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Research report

Evaluation of the spontaneously hypertensive rat as a model of attention deficit hyperactivity disorder: acquisition and performance of the DRL-60s test

Eleanor Bull [a], Charlie Reavill [a], Jim J. Hagan [a], Philip Overend [b], Declan N.C. Jones [a,*]

[a] *Neuroscience Research, SmithKline Beecham Pharmaceuticals plc, New Frontiers Science Park, Third Ave., Harlow, Essex, CM19 5AW, UK*
[b] *Statistical Sciences, SmithKline Beecham Pharmaceuticals plc, New Frontiers Science Park, Third Ave., Harlow, Essex, CM19 5AW, UK*

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Abstract

The spontaneously hypertensive rat (SHR) has been proposed as an animal model of attention deficit hyperactivity disorder (ADHD). It is hyperactive in a variety of behavioural paradigms and has a sustained attention deficit. This study investigated whether the SHR would exhibit impaired acquisition and performance of a differential low rate (DRL) schedule of reinforcement because of increased impulsivity, compared with the Wistar–Kyoto (WKY) rat, its normotensive progenitor. In addition, the performance of both strains was compared with Sprague–Dawley (CD) rats. SHR rats were not impaired in the acquisition of this test compared with WKY or CD rats. Indeed, WKY rats took significantly longer to acquire this task than either SHR or CD rats. The WKY rats performed poorly compared with the other strains in those parts of training that required high response rates (e.g. FR-1), but better where low rates of responding were required (e.g. DRL-30s and DRL-60s). The rank order of efficiency when performance was measured under DRL-60s was WKY > SHR > CD. However, the pattern of responding at DRL-60s suggested poor schedule control for the WKY rats. Therefore, the performance of SHR in the DRL test does not appear to represent a valid model of ADHD. Further, our findings with the WKY rat suggest that this strain is a poor behavioural control for the SHR.

Keywords: Attention deficit hyperactivity disorder; Spontaneously hypertensive rat; Wistar–Kyoto; Sprague–Dawley; Differential reinforcement of low rates of responding; Impulsivity

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a condition characterised by inattention, impulsivity, hyperkinesis, a marked difficulty in following instructions and sustaining attention in tasks or play activities [1,23]. ADHD is most common among children, but it has a strong tendency to progress into adulthood [29]. The disorder occurs more frequently in males than females, with male-to-female ratios ranging from 4:1 to 9:1 depending on the setting [1]. ADHD children are easily distracted from long term goal directed tasks by more immediate, although smaller, rewards which is suggestive of differences in reinforcement processes [26]. Studies have shown that ADHD children will achieve reinforcement but require more trials to reach the same standard as normal controls [4,5].

At present, mild psychomotor stimulants are the most effective treatments, e.g. methylphenidate (Ritalin™), is successful in 70–80% of patients [6]. However, the use of methylphenidate is limited by its relatively short half-life and side effect profile, which include anorexia, insomnia, abdominal pain, tachycardia and headache [2]. Pemoline (Cylert™) is an alterna-

* Corresponding author. Tel.: +44-1279-622091; fax: +44-1279-622211.
E-mail address: declan_jones-1@sbphrd.com (D.N.C. Jones)

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tive to methylphenidate with less sympathomimetic effects. It has the advantage of a longer duration of action, but has a delayed onset and has been linked to hepatic dysfunction, which severely limits its use in patients with pre-existing liver damage [16]. Therefore, there is a clear unmet clinical need for improved ADHD treatment.

The spontaneously hypertensive rat (SHR) has been proposed as an animal model of ADHD [12,17,19–21,23]. The SHR strain was first established in 1963 from outbred Wistar–Kyoto (WKY) rats. Offspring were crossbred with continued selection for high blood pressure [14]. SHR rats exhibit hyperactivity and elevated exploration coupled with high blood pressure, compared to their normotensive progenitor, the WKY rat. SHRs show altered responding in a number of operant procedures suggestive of inattention/impulsivity. In a multiple 2-min fixed-interval 5-min extinction schedule of reinforcement, SHRs showed impulsivity (bursts of responses with short inter-response times) as exhibited by ADHD children [3]. SHRs showed impaired visual discrimination (chance levels) in a variable interval test when reinforcers were infrequent (VI-180s), but not when the rewards were frequent (VI-15s), while the performance of the WKY remained stable under both conditions [22]. The behavioural changes are thought to be related to altered brain reinforcement mechanisms, a suggestion supported by a reported decrease in dopamine (DA) activity in the frontal cortex of SHRs versus the WKY rats [13]. The DA hypofunction may result from impaired vesicular storage of DA compared to WKY rats [18]. Drug-naive SHR rats have a lower DA turnover ratio in the neostriatum and asymmetric DA turnover in the accumbens [3].

