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Effects of Chlorpromazine and Diazepam on Time Estimation Behavior and Motivation in Rats

S. A. FERGUSON[1] AND M. G. PAULE

Division of Neurotoxicology, National Center for Toxicological Research, 3900 NCTR Road, Jefferson, AR 72079

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FERGUSON, S. A. AND M. G. PAULE. *Effects of chlorpromazine and diazepam on time estimation behavior and motivation in rats.* PHARMACOL BIOCHEM BEHAV **53**(1) 115–122, 1996.—The effects of chlorpromazine and diazepam on performance of two operant tasks, one modelling time estimation and the other motivation to work for food reinforcers, were investigated in rats. These same tasks had been used previously in rhesus monkeys to assess the effects of chlorpromazine and diazepam. Rat performance of the time estimation task [temporal response differentiation (TRD)] was nearly identical to that previously described in monkeys. This performance similarity across these two species occurred despite slightly different methodologies. Performance of the motivation task [progressive ratio (PR)] was clearly different between rats and adult monkeys in that rats exhibited lower values on all PR endpoints. Acute administration of chlorpromazine [0.03–5.6 mg/kg, intraperitoneally (IP)] caused decrements in rat TRD and PR performance at doses $\geq$1.0 mg/kg. Acute administration of diazepam (0.25–4.0 mg/kg, IP) altered TRD performance only. The effects of chlorpromazine and diazepam in rats were similar to those previously noted in the monkey, indicating the potential utility of rat performance in these operant tasks to predict drug effects in the rhesus monkey.

Operant test battery Progressive ratio Chlorpromazine Diazepam Motivation Time estimation Temporal response differentiation

THE NATIONAL CENTER for Toxicological Research (NCTR) operant test battery (OTB) has been used to evaluate the cognitive performance of children (18) and rhesus monkeys [see (14) for a general description] on five tasks that are thought to model different central nervous system (CNS) functions. Cross-species comparisons indicated that OTB performance of well-trained rhesus monkeys is nearly identical to that of 4- to 8-year-old children (19), suggesting extremely close parallels in certain aspects of brain function. In that report, it was suggested that operant behaviors in other animals may also serve as useful models of complex brain function (19). Because OTB performance has been previously investigated in two primate species (i.e., the child and the rhesus monkey), modeling these neurobehavioral functions in a nonprimate animal model could provide greater insight into cross-species comparisons of operant performance. Accordingly, the current study reports on the use of similar operant paradigms in rats, comparing baseline performance and performance after acute drug administration to that previously described for rhesus monkeys.

Cross-species comparisons of operant behavior can be particularly useful in pharmacology and toxicology, especially when human and/or monkey performance can be compared with that of rodents. Certain evaluations (e.g., neurochemical, neurohistological) are more easily conducted in rodents than primates. If rodents and monkeys exhibit similar performance on identical operant tasks and the administration of pharmacological compounds alters performance similarly, future investigations can then search for similar neurological processes controlling such behavior. As an initial step in this direction, Pang and colleagues (13) described similar performance between rats and humans on an attentional task and suggested that rats could potentially be used to examine neuronal mechanisms underlying attentional processes.

[1] Requests for reprints should be addressed to S. A. Ferguson, Ph.D., Division of Reproductive & Developmental Toxicology, National Center for Toxicological Research, 3900 NCTR Road, Jefferson, AR 72079. E-mail: sferguson@fdant.nctr.fda.gov

For comparison to previously described monkey performance, two tasks were chosen from the NCTR OTB for use in the current study: the temporal response differentiation (TRD) and progressive ratio (PR) tasks. The TRD task is thought to model time estimation behavior (14), although it differs from performance in differential reinforcement of low response rate (DRL) schedules that are typically used to assess this type of behavior. In the TRD task, subjects must initiate and maintain a response for a specific period of time, rather than withhold responding for a specific period of time as in DRL schedules. TRD behavior has rarely been assessed in rats (but see Refs. 9 and 10 for a similar task, and Ref. 2); however, TRD behavior in rhesus monkeys has been studied in this laboratory for several years. To date, the only cross-species comparison on timing behavior is an early report (10) describing human, monkey, and rat performance. In that study, however, the time estimation required was 1.00–1.27 s whereas in our laboratory, the time estimation required is significantly longer (10–14 s). Finally, McMillan and Patton (10) used different reinforcers for rats and monkeys (water and food, respectively). Here, the reinforcer was food for both species.

