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The Behavior of Spontaneously Hypertensive and Wistar Kyoto Rats Under a Paced Fixed Consecutive Number Schedule of Reinforcement

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EVENDEN, J. AND B. MEYERSON. *The behavior of spontaneously hypertensive and Wistar Kyoto rats under a paced fixed consecutive number schedule of reinforcement.* PHARMACOL BIOCHEM BEHAV **63**(1) 71–82, 1999.—Spontaneously hypertensive (SHR) and Wistar Kyoto rats (WKY) were trained under paced FCN schedules of reinforcement to complete a minimum number of consecutive responses on one lever, before responding on a second. The levers were retracted from the test chamber for a short period after each response to control the speed at which the rats could complete the sequence (paced FCN). Changes in the average chain length may reflect the influence of impulsivity on the execution of behavioral patterns. Although they quickly learned to press the levers, SHR rats performed poorly compared to the WKY rats when the chain length requirement was increased to FCN 6 and FCN 8. Eventually stable performance was obtained under paced FCN 6, although the SHR rats continued to have a consistently lower average chain length. Both strains of rats were treated with imipramine (10 mg/kg), chlordiazepoxide (3 and 10 mg/kg), *d*-amphetamine (0.4 and 0.8 mg/kg), haloperidol (0.05 and 0.1 mg/kg), 8-OH-DPAT (0.1 mg/kg), WAY-100635 (0.1 mg/kg), and DOI (0.3 and 1.0 mg/kg). The SHR rats were less sensitive to the effects of *d*-amphetamine, chlordiazepoxide, and DOI and slightly more sensitive to the effects of haloperidol. All of these drugs reduced the average chain length. There was no difference in the response of the two strains to imipramine and 8-OH-DPAT, both of which increased the average chain length. These results support the suggestion that SHR rats may more impulsive than WKY rats. The data with *d*-amphetamine and haloperidol support biochemical findings that these rats have a deficit in dopaminergic function, and the strain differences in response to chlordiazepoxide and DOI suggest that that there may be differences in GABAergic and 5-HT_2-mediated neurotransmission relevant to regulating impulse control in the rat. © 1999 Elsevier Science Inc.

Spontaneously hypertensive rat Impulsivity Amphetamine Haloperidol 8-OH-DPAT DOI Dopamine Serotonin

IMPULSIVE behavior is an important factor in the symptomatology and course of a number of psychiatric disorders, in particular, antisocial and borderline personality disorders, substance abuse disorders, impulse control disorders, and some developmental disorders such as attention deficit/hyperactivity disorder (ADHD), as well as being an essential element of the "psychopathology of everyday life." Current psychobiological hypotheses ascribe an important role to serotonin in clinically relevant deficits in impulse control, including aggression, suicide, and drug taking, and this has been substantiated by evidence from animal studies (3), although, with the exception of an influential review article by Soubrié (20), until recently the biological basis of impulsive behavior has received surprisingly little attention from animal researchers. Soubrié (20) had the insight that many procedures sensitive to reductions in the CNS serotonergic activity involved a release of inhibited responding, whether this inhibition was appetitively or aversively motivated, and thus the modulation of behavior by central serotonin might reflect alterations in impulse control, rather than appetitive or aversive motivation.

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Evenden (3) identified three separate and potentially independent ways in which impulsivity can modify behavior: in the preparation for action, in the execution of behavior patterns and in the assessment of the consequences of action. The present study concerns the second of these, and utilizes a procedure developed to measure the effects of drugs on the performance of a well-trained behavioral pattern, pressing one lever a fixed number of times before pressing a second to deliver a food reinforcer (the fixed consecutive number schedule of reinforcement, FCN). Evenden (4,5) found that the standard FCN schedule, in which the subject itself determines the pace at which it responds, was sensitive to changes in rate of responding such that a reduction in rate produced, for example, by a sedative drug, resulted in a reduction in the average number of responses made before the rat tried the second lever (a reduction in response chain length). Because almost all drugs reduce the rate of responding if given in sufficiently high doses, all appear to increase impulsivity. However, if the rate of responding was controlled by the experimenter, by withdrawing the levers for a short time between responses, it was found that the tricyclic antidepressant imipramine increased the average chain length, whereas other drugs such as amphetamine, haloperidol, and chlordiazepoxide still reduced average chain length. Thus, in the pace FCN procedure the effects of the drugs on chain length could be dissociated to some extent from their effect on response rate.

In addition to psychoactive drugs, another variable that can be employed in the study of biological factors influencing behavior is the strain of rat used as the subject of the study. In the paced FCN procedure the standard laboratory strains of Sprague–Dawley and Lister Hooded rats appear to behave in a relatively similar way (4,5). However, other strains exist that may be expected to show an impulsive behavior pattern based upon their behavior in other procedures. One of these is the Spontaneously Hypertensive Rat (SHR). In addition to having elevated blood pressure, this rat shows increased locomotor activity, increased exploratory behavior, increased avoidance responding, and increased rates of responding in some schedules of reinforcement compared to its normotensive control strain, the Wistar Kyoto rat (18). The hyperlocomotion and hypertension have been separated genetically by selective breeding (8). The SHR rat has even been proposed as an animal model of ADHD (18).

Much research has been carried out to investigate biological differences between the SHR and normotensive rat strains, mainly concentrating on factors that may contribute to blood pressure regulation, although alterations in mechanisms affecting blood pressure may also affect behavior. Evidence has accumulated for reduced striatal dopaminergic function (16,21), and changes in noradrenaline (9), serotonin (12), and GABA function (10,11) have all been reported. Differences in peptidergic neurotransmitters such as oxytocin and vasopression have also been seen (15,23), although these are not addressed in the present study. The SHR rat may also have a deficit in certain hormonally controlled behaviors. In spite of high testosterone levels, SHR males (of the same substrain as used in the present study) show reduced copulatory behavior and sociosexual approach behavior (25), and a higher dose of testosterone was required to reinstate copulatory behavior in castrated SHR rats (14), suggesting a decrease in sensitivity to circulating testosterone in the SHR strain.

In the present study the two approaches were combined: SHR and WKY rats were trained to respond under a paced FCN schedule of reinforcement, and then treated with a number of psychoactive drugs. The drugs selected were the tricyclic antidepressant imipramine (noradrenaline and serotonin reuptake inhibitor), chlordiazepoxide, (GABA agonist via the benzodiazepine receptor), *d*-amphetamine (primarily dopamine and noradrenaline releaser), haloperidol (primarily D_2 receptor antagonist), 8-OH-DPAT (5-HT_{1A} receptor agonist), WAY-100635 (5-HT_{1A} receptor antagonist), and DOI (5-HT_2 receptor agonist). The doses were selected on the basis of previous studies (4,5).

METHODS

Subjects

The subjects were eight Spontaneously Hypertensive rats (SHR, Möllegaard) and eight Wistar Kyoto rats (WKY, Möllegaard) approx. 3 months of age on starting the experiment and 15 months of age at the end. The rats were housed in groups of four, and each group was fed 45 g laboratory chow per day. Water was available ad lib.

Apparatus

The apparatus consisted of two sets of four operant chambers (Campden Instruments, Model 4102). The chambers were 26.5 × 22 × 20 cm, and were fitted with two retractable levers and a food pellet dispenser. Food pellets (45 mg, Campden Instruments) were delivered to a tray placed centrally between the two levers. Access to the tray was by opening a hinged Perspex flap. The food tray could be illuminated by a 24-V, 1-W lamp, while a second 24-V, 2.8-W lamp placed centrally in the roof of the chamber served as a houselight. Each chamber was housed in a separate soundproof box with a ventilator fan providing low-level background noise. Each set of chambers was controlled by a Paul Fray microcomputer using the Spider programming language. Programs for controlling the apparatus and collecting the data were written by the author.

Training

Twenty-four hours before the start of training the food was removed from the subjects' home cages. On day 1 of training the subjects were provided with food placed in the food tray of the test apparatus for 30 min. On day 2, single 45-mg food pellets were delivered once per minute for a period of 30 min. The number of entries into the food tray was counted. Thereafter, the rats were trained to press both levers under continuous reinforcement (CRF). Only one lever was present during each training session. Training under CRF continued until all the rats had made a minimum of 100 presses on both levers during a 20-min session (a maximum of 10 sessions). Training continued by gradually increasing the number of responses required to obtain a food pellet. At this time the rats were then placed on the paced FCN schedule.