The differential reinforcement of low rates of responding (DRL) schedule requires a hungry rat to withold a lever pressing response for a pre-determined time to obtain a food reinforcement. This test provides a good measure of impulsivity [25]. An impulsive animal will tend to respond inappropriately early in the time interval and will consequently receive fewer reinforcements. The aim of this study was to investigate the acquisition and performance of three rat strains in the DRL schedule to compare the SHR rats with their normotensive progenitor, the WKY, and an additional control strain used previously in this laboratory in this procedure [7], Sprague–Dawley (CD). It was hypothesised that the acquisition and performance of SHRs would be impaired compared with the WKY and CD controls and may represent a model of ADHD to evaluate potential treatments for this disorder.

2. Material and methods

2.1. Subjects

Fifty-four male rats were used in total; 14 CD, 20 WKY and 20 SHR rats. All animals were supplied by Charles River (UK) and were within the weight range 190–250 g at the start of the experiment. Rats were housed in pairs under a 12:12 h light–dark cycle (06:00–18:00) and were food restricted (received a measure of standard laboratory chow at the end of each test day). Typically, each rat received at least 15 g of food per day. The food restriction schedule continued throughout the whole experiment. Water was freely available. Health was checked weekly by an experienced veterinary technician. The study was conducted in strict compliance with the United Kingdom Animals (Scientific Procedures) Act, 1986 and conformed to Smith-Kline Beecham ethical guidelines.

2.2. Apparatus

All training was carried out in one of 12 identical operant chambers contained within a sound attenuating box (Campden Instruments, Loughborough, UK). Each rat was assigned to a specific box for the duration of the training to ensure consistency of results. The operant chamber measured $21.5 \times 24.5 \times 24.5$ cm and was fitted with two retractable levers (4.0×1.5 cm) situated either side of a food magazine (5.0×6.0 cm) gated by a perspex flap. The levers were connected to a food dispenser containing pellets (Bioserv Dustless Precision Pellets [45 mg], Frenchtown, NJ) which provided the reinforcement. Pellets were dispensed into the food magazine and the rat was required to nose poke the perspex flap in order to obtain the pellet. A houselight was on at all times throughout the experiment and a second light illuminated the food magazine when in use. Two additional lights were positioned above each of the levers and illuminated the lever when extended. The box was ventilated by a fan which gave a constant level of background noise. Boxes were controlled and data collected via the Kestrel software package (Dave Fuller, Conclusive Marketing Ltd, Harlow, Essex).

2.3. Training procedure

2.3.1. Habituation and magazine training

Rats were habituated to their assigned operant box over two 30 min sessions, during which food was freely available from the magazine. In a further two sessions, both the house and magazine lights were switched on and a pellet was dispensed every 30 s, to allow association of the magazine with a food reinforcement.

2.3.2. Lever response training

Following habituation and magazine training rats progressed to a fixed ratio (FR-1) schedule of 30 min duration. The left hand lever was extended and illuminated and a pellet was dispensed for every lever response. The number of pellets earned was recorded. Rats commenced DRL training when they reached 80 responses on two consecutive sessions.

2.3.3. DRL training

The DRL schedule was introduced following completion of lever training. All sessions lasted 1 h and rats were tested up to five times a week. The left hand lever was extended and the first lever press of the session was reinforced and initiated a pre-determined inter-response time (see Table 1). If the rat pressed the lever prior to the elapse of the inter-reponse time, the clock was reset to zero. The first lever press made after successfully waiting for the inter-response time to elapse resulted in a food reinforcement. All rats began on DRL-2s and the criterion for progression to the next DRL period is shown in Table 1. Rats were maintained under DRL-60s for at least 4 to 5 sessions. Total time for the completion of training for all strains exceeded 4 months.

