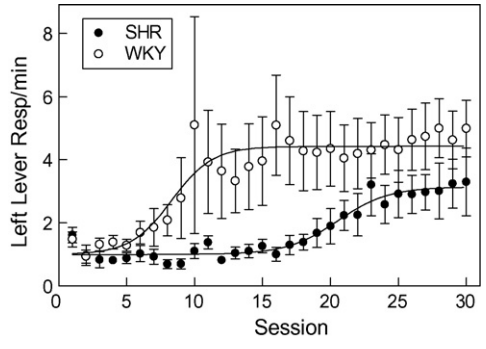

Fig. 1. Average responses per minute are shown by group with error bars representing the standard error of the mean. The lines of fit are from Eq. (2), parameters are presented in Table 1.

Table 1
Parameter estimates by group

Parameter	WKY	SHR
O_{max}	4.4 (0.12)	3.1 (0.11)
k	8.3 (0.44)	21 (0.41)
λ	1.4 (0.38)	1.9 (0.34)
R^2	.88	.96

Eq. (1) describes B (responses/min) as a sigmoidal function of number of sessions. Since the operant level (from the second session) was close to 1 response/min for both groups (SHR = .97; WKY = .94), O_L was set to 1, thus reducing Eq. (1) to the three-parameter equation:

$$B = 1 + \frac{O_{max} - 1}{1^{k-x/\lambda}} \quad (2)$$

Eq. (2) was used to describe the data in Fig. 1 (see Table 1 for the parameter estimates). Eq. (2) accounted for 88 and 96% of the variance in response rate, for the SHR and WKY rats, respectively (while Eq. (2) well described the averaged response rate data, it was inadequate describing acquisition at the individual subject level). The parameter estimates of k indicated that it took 8.3 sessions for WKY and 21 sessions for SHR to reach half of their asymptotic level. The parameter estimates of λ suggest that the rate of acquisition was faster for the WKY rats. Finally, the parameter estimates of O_{max} confirmed the statistical analysis; response rates of the SHRs reached a lower asymptotic level than the WKY rats.

3.2. Reinforcers

Fig. 2 shows the average number of food pellets earned per session by rats in each strain over the course of the 30 sessions. While rats in both strains showed increasing trends across sessions, the SHR earned fewer pellets than the WKY in every session. A mixed-model ANOVA confirmed the main effects of strain [$F(1, 12) = 7.18$, $p = .02$] and session [$F(29, 348) = 22.91$, $p < .001$]. The interaction was not significant [$F(29, 348) = 1.39$, $p = .09$]. It is important to note that even as response rates remained fairly constant for the WKY from sessions 16 to 30 (see Fig. 1), the average number of reinforcers earned over the same time period increased from 45.3 per session to 58.3 per

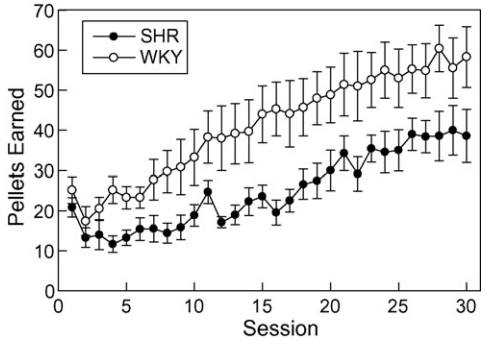

Fig. 2. The average numbers of food pellets earned in each session are shown by group with error bars representing the standard error of the mean.

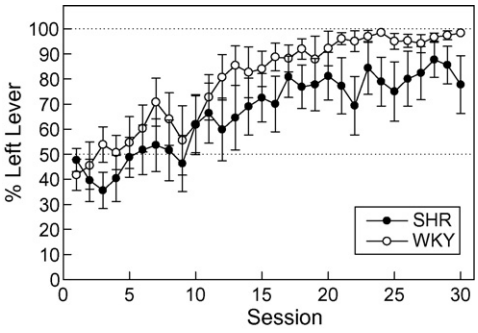

Fig. 3. The average percentages of left lever responses are shown by group with error bars representing the standard error of the mean. Dashed lines indicate no discrimination (50% of responses occurred on each lever) and maximum discrimination (100% of responses occurred on left lever).

session. This suggests that the number of responses emitted by the WKY during the DRO decreased across the final 15 sessions. The same cannot be said for the SHR, however. While the average response rate for the SHR approximately tripled over the final 15 sessions, the average number of pellets earned only doubled. This indicates that the increase in response rate for the SHR was also accompanied by an increase in responding during the DRO period. In sum, the WKY showed increasing efficiency over the final 15 sessions whereas the SHR did not.