In this procedure the rats were trained to make a certain minimum number of consecutive responses on the left lever (FCN lever) before pressing the right lever (reinf. lever) to deliver food. Responses on the reinf. lever before completion of the minimum requirement resulted in a short time out, and the rat was required to restart the sequence of consecutive responses. Sequences of responses on the FCN lever equal to or exceeding the minimum resulted in food delivery the first time the rat pressed the reinf. lever. After each response the two levers were retracted for a short period so that there was a minimum time between two consecutive responses, but no maximum time. Each time the lever was extended into the

chamber a timer was started for a fixed period, for example, in this study, 2.2 s. If the rat responded within this time, as was usual, the lever was retracted until the timer ran out, and after an additional period of 0.3 s it was reextended into the chamber giving a total minimum interresponse time of 2.5 s (mIRT 2.5 s). If the rat waited for longer than 2.2 s, the lever was retracted and reextended after 0.3 s. The fixed period of 0.3 s was chosen, as it was slightly longer than the time taken to retract and extend the lever. An initial period of 10 min with a mIRT of 2.5 s was followed by a 1-min time-out. Thereafter, followed 20 min mIRT of 5 s, 10 min mIRT of 2.5 s, 20 min mIRT of 5 s, completed by a final 10 min mIRT of 2.5 s. Each block was started by the delivery of a noncontingent food pellet and the illumination of the houselight and the blocks were separated by a 1-min time-out, during which time the houselight was turned off. Data for the three mIRT 2.5 s blocks were averaged for the purposes of data analysis (fast component), as were the data from the two mIRT 5 s blocks (slow component).

The training of the rats was adjusted to suit each individual. The schedule started as FCN 1. After 2 days the FCN was gradually increased to 3, 4, 5, 6, and eventually 8. The criterion for increasing the ratio was that the individual subject had to have achieved at least 50 correctly completed ratios for FCN 1, 2, 3, and 4, and 40 completed ratios for FCN 5 and 6. During training it became evident that the SHR rats had difficulties in completing longer ratios (see Table 1). Three of the eight SHR rats could not be trained to criteria under either FCN 4 or FCN 6, whereas all eight of the WKY rats were trained successfully. Those SHR rats that were tested under FCN 8 showed poor and unstable performance. Finally, it was decided to use a paced FCN 6 schedule for both strains. All the rats that eventually entered the drug study were then tested for 16 sessions paced FCN 6. They then received saline IP 15 min for two sessions, before the first drug tests with 10 mg/kg imipramine. Data from this experiment was not analyzed due to equipment failure. Thus, the rats had had 21 sessions paced FCN 6 prior to the first reported drug study. Administration of each drug treatment was separated by at least 1 week, and always preceded by vehicle treatment day.

Measurements and Statistics

First, for each measure, vehicle values were combined with the drug treatment data in separate one-way analyses of variances for the fast and slow components. Specific comparisons were carried out using Bonferroni *t*-tests. All comparisons were made at the 5% level.

The measures submitted to analysis of variance were defined as follows.

Total responses. The total number of responses made on the FCN lever during each component. Because the length of the components was fixed, this gives a measure of the average rate of responding.

Chain time. The average length of time taken to complete a chain of six responses on the FCN lever. This provides a measure of the local rate of responding during the time at which the rats were completing response chains.

Chain length. The average length of the chain of responses made on the FCN lever before a response was made on the reinf. lever. (It is proposed that a reduction in this value indicates a shortening of the average chain length and an increase in impulsivity, whereas an increase in this value reflects an increase in chain length and, thus, a reduction in impulsivity.)

First response on reinf. lever. The proportion of the total reinf. lever responses not preceded by a response on the FCN lever.

In addition to these measures, the distribution of chain lengths in the fast component was also analyzed using a "survival" analysis. That is, the proportion of the total number of chains equal to or greater than length 1, length 2, length 3, and so on was calculated. Obviously all chains have a length of at least 1; thus, the curve always begins at 100%. Statistical analysis of these data was carried out by two-way analysis of variance on cuts through the data at chain lengths ≥ 4, ≥ 6, ≥ 8, and ≥ 10, with factors strain and treatment. In addition, a logistic function of the type

$$f = (a - d)/(1 + (x/c)^b) + d$$

where a = maximum, b = slope, c = inflection, and d = minimum, was fitted to the data for each animal. Analysis of variance was then carried out on the calculated data for "*c*," which indicates the length reached by 50% of the chains (CL_{50}), and for "*b*," the slope of the function. Only data from the Fast component was used in these analyses. A rat had to have made at least five chains to be included in these analyses.

Drugs. The drugs employed in these experiments were *d*-amphetamine sulphate (Sigma Chemical Co., St Louis, MO), haloperidol ("Haldol" injection solution, Janssen-Cilag AB, Sollentuna, Sweden), 8-hydroxy-(di-n-propylamino) tetralin hydrobromide (8-OH-DPAT, Research Biochemicals Inc., Natick, MA), (*N*-(2-(1-(4-(2-methoxyphenyl) piperazinyl))ethyl)-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY-100-635, Astra Arcus, Södertälje, Sweden), (±)-2,5-dimethoxy-4-iodoamphetamine hydrobromide (DOI, Research Biochemicals Inc., Natick, MA), imipramine hydrochloride (Ciba-Geigy, Basel, Switzerland), and chlordiazepoxide hydrochloride (Sigma Chemical Co., St Louis, MO). All the drugs were injected in a volume of 1 ml/kg, and dissolved in 0.9% saline except for the "Haldol" solution, which was diluted with distilled water. The doses, treatment times and routes of injection are given in the Results section. The drugs were administered in the order: WAY-100635, imipramine, DOI, amphetamine, chlordiazepoxide, 8-OH-DPAT, and haloperidol. All rats received the same treatment at the same time. Where more than one dose was used, these were administered in ascending order.

Ethical Comment

The experiments described here were approved by Södra Stockholms Djuretisknämnd in accordance with Swedish national law.

TABLE 1

NUMBER OF DAYS AT EACH TRAINING LEVEL FOR THE TWO STRAINS OF RATS (MEANS AND RANGE, NUMBER OF RATS TESTED)

	SHR	WKY
FCN 2	4.0 (2–8), $n = 8$	2.5 (2–5), $n = 8$
FCN 3	5.4 (1–17), $n = 8$	1.2 (1–3), $n = 8$
FCN 4	5.9 (2–11), $n = 8$	3.1 (2–5), $n = 8$
FCN 5	2.7 (2–4), $n = 6$	2.6 (1–5), $n = 8$
FCN 6	5.5 (4–8), $n = 6$	3.5 (2–6), $n = 8$
FCN 8*	4.0 (2–5), $n = 5$	4.2 (4–5), $n = 8$

* Training terminated after indicated sessions due to poor performance of SHR rats.

RESULTS

Strain Differences

The SHR rats made significantly more entries into the food tray during the FT 60 training than did the WKY rats (SHR: 124.8 ± 44.8, WKY: 21.2 ± 9.9, $df = 14$, $t = 6.38$, $p < 0.001$). In fact, there was no overlap between the groups, with the SHR rats, which made the fewest entries, entering more than the WKY rats, which made the most. SHR rats also made significantly more lever press responses during sessions 1 and 2 of the FR 1 training (SHR: 48 ± 8, WKY: 6 ± 8, $F_{strain}(1, 14) = 13.2$, $p < 0.01$). Although it was not possible to carry out a statistical analysis, Table 1 illustrates the impression that the SHR rats were slower to reach performance criteria from FCN 2 onwards (two rats failed to reach criteria under FCN 4 and one under FCN 6), and unlike the WKY rats, did not show stable performance under FCN 8, with the result that it was necessary to use a paced FCN 6 for the pharmacological tests. Under FCN 6, the SHR rats showed a consistent tendency to make fewer longer chains as shown in Fig. 1. It should be noted that five of the six SHR rats eventually included in the drug experiments (whose data are shown in Fig. 1) had experience with FCN 8 and all of the WKY rats, so that exposure to FCN 8 is not the explanation of this difference.