2.3.4. Data analysis

The total number of sessions to complete training up to DRL-60s and the total sessions to criterion at each training stage were recorded. Upon reaching DRL-60s, the mean number of pellets earned and total number of responses was recorded for each rat. % Efficiency was calculated as (Pellets earned/total responses)*100. The magazine latency, inter-response time and the modal inter-response time were recorded for each rat at the timepoint immediately after achievement of the DRL-60s criterion. Data were analysed by analysis of variance (ANOVA) with post hoc analysis where appropriate. A 5% level of significance was used. Data were log10 transformed to maintain homogeneity of variance when necessary. The pattern of responding across the test period was analysed in a number of ways following calculation as a percentage of total responses; 'Burst Responding' (i.e. responses made in the 0–5 s period immediately after receiving a reinforcement) was analysed using one way ANOVA. Post-burst responding (from 5 to 140 + s) was split into two time intervals (5 to 60 s and >60 s) and the timepoints analysed together using split plot ANOVA following log transformation. Pairwise comparisons between groups were made using Scheffe's test.

Table 1
Criteria for training progression in the DRL task

Conditions	Criterion for progression
DRL-2s	>50 pellets, one session
DRL-5s	>50 pellets, two consecutive sessions
DRL-10s	>40 pellets, two consecutive sessions
DRL-20s	>40 pellets, two consecutive sessions
DRL-30s	>30 pellets, two consecutive sessions
DRL-60s	>20 pellets, two consecutive sessions

3. Results

Out of the 54 rats, 52 successfully completed training. The WKY and SHR groups each contained 19 animals and the CD group contained 14 animals.

3.1. Effects of strain upon body weight

Strain differences in body weight were significant ($F[2,48] = 46.43$, $P < 0.0001$). Further analysis indicated a significant strain versus time interaction ($F[30,48] = 22.4$, $P < 0.0001$). The CD rats tended to be the heaviest throughout the experiment. The weights of WKY and SHR rats were comparable, although the SHR were significantly lighter in the later stages of the experiment (Fig. 1A). Fig. 1B shows the strain body weight at the start of each training stage. There was a significant strain versus training stage interaction ($F[12,294] = 24.35$, $P < 0.0001$). CD and WKY rats were heavier at all stages of training from DRL-2s onwards compared with the SHRs. At DRL-30s and DRL-60s, the weights of the WKY rats were elevated compared with the CD rats, which can be attributed to greater time required by the WKY rats to reach these training stages.

3.2. Effects of strain upon the total sessions to complete training

Strains differed significantly in the number of sessions required to complete training to DRL-60s ($F[2,49] = 44.36$, $P < 0.00001$, Fig. 2). The WKY rats required significantly more training sessions; post hoc analysis (Tukey's t-test) showed a clear difference between WKY and CD ($P < 0.05$) and WKY and SHR ($P < 0.05$) rats. There was no difference between CD and SHR strains. General observations of the three rat strains throughout the study highlighted marked differences in behaviour. The SHRs were more active and tended to move round the operant box. In contrast, the WKY rats were far less active than both SHR and CD rats and tended to spend long periods immobile.

3.3. Effects of strain upon DRL training at each stage

Strains differed significantly in the number of sessions required to reach criterion for each DRL level ($F[2,49] = 35.73$, $P < 0.0001$). Fig. 3 shows a break-