3.3. Response allocation

Fig. 3 depicts the mean percentage of responses on the left (i.e., active) lever across sessions. These percentages were calculated by dividing the total number of responses on the left lever by the total combined left and right lever presses. This measure provides a way to assess the effects of the contingency; a value of 50% would indicate an absence of a simultaneous discrimination between the operative and inoperative levers. Both SHR and WKY showed increasing trends across sessions with the SHR emitting a lower percentage of responses on the active lever than the WKY over each of the last twenty sessions. A mixed-model ANOVA confirmed the main effect of session [$F(29, 348) = 10.36, p < .001$]. However, neither the main effect of strain [$F(1, 12) = 2.94, p = .11$], nor the interaction term [$F(29, 348) = .43$, $p = 1.00$] were statistically significant. One sample t-tests were conducted on the final session for each strain to determine if each of the strains were significantly different from chance allocation using 50% as the test value. The SHR did not respond significantly more than 50% on the active lever [$\bar{X} = 77.71$, $t(6) = 2.41$, $p = .052$] while the WKY did [$\bar{X} = 98.20$, $t(6) = 41.87$, $p = .001$].

4. Discussion

4.1. General discussion

This study examined differences in response acquisition under conditions of delayed reinforcement between spontaneously hypertensive rats and rats from their normotensive, Wistar-Kyoto parent strain. The SHRs have been proposed as a putative rodent model of attention-deficit/hyperactivity disorder, and it was therefore hypothesized that they would show learning deficits relative to the WKYs. While both groups of rats acquired lever pressing, the SHRs took longer to acquire the response, had a slightly lower rate of acquisition and reached a lower asymptotic response rate than the WKYs. Consequently, the SHRs earned significantly fewer reinforcers. The SHRs also caused more delay resets (calculated by subtracting the number of reinforcers earned from the total number of presses on the active lever) and emitted more responses on the inactive lever.

The fact that the SHRs emitted more responses on the inactive lever was an unexpected finding, and there are at least three interpretations of this result. First, previous research has shown that the SHR strain is hyperactive and tends to show greater levels of response variability [12]. It could be argued that the persistence of inactive lever responding by the SHRs in the present study is simply another example of this variability/hyperactivity. Second, if the SHRs are truly hypersensitive to reinforcer delay, it follows logically that they might also be more susceptible to adventitious reinforcement and the development and persistence of superstitious behavior [22]. In other words, responses on the inactive lever, if followed closely in time by food, would be reinforced to a greater extent in the SHRs. Third, the greater amount of responding on the inoperative lever by the SHRs may instead reflect a failure in discrimination between the operative and inoperative levers. This interpretation would imply that delayed reinforcement differentially impairs the acquisition of discriminative stimulus control in the SHR relative to the WKY rats. Future research will have to explore the viability of these alternative explanations, which incidentally are not necessarily competing.

The results of the present study, which show acquisition of lever pressing by both SHRs and WKYs under a 15-s, resetting delay of reinforcement, replicate the general findings of Lattal and Gleeson [14], which showed that behavior can be acquired, in the absence of shaping, even when reinforcers were delayed up to 30 s. The results of the current study also extend the previous research on response acquisition of delayed reinforcement to two more strains of rat, further establishing the robust nature of the effect.

Lattal and Gleeson [14] employed both resetting and nonresetting delays. A resetting delay procedure was used in the current study because it allows precise experimenter control over the delay and also ensures that each rat experiences the same delay. When comparing response acquisition between groups, it is important to control and equate delays between the groups to ensure that between-group differences in acquisition are a function of the delay and not some other variable such as response rate. To illustrate the problem with nonresetting delays, imagine a scenario where one group had higher baseline response rates. Higher response rates in this group could result in shorter obtained response-reinforcer delays (remember responses can occur during the delay in nonresetting procedures) and consequently could result in a shallower delay-of-reinforcement gradient. Such a finding would be misinterpreted if the differences in the obtained gradients were inferred to reflect group differences in reinforcer delay sensitivity.

4.2. SHR delay hypersensitivity

Previous studies have reported that ADHD-diagnosed humans are hypersensitive to delayed reinforcers. Specifically, children with ADHD will become frustrated when reinforcers are delayed and prefer smaller, more immediate reinforcers over larger delayed ones [23,24]. This preference for smaller, more immediate reinforcers translates to a steeper delay-of-reinforcement gradient. In other words, as the response-reinforcer delay increases, the number of times an ADHD-diagnosed human makes that response decreases at a rate greater than would be found in a non-ADHD-diagnosed human. Steeper delay-of-reinforcement gradients have also been found in the SHRs [11], which suggested that this strain would also show deficits in the acquisition of lever pressing under a 15-s delayed reinforcement contingency relative to a non-SHR strain of rat. These deficits would expected to be manifest in longer time to acquisition, slower rate of acquisition, lower asymptotic response rates and fewer earned reinforcers. These predictions were all confirmed in the present study.