Imipramine (Table 2)

A dose of 10.0 mg/kg imipramine (IP 60 min) significantly reduced the number of responses in the slow component, $F_{treat}(1, 12) = 6.60$, $p < 0.05$, but had no significant effect on the total in the fast component, although the time to complete a chain was significantly increased, $F_{treat}(1, 12) = 12.24$, $p < 0.01$. The drug significantly increased the average chain length in the fast component, $F_{treat}(1, 12) = 6.45$, $p < 0.05$, but although there was a tendency to an increase in the slow component, this did not reach statistical significance. Imipramine had no effect on the number of first responses made on the reinf. lever in either component. There were no differences between the two strains on any measure.

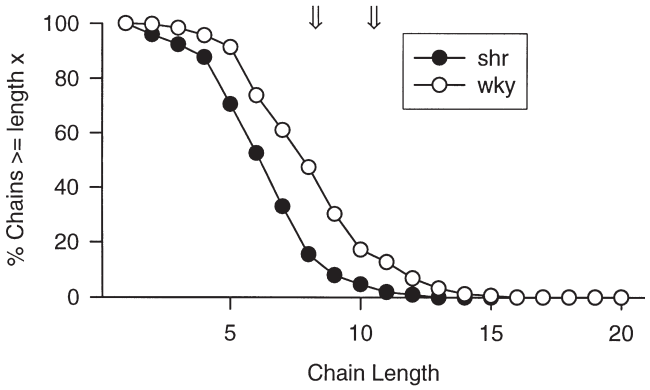

FIG. 1. The distribution of chain lengths of SHR and WKY rats responding under a paced FCN 6 schedule of reinforcement after an injection of saline (baseline performance). The horizontal axis shows the chain length up to a maximum of 20, and the vertical axis shows the percentage of the total chains greater than or equal to each length, a so-called "survival" plot. Differences between the curves were tested at chain lengths ⩾6, ⩾8, ⩾10, and ⩾12. Key: open symbols, WKY strain; closed symbols, SHR strain, ⇓ significant difference between the strains.

Analysis of the chain length distribution revealed that 10 mg/kg imipramine significantly increased the CL_{50}, but there was no difference between the two groups, $F_{treat}(1, 12) = 10.90$, $p < 0.01$. However, analysis of the slope of the function revealed a strain by treatment interaction, $F_{int}(1, 12) = 5.13$, $p < 0.05$, reflecting the fact that the SHR strain had a steeper slope under the drug than on the baseline, whereas slope became shallower for the WKY rats. There was no effect of imipramine on the number of chains ⩾4 or ⩾6 responses in length, but that the number of chains ⩾8 and ⩾10 responses in length were significantly increased, $F_{treat}(1, 12) = 6.06$, $p < 0.05$, and $F_{treat}(1, 12) = 17.1$, $p < 0.01$, respectively Fig. 2, upper panel). It is also worth noting that in this study the WKY rats made significantly more chains of length ⩾10 responses than the SHR rats, $F_{strain}(1, 12) = 5.54$, $p < 0.05$.

Chlordiazepoxide (Table 2)

A dose of 3.0 mg/kg chlordiazepoxide (IP 15 min) had no effect on any of the measures used in this experiment. The WKY rats made significantly fewer responses in the slow component than the SHR rats, but there was no effect of the drug, $F_{strain}(1, 11) = 6.4$, $p < 0.05$. In contrast, 10.0 mg/kg chlordiazepoxide (IP 15 min) significantly reduced the number of responses completed in the fast component by the WKY but not by the SHR rats, $F_{int}(1, 12) = 9.84$, $p < 0.01$. The WKY rats also made significantly fewer responses in the slow component than the SHR rats, but there was no effect of the drug, $F_{strain}(1, 12) = 10.2$, $p < 0.01$. The average time to complete a chain was unaffected in either strain. This dose of chlordiazepoxide also significantly reduced the average chain length. This effect was, again, only statistically significant for the WKY group [post hoc statistics following $F_{int}(1, 12) = 7.15$, $p < 0.05$]. There was no effect of the drug on chain length in the slow component. The drug significantly increased the proportion of responses made first on the reinf. lever. This was equivalent for both strains, and occurred in both the fast and slow component [fast: $F_{treat}(1, 1) = 11.48$, $p < 0.01$; slow: $F_{treat}(1, 12) = 7.78$, $p < 0.05$].

Analysis of the response chain length distribution revealed no significant effect of 3.0 mg/kg chlordiazepoxide on the CL_{50} or slope at any of the chain lengths (data not shown). However, the analysis did reveal that in this experiment the WKY rats completed significantly more chains of more than 10 responses in length, $F_{strain}(1, 11) = 5.33$, $p < 0.05$, and slope of their distribution function was significantly steeper, $F_{strain}(1, 11) = 18.40$, $p < 0.01$. Analysis of the effects of 10.0 mg/kg chlordiazepoxide revealed a strain by treatment interaction, $F_{int}(1, 12) = 9.89$, $p < 0.01$. The drug reduced the CL_{50} of the WKY strain, but had no significant effect on the CL_{50} for the SHR strain. The drug also reduced the slope of the function, $F_{treat}(1, 12) = 11.37$, $p < 0.01$. There was no difference in the response to the drug of the two strains, but, once again, the SHR rats had a significantly steeper slope, $F_{strain}(1, 12) = 5.15$, $p < 0.05$. There was an effect of the drug on chains ⩾4, ⩾6, and ⩾10 responses in length [⩾4: $F_{treat}(1, 12) = 16.40$, $p < 0.01$; ⩾6: $F_{treat}(1, 12) = 30.19$, $p < 0.001$; and ⩾10: $F_{treat}(1, 12) = 4.81$, $p < 0.05$], but no difference between the strains. For the proportion of chains greater than eight responses in length, there was a statistically significant interaction, $F_{int}(1, 12) = 5.34$, $p < 0.05$. Chlordiazepoxide significantly reduced the number of such chains in the WKY strain, but had no significant effect on the SHR strain, who completed many fewer such chains under baseline conditions.

TABLE 2

THE EFFECTS OF IMIPRAMINE AND CHLORDIAZEPOXIDE ON RESPONDING BY SHR AND WKY RATS UNDER A PACED FCN 6 SCHEDULE OF REINFORCEMENT

Strain	Treat	Comp	Total Resp.	Chain Time (s)	Chain Length	First Resp. Ratio (%)
10.0 mg/kg imipramine						
SHR	Veh	Fast	309 ± 110	27.2 ± 7.4	6.1 ± 0.8	5.2 ± 7.8
SHR	Drug		311 ± 58	31.5 ± 8.0†	6.9 ± 1.3†	0.0 ± 0.0
WKY	Veh		396 ± 143	20.6 ± 3.9	7.0 ± 1.8	17.8 ± 21.6
WKY	Drug		254 ± 158	31.2 ± 12.0†	7.9 ± 1.8†	22.9 ± 19.4
SHR	Veh	Slow	177 ± 155	—	4.1 ± 2.0	35.8 ± 34.4
SHR	Drug		168 ± 121†	—	6.0 ± 1.4	28.4 ± 37.5
WKY	Veh		108 ± 91	—	3.8 ± 2.0	37.8 ± 25.3
WKY	Drug		19 ± 33†	—	4.2 ± 1.5	73.3 ± 29.6
3.0 mg/kg chlordiazepoxide						
SHR	Veh	Fast	375 ± 56	26.23 ± 7.58	6.6 ± 0.8	1.3 ± 2.0
SHR	Drug		373 ± 56	26.09 ± 6.60	6.6 ± 0.9	2.5 ± 1.0
WKY	Veh		423 ± 99	20.63 ± 4.37	7.6 ± 1.6	13.2 ± 16.6
WKY	Drug		416 ± 122	22.11 ± 7.72	7.3 ± 1.5	13.4 ± 13.5
SHR	Veh	Slow	192 ± 157	—	4.7 ± 1.7	33.6 ± 36.2
SHR	Drug		58 ± 15	—	4.8 ± 0.8	17.6 ± 10.3
WKY	Veh		85 ± 74*	—	4.3 ± 1.9	37.4 ± 27.2
WKY	Drug		32 ± 25*	—	4.4 ± 1.3	38.6 ± 12.0
10.0 mg/kg chlordiazepoxide						
SHR	Veh	Fast	358 ± 50	27.3 ± 8.3	6.7 ± 0.9	0.3 ± 0.7
SHR	Drug		311 ± 81	25.8 ± 5.1	5.6 ± 1.0	16.3 ± 13.4†
WKY	Veh		410 ± 134	20.8 ± 5.2	7.9 ± 2.0	10.7 ± 14.2
WKY	Drug		192 ± 105‡	20.4 ± 1.9	5.0 ± 1.7‡	26.0 ± 17.0‡
SHR	Veh	Slow	198 ± 144	—	5.1 ± 1.4	12.9 ± 13.0
SHR	Drug		57 ± 17	—	4.1 ± 0.8	34.3 ± 17.9†
WKY	Veh		85 ± 94*	—	3.6 ± 1.6	31.6 ± 21.0
WKY	Drug		16 ± 8*	—	2.9 ± 0.8	51.3 ± 16.0†