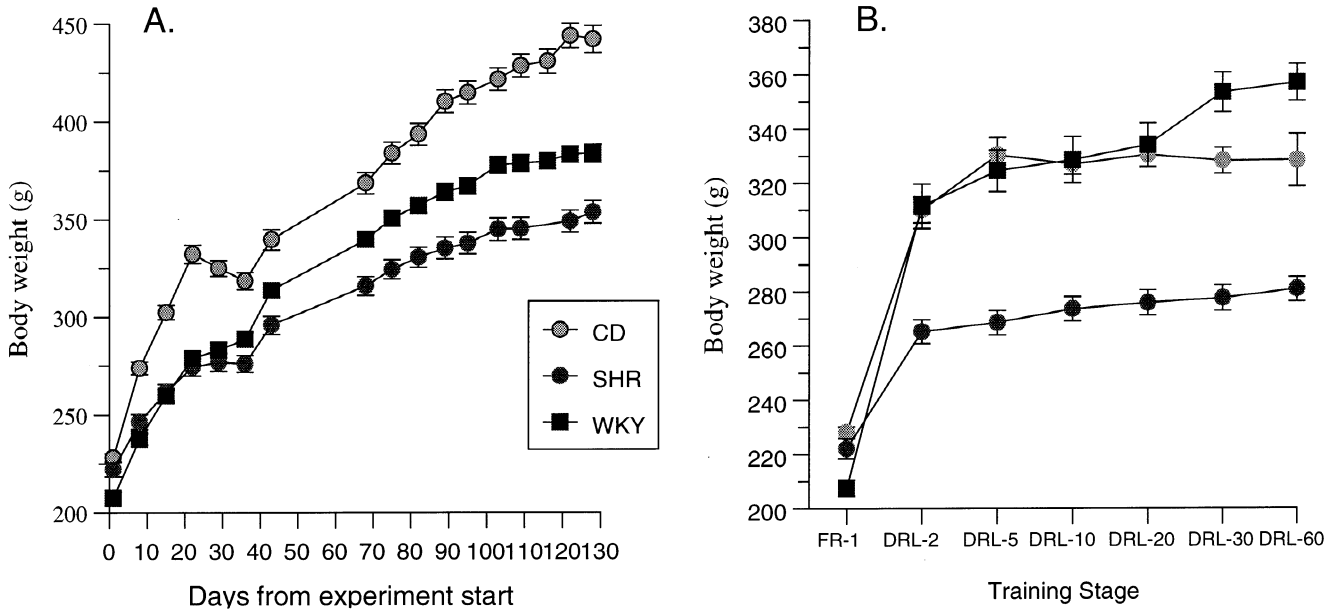

Fig. 1. Body weight change (g) over the course of the experiment (A) and at the start of each training stage (B). Rats ($n = 14–19$) were weighed weekly.

down of each stage of the training. There was a significant interaction between strain and DRL training stage ($F[12,294] = 20.4$, $P < 0.00001$). Post hoc analysis showed that WKYs required significantly ($P < 0.05$) more sessions than the SHR and CD rats at each training stage except DRL-2s and DRL-30s (except CD). In contrast, WKY rats required fewer session to reach criterion at DRL-60s than SHR and CD rats. There were no differences between CD and SHR rats, except at DRL-30s.

3.4. Effects of strain upon performance under DRL-60s

Once the rats had reached the criterion for DRL-60s of 20 pellets on two consecutive sessions, they were maintained at this level for a further four or five sessions in order to assess their performance (pellets earned, total responses and % efficiency). Fig. 4 shows performance under DRL-60s. There was a significant strain effect on the number of pellets earned ($F[2,49] = 32.84$, $P < 0.00001$, Fig. 4A), with WKY rats earning significantly more pellets than both SHR and CD ($P < 0.05$). Further, SHRs earned significantly more pellets than CDs ($P < 0.05$). There was a significant strain effect on total responses made within a session ($F[2,49] = 43.5$, $P < 0.00001$, Fig. 4B). The total number of responses made by WKY rats was significantly lower than those made by both SHR and CD rats ($P < 0.05$), while SHRs made fewer responses than CDs ($P < 0.05$). Consequently, % efficiency followed the same pattern ($F[2,49] = 86.90$, $P < 0.00001$, Fig. 4C). WKYs were more efficient than SHRs and CDs ($P < 0.05$) and SHRs more efficient than CDs ($P < 0.05$).

3.5. Additional parameters at DRL-60s

There were significant strain differences on the mean inter-response time ($F[2,49] = 15.95$, $P < 0.0001$, Fig. 5A). The mean inter-response interval for WKY rats was significantly longer than SHR and CD rats ($P < 0.05$), but there was no difference between CD and SHR. There was a significant effect of strain upon magazine latency ($\chi^2 = 6.36$, $df = 2$, $P < 0.05$, Fig. 5B). Post hoc analysis (Mann–Whitney U-test) showed that there was a significant difference between the SHR and

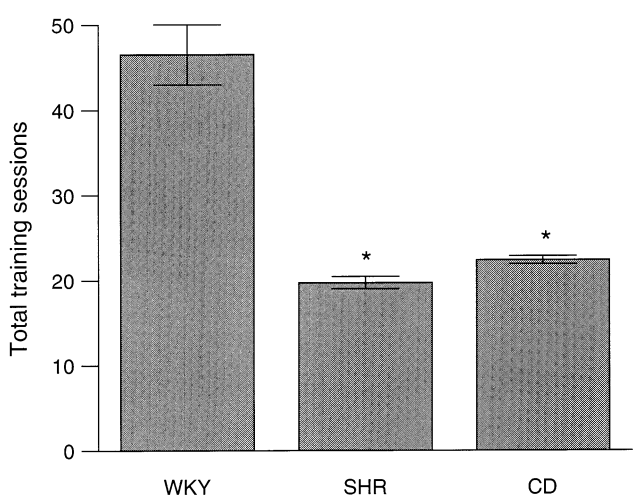

Fig. 2. The total number of training sessions required by each strain ($n = 14–19$) to complete training up to DRL-60s. Significant differences from WKY are shown by * ($P < 0.05$).