Based on the SHRs' hyperactivity and hypersensitivity to delay it would be expected that they would respond at a higher rate than the WKYs when reinforcers were delivered immediately following a response. Although the difference was small, the SHRs responded at a significantly higher rate than the WKYs under the FR 1 schedule of immediate reinforcement. This result bolsters the delay hypersensitivity account of the SHRs because it suggests that the deficits in response acquisition seen in the SHRs were due to the response-reinforcer delay and not because of a general lower level of lever pressing by the SHRs.

4.3. Model discussion

The course of acquisition for both the SHRs and WKYs was well described by a three-parameter sigmoidal equation (see Table 1). A key advantage of this model (Eq. (2)) is that it provides an index of performance that allows one to readily quantify several important characteristics of response acquisition such as the asymptotic maximum response rate, the number of sessions completed before reaching half of the maximum response rate and the slope, which can be interpreted as the rate of acquisition. The parameter estimates of the model characterized the deficits seen in the SHRs and provided precise quantitative measures of the delayed onset of responding, the reduced rate of acquisition and the lower asymptotic response rate.

It has been argued that response acquisition at the level of the individual is less smooth and uniform, and that the averaged curve is an artifact [7,8]. Furthermore, Estes and Maddox [7] demonstrated that averaging a group of individual data sets increases R^2 while possibly reducing the ability to make predictions at the individual subject level. While Eq. (2) was used to fit averaged data, and indeed those curves were smoother at the group level, the individual acquisition curves were in general agreement with the averaged data. It is also important to note that the model was used only in a descriptive sense and not for the purpose of confirming specific hypotheses about the learning of individual WKYs or SHRs.

4.4. Limitations

Maintaining a constant response-reinforcer delay is important when studying response acquisition with delayed reinforcement (see comments above) which is why a resetting delay procedure was employed in the present study. However, a DRO schedule, which is inherent to the resetting delay procedure, can also actively suppress responding because it is a negative punishment contingency; responses during the DRO period extend the time-out from reinforcer delivery. Thus, the differences between SHRs and WKYs in response acquisition could have reflected differential sensitivities to the response-suppressing aspects of the DRO in addition to the response-reinforcer delay. This alternative interpretation cannot be ruled out by the present experiment and will have to be explored in subsequent research. The preferred interpretation, i.e., that the present results reflect an SHR hypersensitivity to reinforcer delay, is consistent with previous research that has reached similar conclusions.

An alternative method for programming a constant response-reinforcer delay would be to utilize a nonresetting (i.e., FT) procedure and retract the lever during the delay, which would preclude responding during the delay. This method, however, introduces a signal (the absent lever) that could further complicate interpretation because signaled delays of reinforcement have been shown to decrease the steepness of delay-of-reinforcement gradients presumably because of their conditioned reinforcing function [18]. We opted for the unsignaled, resetting delay procedure in the present study in order to minimize the complexity associated with the addition of delay signal functions.

4.5. Dopamine dysfunctions

The results of the current study are consistent with the hypotheses made based on the SHRs being a model of human ADHD. These results add to the literature validating the behavioral characteristics of the SHR strain as being consistent with human ADHD. The current study highlights behavioral differences between the SHR and WKY strains. Further research is needed to elucidate the structural and functional differences that may exist in the central nervous system of SHRs. Interestingly, common abnormalities in dopamine transporter proteins have been found in both ADHD-diagnosed humans [3] and the SHR strain of rat [17]. It has been argued that altered dopamine function in the meso-limbo-cortical area may account for the hyperactivity, impulsivity, and behavioral variability that characterize ADHD [10]. The Dat1 gene is active in sequencing dopamine transporter proteins, so it has been suggested that these differences in the dopamine transporter protein may be a player in the behavioral differences found between the SHR and WKY strains [17]. Other dopamine system abnormalities have been found in humans diagnosed with ADHD, such as malformed D4 dopamine receptors [13] and variations in DOPA decarboxylase activity [6]. The continued integration at the behavioral and physiological levels is necessary for further validation of the SHR model of ADHD. This will hopefully lead to a better understanding of the underlying behavioral and neurophysiological mechanisms underlying this disorder.

5. Conclusions

The results of the present study build upon the existing literature by showing that spontaneously hypertensive rats are hypersensitive to delayed reinforcers in a learning paradigm and further validate the SHR model of ADHD. When exposed to a resetting delay of reinforcement, experimentally naïve SHRs displayed deficits in the acquisition of a novel behavior. The deficits were characterized by longer latencies to acquisition of the target response, lower asymptotic rates of responding and fewer earned reinforcers. By establishing the usefulness of the response acquisition procedure and the quantitative model, further studies may be conducted to examine the effects of environmental and pharmacological manipulations on the pattern of learning in this and in other animal models.

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