* Significant difference between the strains irrespective of treatment.
† Significant difference between the treatments irrespective of strain.
‡ Significant difference in the effect of the treatment between the strains.
Abbreviations: Veh. — vehicle; Treat — Treatment; Comp. — component; First Resp. Ratio — First response ratio. Data shown is the mean ± standard deviation. It should be noted that the SD refers to the within group variation and is only relevant to comparisons between the strains and interactions between treatment and strain. All comparisons $p < 0.05$.

d-*Amphetamine (Table 3)*

A dose of 0.4 mg/kg *d*-amphetamine (SC 15 min) had no significant effect on the number of responses made during either the fast or the slow component. Nor did the drug affect the time to complete the response chain. However, this dose of amphetamine significantly reduced the average chain length irrespective of the strain of rat in both the fast and the slow components [fast: $F_{treat}(1, 10) = 18.0$, $p < 0.01$, slow: $F_{treat}(1, 10) = 9.17$, $p < 0.05$]. There was no effect of this dose of *d*-amphetamine on the number of responses made first on the reinf. lever in either component.

Distribution analysis revealed that the number of chains ⩾4 responses in length was unaffected by amphetamine, whereas the number ⩾6 and ⩾8 were reduced by the drug without any significant differences between the strains [⩾6: $F_{treat}(1, 10) = 22.1$, $p < 0.001$, ⩾8: $F_{treat}(1, 10) = 9.01$, $p < 0.05$]. There was no reduction in the number of chains ⩾10 due to a floor effect. This dose of amphetamine significantly reduced the CL_{50}, $F_{treat}(1, 12) = 16.12$, $p < 0.01$, but there was no difference between the strains. The drug also significantly reduced the slope of the function, $F_{treat}(1, 12) = 8.66$, $p < 0.05$. There was once again a significant difference between the two strains, $F_{strain}(1, 10) = 23.0$, $p < 0.001$, but the treatment by strain interaction failed to reach statistical significance.

The dose of 0.8 mg/kg *d*-amphetamine (SC 15 min) significantly reduced the total number of responses made in the fast component, $F_{treat}(1, 11) = 25.68$, and in the slow component, $F_{treat}(1, 11) = 6.32$, $p < 0.05$, and also reduced the time taken to complete a chain in the fast component, $F_{treat}(1, 8) = 8.67$, $p < 0.05$. The drug also reduced the average chain length in both components [fast: $F_{treat}(1, 11) = 41.5$, $p < 0.0001$; slow: $F_{treat}(1, 9) = 34.4$, $p < 0.001$], and also increased the number of responses made first on the reinf. lever [fast: $F_{treat}(1, 11) = 15.3$, $p < 0.01$, slow: $F_{treat}(1, 11) = 21.4$, $p < 0.001$]. The treatment by strain interaction was also statistically significant for the chain length measure for the fast component, $F_{int}(1, 11) = 7.03$, $p < 0.05$. However, because this was a crossover interaction (see Table 3), none of the relevant post hoc comparisons reached statistical significance.

This statistically significant interaction was supported by data from the distribution analysis. The dose of 0.8 mg/kg *d*-amphetamine significantly reduced the CL_{50} of the WKY strain, but had no significant effect on that of the SHR strain [post hoc tests following $F_{int}(1, 8) = 17.18$, $p < 0.01$]. *d*-Amphetamine also significantly reduced the slope of the function,

$F_{treat}(1, 8) = 8.03$, and despite the few degrees of freedom, the strain by treatment interaction almost reached statistical significance, $F_{int}(1, 8) = 5.25$, $p = 0.051$. The drug reduced the proportion of chains ⩾4 in both strains, $F_{treat}(1, 8) = 21.9$, $p < 0.01$. However, for the proportion of chains ⩾6, ⩾8, and ⩾10, the drug only reduced the number of chains in the WKY group, whereas there was no effect of the drug on this part of the chain length distribution for the SHR rats [⩾6: $F_{int}(1, 8) = 15.9$, $p < 0.01$; ⩾8: $F_{int}(1, 8) = 23.8$, $p < 0.01$; and ⩾10: $F_{int}(1, 8) = 26.9$, $p < 0.001$]. As can be seen from Fig. 3, upper panel, after saline treatment the distribution of chain lengths for the WKY group lay to the right of the SHR group, whereas under 0.8 mg/kg amphetamine it lies to the left. It is not possible to explain this difference between the strains solely in terms of a floor effect.

Haloperidol: (Table 3)

Two doses of haloperidol were tested (SC 60 min). The lower dose, 0.05 mg/kg, significantly reduced the total number of responses made during the fast component, $F_{treat}(1, 10) = 47.8$, $p < 0.001$, and in the slow component, $F_{treat}(1, 10) = 11.8$, $p < 0.01$, but had no effect on the time to complete a chain in the fast component. This dose of haloperidol had no effect on the average chain length in either component, although there was a significant difference between the strains in the fast component, $F_{strain}(1, 10) = 10.1$, $p < 0.05$. The average chain length completed by the SHR rats was significantly shorter than that of the WKY rats. The dose of 0.05 mg/kg haloperidol significantly increased the number of first responses made on the reinf. lever in both components [fast: $F_{treat}(1, 10) = 16.4$, $p < 0.01$; slow: $F_{treat}(1, 10) = 9.0$, $p < 0.05$].

The distribution data supported this analysis. There was no effect of the drug on CL_{50}, but the CL_{50} of the SHR strain was less than that of the WKY strain, $F_{strain}(1, 10) = 9.21$, $p < 0.05$. There was a significant increase in the number of very short chains postdrug [⩾4: $F_{treat}(1, 10) = 8.7$, $p < 0.05$]. Otherwise, there was no significant effect of the drug treatment, but a difference in the behavior of the two strains, with the SHR rats showing fewer longer chains [⩾6: $F_{strain}(1, 10) = 7.6$, $p < 0.05$; ⩾: $F_{strain}(1, 10) = 6.9$, $p < 0.05$; ⩾10: $F_{strain}(1, 10) = 5.8$, $p < 0.05$]. However, when the slope of the function was analyzed, a significant strain by treatment interaction was obtained, $F_{int}(1, 10) = 5.47$, $p < 0.05$. The SHR rats had a steeper slope when treated with vehicle, but there was no difference between the two strains under the drug.

The higher dose of haloperidol (0.1 mg/kg) significantly reduced the number of responses made in both components [fast: $F_{treat}(1, 10) = 139.5$, $p < 0.001$; slow: $F_{treat}(1, 10) = 15.9$, $p < 0.01$]. No further data analysis was possible on performance in the slow component. Time to complete the chain was also increased by this dose of the drug, $F_{treat}(1, 10) = 13.3$, $p < 0.01$, the average chain length was significantly reduced, $F_{treat}(1, 10) = 9.9$, $p < 0.05$, and the number of first responses made on the reinf. lever significantly increased, $F_{treat}(1, 10) = 12.6$, $p < 0.01$. There were no significant differences between the strains.

Some evidence of a significant difference between the strains was revealed by the analysis of the distribution data (Fig. 3, lower panel). Although haloperidol reduced the CL_{50} in both strains, $F_{treat}(1, 9) = 16.8$, $p < 0.01$, and the slope of the function was shallower, $F_{treat}(1, 9) = 7.73$, $p < 0.05$, there was no significant difference between the strains. However, the SHR rats made significantly fewer chains ⩾4 responses in length after 0.1 mg/kg haloperidol than the WKY rats, although baseline performance was similar, $F_{int}(1, 9) = 9.6$, $p < 0.05$. This difference was not evident when the proportion of chains ⩾6 or ⩾8 responses was analyzed. Both strains completed fewer such chains under the drug [⩾6: $F_{treat}(1, 9) = 25.0$, $p < 0.001$; ⩾8: $F_{treat}(1, 9) = 9.1$, $p < 0.05$]. There were no significant effects of the drug or strain differences on the number of chains ⩾10 responses in length.