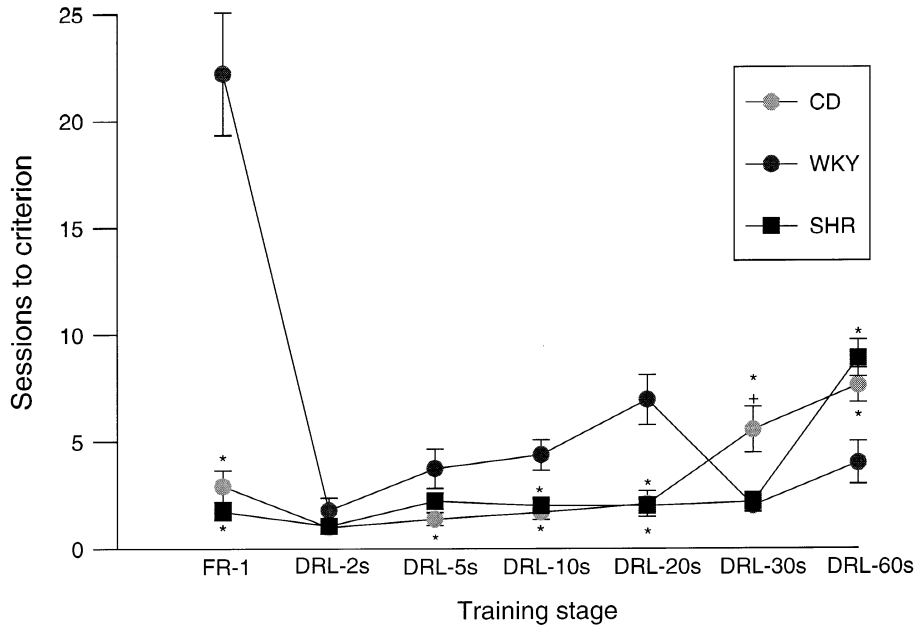

Fig. 3. The number of training sessions required to reach criterion at each training stage. Significant differences from WKY are shown by * ($P < 0.05$) and significant differences from SHR are shown by + ($P < 0.05$). Data were analysed by ANOVA with repeated measures and were log10 transformed to maintain homogenity of variance.

CD rats ($P < 0.05$), but no differences when either of these strains were compared with the WKY rats.

3.6. Effects of strain upon response distribution

Fig. 6A–C shows the mean distribution of responses over time at DRL-60s for each strain expressed as a percentage of total responses. All strains showed 'burst responding', i.e. responding within the first 5 s immediately after receiving a food reinforcement. There were no differences between strains in the percentage of burst responses [WKY ($23.4 \pm 2.04\%$), SHR ($24.97 \pm 2.6\%$), CD ($25.61 \pm 3.7\%$)]. However, analysis of the distribution of responses between the first (5–60 s) and second (> 60s) recording periods revealed a significant strain × time period interaction ($F[2,980] = 80.8$, $P < 0.0005$, Fig. 6d), suggesting that the strains responded differently in the two time intervals. For CD and SHRs, the proportion of responses fell significantly from the first to second interval ($P < 0.05$). In contrast, the pattern of responding for WKY rats was not altered by time i.e. there was no difference in the number of responses in the two recording periods. The percentage of total responses made by CD and SHR rats was almost identical during the first time interval and both strains made a significantly greater proportion of their responses in this period than WKY rats ($P < 0.05$). During the second time period, CD rats made less responses than SHR rats ($P < 0.05$), but both strains made proportionally less responses during this period than WKYs ($P < 0.05$).

3.7. Body weight under DRL-60s

Body weight continued to be recorded once the rat had acquired the DRL-60s criterion. There were significant differences in body weights at DRL-60s ($P < 0.0001$); WKY (364 ± 6.4 g) and CD (355 ± 6 g) rats were heavier than SHR (310 ± 5 g) rats ($P < 0.05$), but not different from each other.

4. Discussion

The purpose of the study was to compare the acquisition and performance of the SHR rats in the DRL paradigm with that of its normotensive progenitor, the WKY rat. An additional control strain, the CD rat, was included as we have routinely used this strain in previous studies [7]. As the DRL test is regarded as a behavioural screen for impulsive behaviour [25], it was hypothesised that SHR rats would be unable to inhibit premature responding and would subsequently perform badly in this test compared with both WKY and CD rats. However, our overall findings fail to support this hypothesis.

The WKY rats required more sessions to complete training than the SHR and CD rats. The clearest difference between WKY and other strains occurred at FR-1. A high rate of responding is required to reach criterion at this stage. In the early training sessions under FR-1, WKY rats tended to make approx. 30–40 responses in a session and then stop responding, failing

to reach the criterion of 80 reinforcements. Once the WKY rats had completed FR-1, they continued to require more training sessions to reach criterion at DRL-5s, DRL-10s and DRL-20s compared with the SHR and CD rats. In contrast, at the final two DRL levels, DRL-30s and DRL-60s, the WKY rats required fewer sessions than CD or SHR (DRL-60s only) rats. Thus, it appears that when a high rate of responding was required, the SHR and CD rats were more proficient than the WKY, which was reversed when a low rate of responding was more appropriate (e.g. DRL-60s). Therefore, although acquisition of SHR and CD rats was apparently impaired at DRL-60s compared with the WKY rats, we are unable to conclude that SHRs or CDs show excessive impulsivity, rather that WKY rats show a uniformly low response rate.

The data obtained when rats were maintained at DRL-60s appears to support the hypothesis that SHR rats are impaired in this task, i.e. WKY rats performed with greater efficiency than both the SHR and CD rats. However, the CD rats rather than the SHR, were the least efficient strain. The mean inter-response time for the WKY rats was 58.3 s, approximately the length of the DRL delay, suggesting that the WKY rats were able to inhibit their responding for an appropriate period, unlike SHR and CD rats. However, the overall pattern of responding suggests that this was not the case. All strains exhibited equal burst responding immediately post-reinforcement suggesting an equal 'saliency' of reinforcement, however, the pattern during the remaining period revealed marked differences between the strains. CD and SHR rats showed a pattern of responding that was governed by the schedule, with significantly more responses made prior to 60 s than after this time point. In contrast, WKY rats showed poor schedule control, evidenced by the even pattern of responding across time, i.e. WKY rats were just as likely to respond inappropriately early (e.g. <40–50 s) as inappropriately late (e.g. >90 s). This pattern suggests that the greater efficiency of the WKY strain was

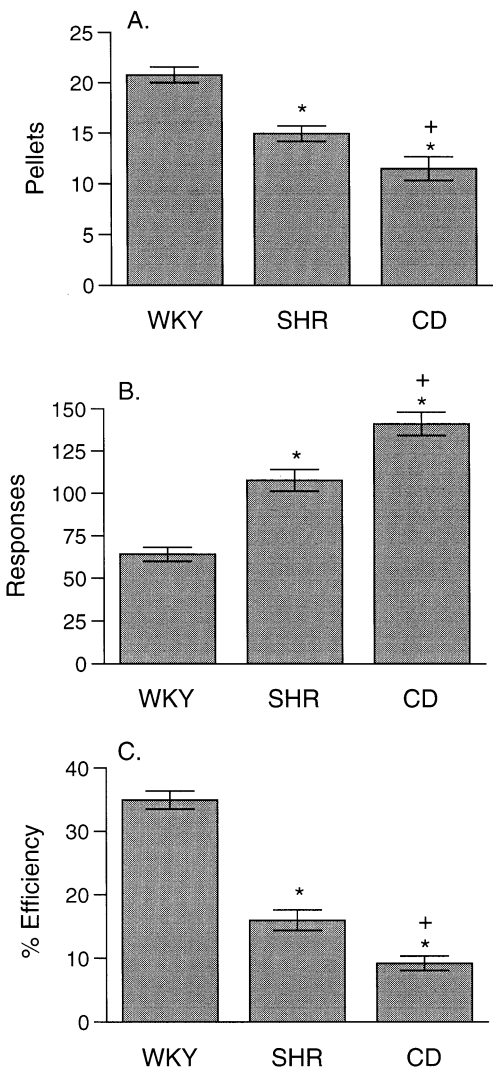

Fig. 4. Effects of rat strain upon number of pellets, total responses and % efficiency under DRL-60s. Significant differences from WKY are shown by * ($P<0.05$) and from SHR by + ($P<0.05$).