8-OH-DPAT (Table 4)

A dose of 0.1 mg/kg 8-OH-DPAT (SC 15 min) was used. This dose significantly reduced the number of responses made in the fast component, $F_{treat}(1, 12) = 6.07$, but had no effect on the same measure in the slow component. Nor was the time to complete the chain affected. 8-OH-DPAT also significantly increased the average chain length in both components, irre-

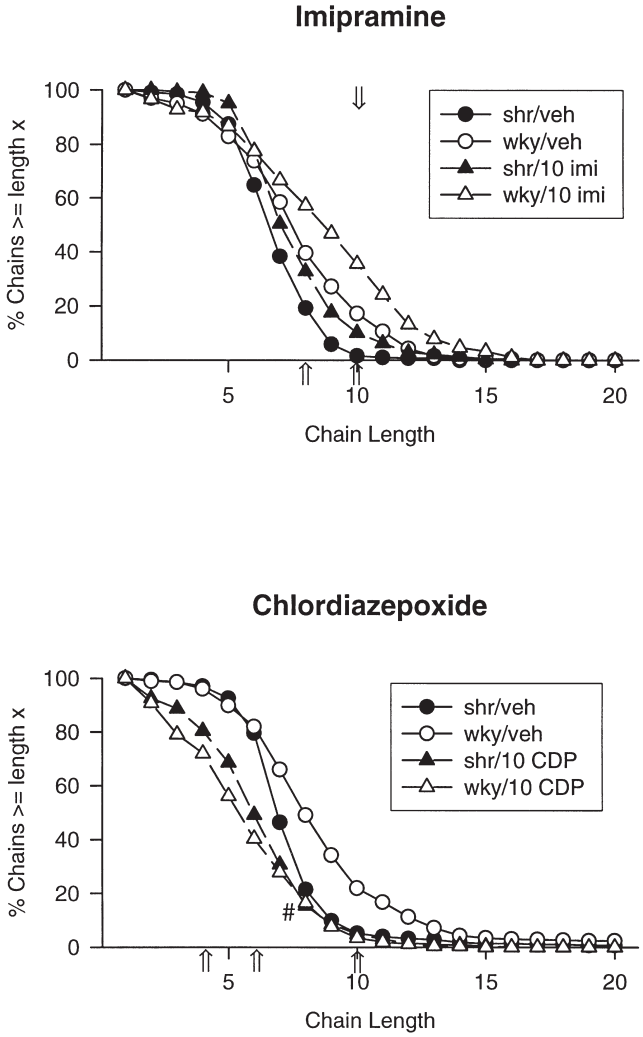

FIG. 2. This shows the distribution of chain lengths of SHR and WKY rats responding under a paced FCN 6 schedule of reinforcement after treatment with imipramine (imi, upper panel) or chlordiazepoxide (CDP, lower panel). The data are plotted in the form of a survivor plot, showing the percentage of the total number of chains (vertical) a certain length (horizontal axis). All chains must be at least one response in length. Key: open symbols, WKY strain; closed symbols, SHR strain; circles, vehicle treatment; triangles, drug treatment; ⇑ significant effect of the drug similar in the two strains; ⇓ significant difference between the strains regardless of the drug treatment; and *# difference in response to the drug between the two strains.

TABLE 3

THE EFFECTS OF AMPHETAMINE AND HALOPERIDOL ON RESPONDING BY SHR AND WKY RATS UNDER A PACED FCN SCHEDULE OF REINFORCEMENT

Strain	Treat	Comp	Total Resp.	Chain Time (s)	Chain Length	First Resp. Ratio (%)
0.4 mg/kg *d*-amphetamine						
SHR	Veh	Fast	375 ± 73	25.9 ± 9.7	6.2 ± 0.6	1.4 ± 1.4
SHR	Drug		266 ± 133	24.6 ± 7.6	5.2 ± 1.1†	24.2 ± 27.8
WKY	Veh		337 ± 146	23.2 ± 8.6	7.3 ± 1.5	12.7 ± 14.8
WKY	Drug		313 ± 192	18.4 ± 2.7	5.6 ± 1.8†	21.2 ± 30.8
SHR	Veh	Slow	116 ± 132	—	3.8 ± 1.9	44.6 ± 25.5
SHR	Drug		96 ± 62	—	3.5 ± 1.5†	44.0 ± 42.0
WKY	Veh		73 ± 92	—	4.1 ± 1.0	18.2 ± 23.0
WKY	Drug		49 ± 41	—	2.9 ± 1.2†	49.8 ± 29.8
0.8 mg/kg/ *d*-amphetamine						
SHR	Veh	Fast	364 ± 79	26.3 ± 10.9	6.3 ± 0.9	1.2 ± 1.6
SHR	Drug		167 ± 135†	24.6 ± 7.6	4.6 ± 1.9†	53.2 ± 34.8†
WKY	Veh		401 ± 124	22.0 ± 7.0	7.6 ± 0.7	10.2 ± 7.5
WKY	Drug		233 ± 187†	16.1 ± 2.7	3.6 ± 1.6‡	41.4 ± 40.2†
SHR	Veh	Slow	173 ± 153	—	4.5 ± 2.3	28.8 ± 33.2
SHR	Drug		167 ± 135	—	4.6 ± 1.9	53.2 ± 34.9†
WKY	Veh		139 ± 126	—	5.0 ± 2.1	24.1 ± 16.1
WKY	Drug		233 ± 187	—	3.6 ± 1.6	41.4 ± 40.2†
0.05 mg/kg haloperidol						
SHR	Veh	Fast	355 ± 90	28.4 ± 11.2	6.2 ± 0.6	2.2 ± 2.8
SHR	Drug		184 ± 133†	27.2 ± 3.6	5.8 ± 1.1	10.9 ± 10.9†
WKY	Veh		411 ± 75	20.6 ± 4.0	7.4 ± 0.6*	8.9 ± 8.5
WKY	Drug		242 ± 110†	23.2 ± 5.7	6.8 ± 0.8*	17.3 ± 12.2†
SHR	Veh	Slow	192 ± 154	—	4.7 ± 2.0	8.8 ± 15.3
SHR	Drug		138 ± 165	—	4.3 ± 2.2	38.7 ± 24.7
WKY	Veh		112 ± 108	—	4.2 ± 2.0	33.1 ± 33.6
WKY	Drug		45 ± 58	—	4.5 ± 1.9	54.0 ± 19.2
0.1 mg/kg haloperidol						
SHR	Veh	Fast	369 ± 115	28.0 ± 9.8	7.0 ± 1.3	2.4 ± 3.6
SHR	Drug		100 ± 66†	35.6 ± 13.6†	5.1 ± 1.1†	19.2 ± 18.2†
WKY	Veh		437 ± 74	20.1 ± 3.0	8.0 ± 1.1	11.9 ± 12.4
WKY	Drug		102 ± 60†	27.2 ± 7.6†	6.8 ± 1.5†	34.0 ± 23.2†
SHR	Veh	Slow	162 ± 152	—	5.3 ± 2.1	24.4 ± 35.5
SHR	Drug		22 ± 20†	—	—	—
WKY	Veh		136 ± 105	—	4.5 ± 2.0	32.8 ± 22.3
WKY	Drug		9 ± 10†	—	—	—

* Significant difference between the strains irrespective of treatment.
† Significant difference between the treatments irrespective of strain.
‡ Significant difference in the effect of the treatment between the strains.
Abbreviations: Veh. — vehicle; Treat — Treatment; Comp. — component; First Resp. Ratio — First response ratio. Data shown is the mean ± standard deviation. It should be noted that the SD refers to the within group variation and is only relevant to comparisons between the strains and interactions between treatment and strain. All comparisons $p < 0.05$.

spective of strain [fast: $F_{treat}(1, 12) = 41.6$, $p < 0.0001$; slow: $F_{treat}(1, 11) = 9.01$, $p < 0.05$]. There was no effect of this dose of 8-OH-DPAT on the total number of first responses made on the reinf. lever.

The distribution data supported this analysis (see Fig. 4, upper panel). There was a significant increase in the CL_{50}, $F_{treat}(1, 12) = 28.1$, $p < 0.001$, but no difference between the strains. The drug had no effect on the slope of the function, but a difference between the two strains was revealed, $F_{strain}(1, 12) = 5.06$, $p < 0.05$. A significantly increased number of chains of all lengths were completed after treatment with 0.1 mg/kg 8-OH-DPAT, and there were no significant differences between the strains [$\geq$4: $F_{treat}(1, 12) = 6.95$, $p < 0.02$; $\geq$6: $F_{treat}(1, 12) = 45.1$, $p < 0.0001$; $\geq$8: $F_{treat}(1, 12) = 33.2$, $p < 0.0001$; $\geq$10: $F_{treat}(1, 12) = 14.1$, $p < 0.01$].

WAY-100635 (Table 4)

There was no significant effect of a dose of 0.1 mg/kg WAY-100635 (SC 15 min) on the number of responses made in the fast component, and although there was a significant treatment by strain interaction in the slow component, $F_{int}(1, 10) = 5.67$, $p < 0.05$, none of the specific comparisons reached statistical significance. However, in the fast component, time to complete the chain was increased under the drug in both strains, $F_{treat}(1, 10) = 6.10$, $p < 0.05$. The effects of the drug on chain length were complex. In the fast component, the drug had no effect, but the SHR rats had a significantly shorter average chain length than the WKY rats, $F_{strain}(1, 10) = 7.38$, $p < 0.05$. In the slow component there was no significant difference between the strains, but the average chain length was

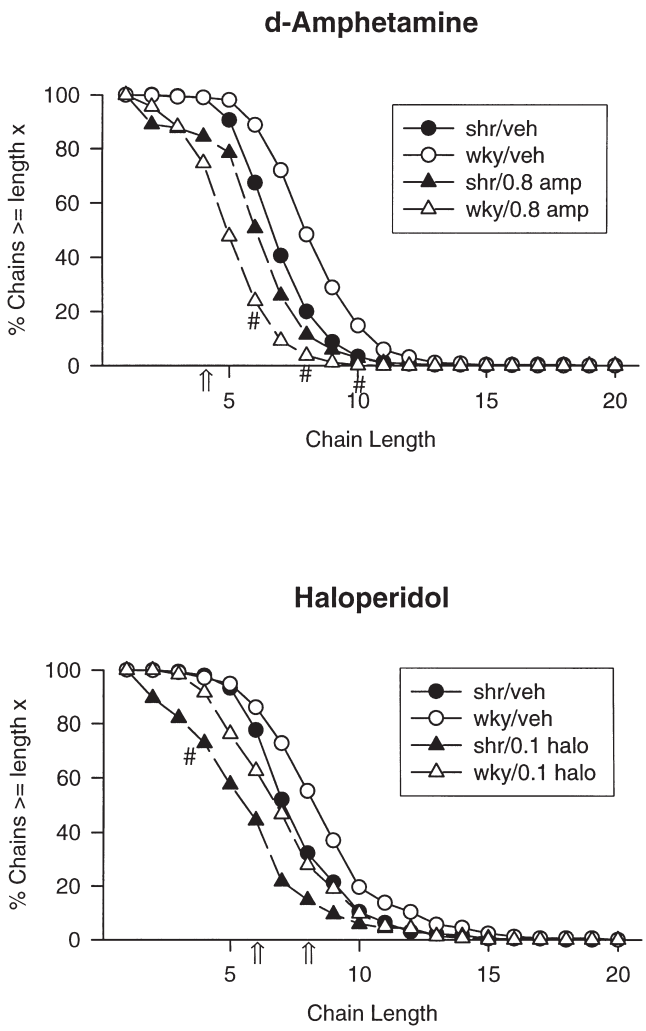

FIG. 3. This shows the distribution of chain of SHR and WKY rats responding under a paced FCN 6 schedule of reinforcement after treatment with *d*-amphetamine (amp, upper panel) and haloperidol (halo, lower panel). For further details, see legend to Fig. 2.

significantly shorter when the rats were treated with WAY-100635, $F_{treat}(1, 9) = 5.42$, $p < 0.05$. There was no difference between the strains or effect of the drug on the proportion of first responses made on the reinf. lever.

When the distribution data for the fast component were analyzed, it was established that the SHR rats had a significantly lower CL_{50}, $F_{strain}(1, 10) = 5.6$, $p < 0.05$, and made significantly fewer chains of lengths ≥ 8 and ≥ 10, $F_{strain}(1, 10) = 8.4$, $p < 0.05$, and $F_{strain}(1, 10) = 5.21$, $p < 0.05$, but there was no effect of the drug treatment (vehicle data shown in Fig. 1, but otherwise data not shown). There were no significant effects of either strain or treatment on the slope of the function.

DOI (Table 4)

The dose of 0.3 mg/kg DOI (SC 15 min) had dramatic effects on performance, which differed somewhat between the two strains. The total number of responses made by the WKY rats in the fast component was significantly reduced by the drug, but there was no effect on the SHR rats, $F_{int}(1, 11) = 21.6$, $p < 0.001$. There was no effect of the drug on either strain in the slow component. Nor was there an effect of the drug on the time to complete the chain in the fast component. There was a similar interaction between strain and treatment on the average chain length in the fast component, $F_{int}(1, 11) = 14.6$, $p < 0.01$. Again, the dose of 0.3 mg/kg DOI significantly shortened the average chain length in the WKY group, but had no effect on the SHR rats. There was a significant main effect of treatment, $F_{treat}(1, 10) = 6.8$, $p < 0.05$, in the slow component. The dose of 0.3 mg/kg DOI reduced chain length for both strains indistinguishably. At this dose, DOI also slightly increased the percentage of first response made on the reinf. lever in the fast component, $F_{treat}(1, 11) = 6.4$, $p < 0.05$. Again, there was no difference between the two strains. Nor was there any significant effect in the slow component.

The effects of 0.3 mg/kg DOI on the response chain distribution can be seen in Fig. 4, lower panel. In general, it can be seen that the drug shifted the distribution of the WKY rats so that it lay parallel with that of the SHR rats, which were not affected by the drug. This was reflected by a significant strain by treatment interaction for the CL_{50}, $F_{int}(1, 10) = 14.8$, $p < 0.01$. There was no difference between the strains in the effects of the drug on the slope of the function, but the SHR rats once more had a significantly steeper slope than the WKY rats, $F_{strain}(1, 10) = 6.07$, $p < 0.05$. There was no effect of DOI on the number of chains ≥ 4 responses or ≥ 10 responses. However, for the intermediate part of the curve, there were statistically significant interactions for the number of chains ≥ 6 and ≥ 8 responses, $F_{int}(1, 10) = 9.95$, $p < 0.05$, and $F_{int}(1, 10) = 12.4$, $p < 0.01$, respectively). In both cases the drug had a selective effect on the WKY rats.

The dose of 1.0 mg/kg DOI (SC 15 min) had similar effects, but greater in magnitude and with similar effects on both strains. (No statistics were carried out on the slow component for this treatment.) In the fast component the total number of responses on the FCN lever was significantly reduced by the drug irrespective of strain, $F_{treat}(1, 12) = 68.5$, $p < 0.0001$. There was an insufficient number of completed chains to measure chain time because 1.0 mg/kg DOI also significantly reduced the average chain length, $F_{treat}(1, 9) = 94.97$, $p < 0.0001$. The percentage of response made first on the food lever was significantly increased by DOI in both strains, $F_{treat}(1, 11) = 19.3$, $p < 0.01$.

The effects of 1.0 mg/kg DOI on the response distribution depended in part upon the baseline level of performance. The number of chains ≥ 4 and ≥ 6 responses in length were equally common in both strains, and were thus equally reduced by the drug, $F_{treat}(1, 8) = 20.7$, $p < 0.01$, and $F_{treat}(1, 8) = 36.5$, $p < 0.001$, respectively. However, the SHR rats made relatively fewer chains ≥ 8 and ≥ 10 responses in length, and thus the finding that the drug only reduced the proportion of such chains in the WKY strain was probably due to a floor effect, $F_{int}(1, 8) = 20.1$, $p < 0.01$, and $F_{int}(1, 8) = 10.9$, $p < 0.05$, respectively. There was an effect of the drug on the CL_{50}, $F_{treat}(1, 8) = 34.3$, but no difference between the two strains. There was a highly significant strain by treatment interaction for the slope measure, $F_{int}(1, 8) = 25.42$, $p < 0.001$. This was indicative of a complete crossover interaction—the SHR rats had a clearly steeper slope than the WKY rats when treated with vehicle, but this became shallower under the drug, whereas the slope of the function for the WKY rats became steeper under the drug (SHR veh, 11.49, WKY veh, 6.13, SHR 1.0 DOI, 6.19, WKY 1.0 DOI, 11.3).