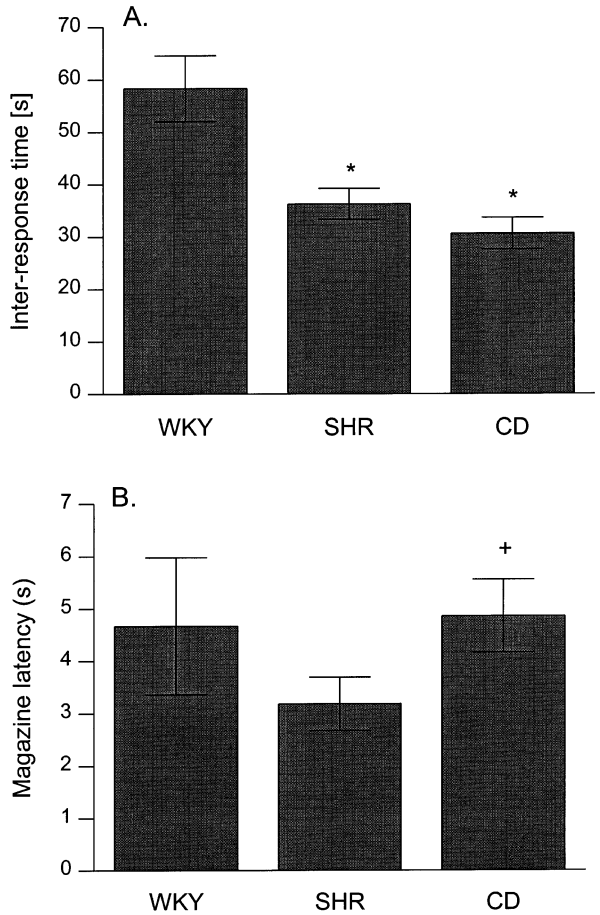

Fig. 5. Effects of rat strain upon mean inter-response time and magazine latency under DRL-60s. Significant differences from WKY are shown by * ($P<0.05$) and differences from SHR are shown by + ($P<0.05$).

not due to rats making their responses according to the schedule, but a result of randomly timed responding.

The data showing poor schedule control with WKY rats in the present study is in contrast with those found by other workers. For example, using a conjunctive 120-s variable interval DRL-16s schedule of reinforcement, Sagvolden and Berger [21] showed that WKY rats appeared to time their responses well. The differences between these data and the present study may be explained by methodological differences, including different schedules and reinforcers (water vs. food).

Although there were clear body weight differences between the rat strains, this is unlikely to account for the differences in acquisition or performance of this task. There was no clear relationship between the number of sessions to acquire the task and body weight. Further, under DRL-60s, there were no differences in magazine latencies between WKY and other strains suggesting that differing levels of motivation was not a factor in performance.

The results of the present study suggest that the performance of the SHR rat in the DRL test does not represent a valid animal model of ADHD. The inclusion of the CD rats highlighted that SHR rats were more efficient than a widely used laboratory rat. The CD rats have been used previously in this laboratory in the DRL procedure [7] and were included to provide a positive control with which to compare the performance of the SHR and WKY rats. The data from the CD rats supports our suggestion that SHR rats do not show excessive impulsivity.

Previous studies have questioned the validity of using the WKY as a genetic control for the SHR. Johnson et al. [8] reported genetic divergence between SHR and WKY rats, such that these strains have more genetic similarity with other strains than with each