TABLE 4

THE EFFECTS OF 8-OH-DPAT, WAY-100635, AND DOI ON SHR AND WKY RATS RESPONDING UNDER A PACED FCN 6 SCHEDULE OF REINFORCEMENT

Strain	Treat	Comp	Total Resp.	Chain Time (s)	Chain Length	First Resp. Ratio (%)
0.1 mg/kg 8-OH-DPAT						
SHR	Veh	Fast	365 ± 56	25.5 ± 7.4	5.9 ± 0.6	0.8 ± 0.9
SHR	Drug		294 ± 84†	27.2 ± 7.7	7.6 ± 1.4†	0.4 ± 1.0
WKY	Veh		342 ± 145	24.7 ± 10.8	6.7 ± 1.5	12.5 ± 11.8
WKY	Drug		270 ± 107†	26.4 ± 15.1	9.2 ± 2.2†	15.6 ± 21.6
SHR	Veh	Slow	189 ± 137	—	4.6 ± 1.6	10.9 ± 13.9
SHR	Drug		35 ± 15	—	5.6 ± 2.3†	13.5 ± 20.4
WKY	Veh		79 ± 98	—	4.6 ± 1.0	33.7 ± 35.4
WKY	Drug		36 ± 42	—	5.5 ± 0.7†	14.8 ± 21.8
0.1 mg/kg WAY-100 635						
SHR	Veh	Fast	264 ± 103	25.6 ± 10.4	6.0 ± 0.8	26.9 ± 32.0
SHR	Drug		294 ± 110	28.9 ± 13.1†	6.1 ± 0.6	14.5 ± 20.9
WKY	Veh		326 ± 161	19.0 ± 2.7	7.4 ± 1.0*	16.4 ± 13.2
WKY	Drug		327 ± 155	22.1 ± 5.1†	7.2 ± 1.2*	14.4 ± 9.5
SHR	Veh	Slow	83 ± 88		4.0 ± 2.4	55.6 ± 24.1
SHR	Drug		35 ± 16		3.9 ± 2.2†	50.4 ± 24.1
WKY	Veh		80 ± 83		5.0 ± 2.11	30.7 ± 20.0
WKY	Drug		14 ± 10		3.5 ± 1.2†	27.4 ± 20.9
0.3 mg/kg DOI						
SHR	Veh	Fast	328 ± 100	23.8 ± 8.8	5.6 ± 0.4	2.6 ± 2.6
SHR	Drug		294 ± 74	23.5 ± 7.1	5.1 ± 0.6	7.8 ± 7.7†
WKY	Veh		397 ± 96	19.4 ± 3.5	7.2 ± 0.9	11.9 ± 11.5
WKY	Drug		144 ± 109‡	19.6 ± 3.1	4.6 ± 1.5‡	41.1 ± 28.6†
SHR	Veh	Slow	152 ± 148	—	4.1 ± 1.6	37.6 ± 36.5
SHR	Drug		127 ± 116	—	3.2 ± 1.4†	50.1 ± 32.9
WKY	Veh		92 ± 105	—	4.1 ± 2.0	38.6 ± 27.0
WKY	Drug		25 ± 32	—	2.3 ± 1.2†	63.9 ± 26.6
1.0 mg/kg DOI						
SHR	Veh	Fast	376 ± 86	25.4 ± 9.4	6.1 ± 0.4	3.3 ± 6.8
SHR	Drug		116 ± 77†	—	3.9 ± 0.9†	41.9 ± 21.0†
WKY	Veh		347 ± 156	20.7 ± 4.7	7.3 ± 1.8	17.8 ± 17.5
WKY	Drug		45 ± 57†	—	4.3 ± 1.2†	55.7 ± 37.8†
SHR	Veh	Slow	145 ± 143	—	4.3 ± 1.4	45.4 ± 31.9
SHR	Drug		40 ± 29	—	—	—
WKY	Veh		92 ± 106	—	3.8 ± 1.6	35.0 ± 27.0
WKY	Drug		9 ± 11	—	—	—

* Significant difference between the strains irrespective of treatment.
† Significant difference between the treatments irrespective of strain.
‡ Significant difference in the effect of the treatment between the strains.
Abbreviations: Veh. — vehicle; Treat — Treatment; Comp. — component; First Resp. Ratio — First response ratio. Data shown is the mean ± standard deviation. It should be noted that the SD refers to the within group variation and is only relevant to comparisons between the strains and interactions between treatment and strain. All comparisons $p < 0.05$.

DISCUSSION

SHR rats entered the food tray more during initial training and pressed the levers more during FR 1 training than did the WKY rats. Decreased neophobia has been reported previously in this strain by (2). Furthermore, SHR rats have been reported to show increased rates of responding during schedules of intermittent reinforcement [FI 120s, (17)]. However, the SHR rats proved more difficult to train on FCN, with two of eight rats failing to show adequate performance under paced FCN 4 schedule, with the result that it was necessary to omit them from the drug studies. Throughout the drug experiments there was tendency for the SHR rats to make fewer long chains in the fast component, a difference that was statistically supported in several of the drug experiments, despite the small number of subjects involved. Similarly, the SHR rats generally showed a steeper slope of response chain distribution function, indicating less variability in the chain length, which may also have impaired the ability to adjust when the chain length was increased during training. (It is worth noting that the experiments with the drugs revealed that the slope of the function and the CL_{50} varied independently of one another.) Given that the SHR rats show no apparent deficit in motivation or motoric impairments, as shown by the total number of responses completed and the average time to complete a six-response chain, and no impairment in task comprehension, as demonstrated by the lower variability, it seems reasonable to hypothesize that this behavior pattern is an example of increased impulsive behavior in the SHR strain com-

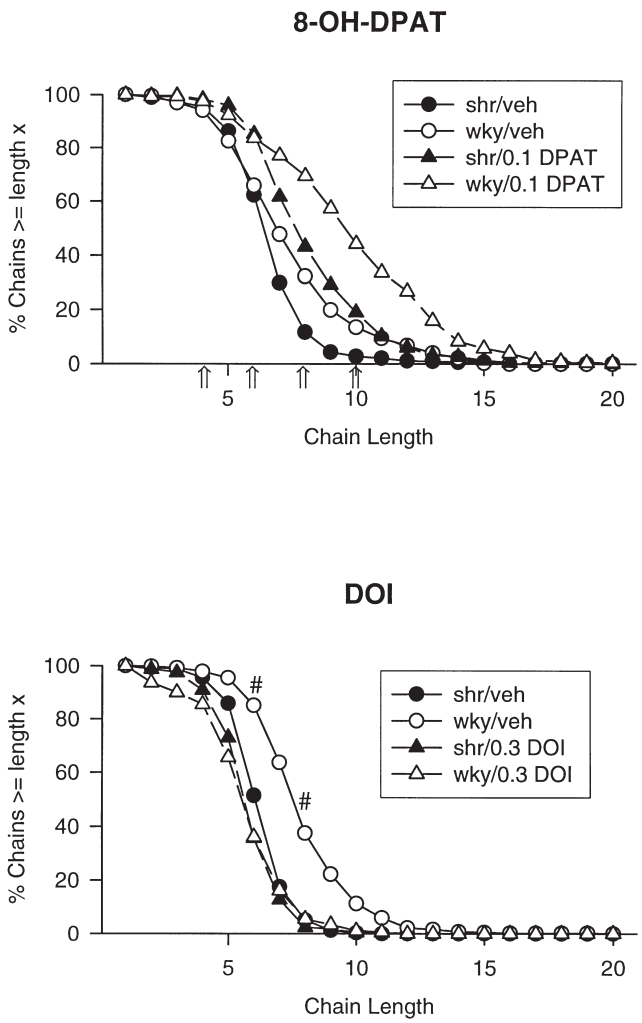

FIG. 4. This shows the distribution of chain of SHR and WKY rats responding under a paced FCN 6 schedule of reinforcement after treatment with 8-OH-DPAT (DPAT, upper panel) and DOI (lower panel). For key, see legend to Fig. 2.

pared to the WKY strain. It is also important to note that the WKY strain showed a similar pattern of behavior in terms of learning and performance parameters as other rat strains (Sprague–Dawley and Lister Hooded) previously used in the paced FCN procedure (4,5). It is also worth noticing, however, that there is some evidence that the SHR rats were less affected by being forced to respond more slowly in the slow component. In this component there was never any significant difference in the average chain length, unlike in the fast component, and there was a general tendency for the SHR rats to make more responses, which reached statistical significance in two of the drug studies. It is unclear what this means, but Sagvolden and colleagues (18) have demonstrated that SHR rats have a tendency to overrespond when food delivery is stopped (extinction). Resistance to extinction might help the SHR rats to continue responding when conditions were suboptimal as they clearly were in the slow component. The relatively small numbers of responses made by the WKY rats in this component, especially after drug treatment, mean that in some caution must be exercised in interpreting the data from

TABLE 5

SIMILARITIES AND DIFFERENCES IN THE EFFECTS OF THE CHALLENGE DRUGS PERFORMANCE OF SHR AND WKY RATS UNDER A PACED FCN 6 SCHEDULE OF REINFORCEMENT MEASURED BY RESPONSE RATE AND CHAIN LENGTH

Drug Tested	Total Responses			Chain Length		
	SHR		WKY	SHR		WKY
imipramine	–		–	↑		↑
CDP	–	<	↓	–	<	↓
d-Amphetamine	↓		↓	↓	<	↓*
Haloperidol	↓		↓	↓	>	↓*
8-OH-DPAT	↓		↓	↑		↑
WAY 100 635	–		–	–		–
DOI	–	<	↓	–	<	↓

The table summarizes the data from the Fast component.

Key ↑ increase, – no change, ↓ small reduction, ↓ large reduction, < or > significant difference in response to the treatment between strains.

* From distribution analysis.

the slow component. The major conclusions discussed below are all based on data from the fast component (see Table 5).

The general effects of the drugs on responding under the paced FCN 6 schedule were similar to those previously reported on a paced FCN 8 schedule using Sprague–Dawley or Lister Hooded rats (Table 5), and a more detailed discussion of the effects all the drugs used here on paced FCN and related schedules of reinforcement may be found in elsewhere (4,5). Briefly, 10.0 mg/kg imipramine slightly reduced the response rate and significantly increased the average chain length. This effect has now been seen in all four rat strains tested using paced FCN schedules. Chlordiazepoxide, at a minimum effective dose of 10.0 mg/kg, reduced the total number of responses and the average chain length, but only in the WKY rats (see below). *d*-Amphetamine significantly reduced the number of responses and the average chain lengths, but the effect on the WKY strain was greater. As previously reported (4,5), haloperidol at a dose of 0.1 mg/kg significantly reduced response rate and reduced the average chain length. The effect on the chain length distribution was somewhat greater in the SHR strain (Fig. 3). A dose of 0.1 mg/kg 8-OH-DPAT significantly reduced the total number of responses, but increased the average chain length. The effect was similar in both strains, and has been reported previously in Lister Hooded rats (5). WAY 100635, at a dose of 0.1 mg/kg, had little effect on the total number of responses. The drug slightly reduced the average chain length but only in the slow component. A similar, small, but consistent effect was also found by Evenden (5). DOI had a greater effect on the WKY rats than on the SHR rats. The total number of responses and the average chain length were both reduced by the drug.

The main difference in drug response between the strains concerned the two dopaminergic agents, the indirect agonist, *d*-amphetamine, and the D_2 antagonist haloperidol. Essentially the SHR rats were less sensitive to *d*-amphetamine than the WKY rats, and somewhat more sensitive to haloperidol. In both cases, this strain difference was revealed best in the analysis of the chain length distribution. Both *d*-amphetamine and haloperidol reduce the average chain length, so it is hard to argue that both an increase and a decrease in sensitivity are secondary to the small but consistent difference in baseline

performance between the two strains. The relative difference in sensitivity to the two drugs is more likely to arise from their opposing pharmacological effects on the dopaminergic systems. As noted in the introduction, several authors have found biochemical evidence of a deficit in dopaminergic function in SHR rats. Russell et al. (16) used a superfusion technique and found that electrically stimulated release of dopamine was slightly but significantly reduced in the prefrontal cortex and caudate-putamen of the SHR rats, but not in the nucleus accumbens. Similar effects in striatum had previously been reported by Tsuda et al. (21). Watanabe et al. (26) also found an increase in brain dopamine transporter in the caudate putamen of SHR rats using the radioligand [^{125}I]β-CIT. The diminished response to amphetamine and slightly exaggerated response to haloperidol found in the present study also suggest that the dopamine systems may be deficient in some way such that they are especially vulnerable to blockade of D_2 receptors and fail to respond the dopamine-releasing effects of amphetamine. Together, these findings suggest that hyperactivity and an impulsive execution of behavioral chains are compatible with an alteration in dopamine function, possibly at the level of release and reuptake of the neurotransmitter. The exact relationship between the biochemical and behavioral changes, if any, is unknown, although it has been speculated that a prefrontal cortical dopaminergic deficit may be most important (24). On the other hand, pharmacological effects of amphetamine and dopaminergic blockade resembling those seen in the present study are often mediated by the nucleus accumbens (6).

Of the other drugs, CDP had selective effects on the WKY rats, in that it reduced the total number of responses (i.e., the rate of responding) in this strain, and reduced the average chain length. The selective effect on rate of responding cannot be due to a difference in baseline, because on the baseline the two strains made the same number of responses. There is no reason to suppose the effect is secondary to the reduction in chain length, because such an association was not evident in the case of the other drugs tested. The effects of benzodiazepines on the behavior of SHR and WKY rats has been little studied, but evidence for a dysfunction in the $GABA_A$ receptors of the SHR rat comes from studies on the effects of chlordiazepoxide and the $GABA_A$ agonist, muscimol, on blood pressure (19,22) and reduced $GABA_A$ receptor binding in the amygdala and hypothalamus of SHR rats (1,7,11), all suggesting reduced GABA activity in the SHR rat. In contrast, muscimol produced a greater inhibition in pituitary vasopressin release in SHR rats (13).

Four agents acting on the serotonin system were examined in this study. Of these imipramine, 8-OH-DPAT and WAY-100635 had the same effects as reported previously, and these did not differ significantly between the strains. The results are consonant with the lack of difference in the number of 5-HT_{1A} receptors in hippocampus (postsynaptic) and midbrain (somatodendritic autoreceptors) measured using [^{3}H]-8-OH-DPAT reported by Kulikov et al. (12), and using Lewis rats as the control. In contrast, 0.3 mg/kg DOI, a 5-HT_2 agonist, reduced the total number of responses made by WKY rats, and also reduced the average chain length produced by these rats. On neither measure were the SHR rats affected by this dose. Although it is possible to argue that the effect of this dose of DOI is secondary to a floor effect in the SHR strain, a genuine difference in the pharmacological response cannot be ruled out. Kulikov et al. (12) found that DOI produced a significantly greater number of head shakes in SHR rats in the dose range employed in the present study, although these authors found no difference in the number of 5-HT_2 receptors, this time measured by [^{3}H] ketanserin binding in frontal cortex and striatum.

Finally, these data demonstrate that it is possible to have an impulsive behavioral profile associated with a decreased sensitivity to testosterone, because both of these are evident in the SHR strain (14,25). Together with recent findings that chronic treatment with supraphysiological doses of testosterone does not affect performance in the paced FCN procedure (3), the results of this study support the proposition that testosterone is not involved in the regulation of appetitively motivated impulsive behavior.

In summary, SHR rats showed a behavioral pattern in this study of impaired acquisition of long chain requirements under a paced FCN schedule, and a consistently lower average chain length during performance. The SHR strain showed lower sensitivity to *d*-amphetamine, chlordiazepoxide, and DOI, and increased sensitivity to haloperidol, suggesting differences in dopaminergic, GABA-ergic and 5-HT_2 receptor-mediated serotonergic function. These results suggest that the dopaminergic deficit identified in biochemical studies is compatible with a syndrome of hyperactivity and impulsive behavior, which has previously led to this strain being employed as an animal model of ADHD. Strain differences in the effects of CDP and DOI suggest it is worth continuing to pursue other biochemical mechanisms that may influence this behavior.

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