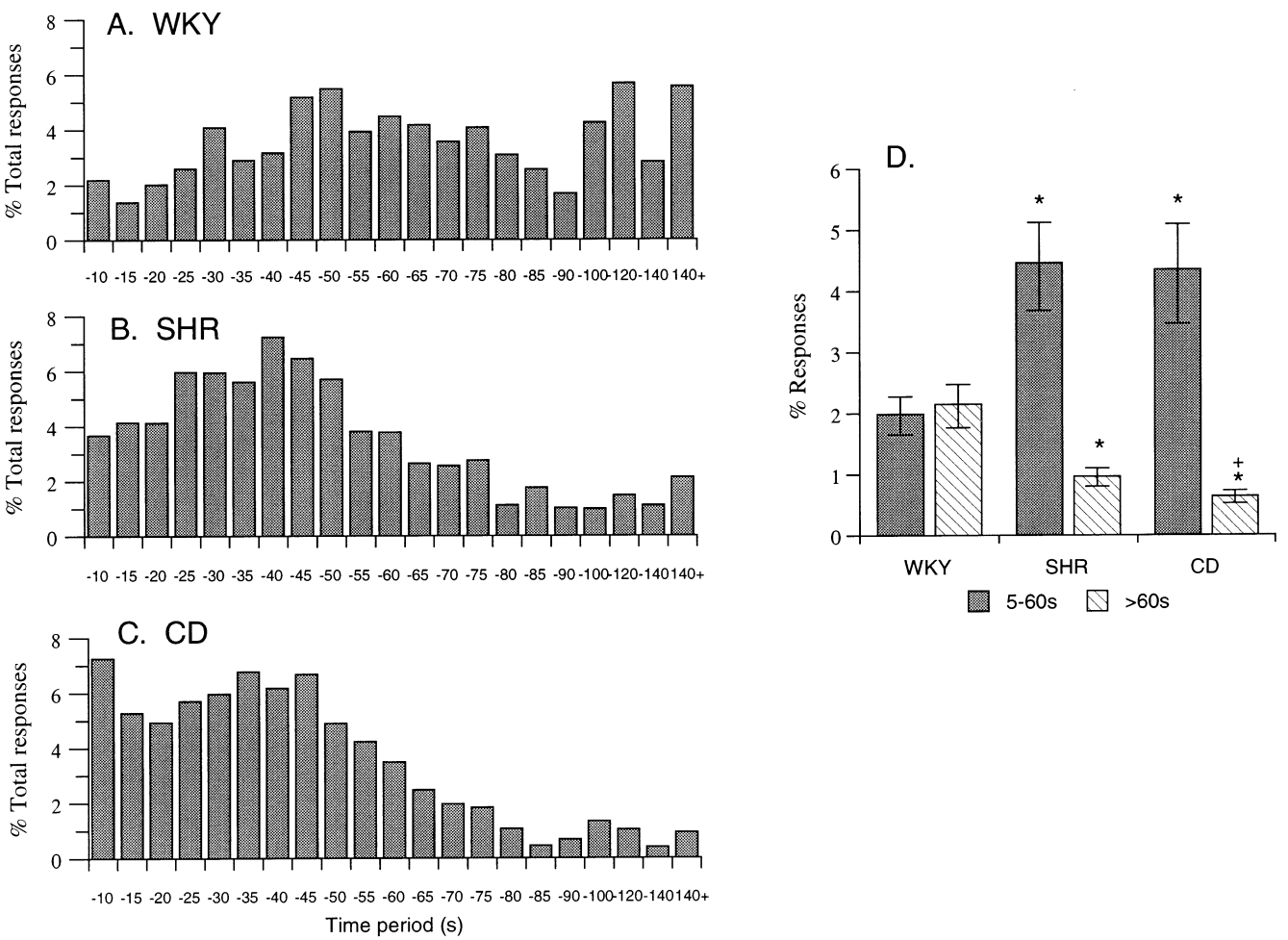

Fig. 6. Effects of rat strain upon the distribution of responses under DRL-60s expressed as a percentage of total responses. Data are shown as the mean percentage of total responses at each 5 s time bin excluding the 'burst' responses from 0–5 s (A–C). D represents the geometric mean ± 95% confidence intervals (backtransformed from log transformed values) of the percentage of total responses for each single recording period (e.g. 5–10 s) during the periods 5–60 s and >60 s post-reinforcement. Significant differences from WKY are shown by * $P < 0.05$ and from SHR by + $P < 0.05$.

other. These findings were supported by St. Lezin et al. [27]. Using DNA fingerprinting techniques they discovered multiple genetic differences between the Charles River SHR and its WKY control. Pare [15] reported open field activity was similar for both SHR and Wistar rats, while WKY were significantly hypoactive. Others have reported similar findings [11,20,24]. Similarly, in a number of studies comparing the behavioural response of either normal outbred CD rats or several inbred strains to the forced swim test, WKY rats display lower levels of activity and higher levels of immobility (see [10] for references). Our own informal observations suggest differences between the strains. The initial speed with which the SHR acquired the task compared with the WKY rats may be attributable to their greater exploratory behaviour. We have observed that SHR rats are more active than the WKY control (Reavill, unpublished data). In addition, the superior learning ability of the SHR in avoidance paradigms may be linked to elevated levels of locomotor activity [9,28]. Pare [15] suggested that although WKY rats serve as an appropriate control for hypertension studies, they may be inappropriate as controls for behavioural studies.

In conclusion, the results of the present study do not support the use of the SHR in a DRL procedure as an animal model of ADHD. Although the performance of the SHRs at DRL-60s was impaired compared to that of the WKY rat, the SHRs were more proficient than the CD rats at this task. The SHR did not exhibit impaired acquisition of the DRL task as expected and together with the CD rats they were significantly quicker to learn the task than the WKY control strain. In addition, these results question the validity of using the WKY as a control strain in this behavioural paradigm.

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