The PR task is thought to model motivation to work for reinforcers [food pellets in the previous monkey studies and money (nickels) in the previous human studies] in that the subject must make an increasing number of responses for each subsequent reinforcer. Rat PR performance as an index of motivation has been studied previously (7,8,28); however, a cross-species comparison has not been previously reported.

In addition to extensively describing rhesus monkey operant performance, the NCTR monkey OTB has been used in a variety of psychopharmacological assessments. Those studies have demonstrated the differential sensitivity of the five OTB tasks in rhesus monkeys to the acute effects of a variety of psychotropic agents (e.g., caffeine, pentobarbital, physostigmine, phencyclidine, MK-801, cocaine, *d*-amphetamine, morphine, Δ-9-tetrahydrocannabinol, marijuana smoke, diazepam, and atropine) (1,4,16,19,20–27), indicating that such compounds affect neurobehavioral functions in unique ways (see Ref. 14 for a discussion).

Whether such compounds might differentially affect rat neurobehavioral functions in a manner similar to that previously described in the monkey was of particular importance for the current study. The phenothiazine chlorpromazine and the benzodiazepine diazepam were selected for investigation because of their effects on TRD and PR performance in the monkey. Specifically, TRD and PR behavior were equally sensitive to the acute effects of chlorpromazine (3); however, TRD behavior was more sensitive to disruption by diazepam administration than was PR behavior (27). Such a psychopharmacological comparison of drug effects on rat and primate behavior using identical tasks modeling time estimation and motivation has not been previously reported.

The acute effects of chlorpromazine and diazepam on forelimb and hindlimb grip strength were also measured in the rat as a general indication of motor effects. Similar assessments were not performed as part of the previous monkey studies; however, such measurements in the rat have been described as providing valuable information about fore- and hindlimb neuromuscular function, particularly with regard to the effects of psychopharmacological compounds (11). Thus, if performance of the operant tasks indicated drug-induced impairments, grip strength data allowed concomitant assessments of the fore- and hindlimb neuromuscular alterations caused by these drugs. In addition, these measurements allowed an evaluation of whether drug-induced operant deficits might be related to a more generalized drug effect on neuromuscular dysfunction.

METHODS

Subjects

The subjects were six male Sprague–Dawley rats (nonlittermates) obtained from the NCTR breeding colony. Subjects were individually housed at weaning [postnatal day (PND) 21] in standard plexiglas cages lined with wood chips with ad lib access to water. The housing room was maintained on a 12 : 12 hour light cycle, and temperature and humidity were maintained at 21°C and 45–55%, respectively.

Apparatus

All operant test sessions were conducted in two identical operant behavior chambers with internal measurements of 24.8 × 22.9 × 21.0 cm. Each chamber contained a front panel instrumented with two retractable response levers, each positioned below a stimulus light and separated by a reinforcer trough. Individual chambers were inside a sound-attenuated box. Reinforcer (45 mg dustless precision food pellet, Bio-Serve, Frenchtown, NJ) delivery was accompanied by the noise of the pellet dispenser operation and illumination of a light above the reinforcer trough. Each chamber and panel were controlled by a microcomputer, which administered the behavioral tasks and recorded the behavioral responses.

Forelimb and hindlimb grip strength were measured using a push–pull strain gauge apparatus (Chatillon Model DPP, San Diego Instruments, San Diego, CA) (see Ref. 11 for a description of the apparatus).

Behavioral Procedure

Operant testing. Beginning on PND 70, subjects were gradually food-deprived to 80–85% of their free-feeding weights and maintained at this weight throughout the experiment. On PND 90, training for the TRD task began, and after a specific criterion (i.e., subjects were working at a minimum 7 s duration lever hold) was achieved on that task, training for the PR task began. Details of the training and final parameters for these tasks are described in Ferguson et al. (2). All subjects were performing under the final TRD and PR parameters by PND 170. Each test session was 50 min (40 min for the TRD task and 10 min for the PR task) and sessions were conducted Monday through Friday at the same time each day and in the same operant chamber for individual subjects.

Grip strength. Beginning on PND 150, forelimb and hindlimb grip strengths were measured three times a week (Tuesday, Thursday, and Friday) immediately after completion of operant testing. Each rat was placed on the apparatus and pulled gently by the tail until its forelimbs first grasped and then pulled away from the forward-facing bar. The subject was then pulled by the tail until its hindlimbs contacted, grasped, and released the rear bar. Three trials were conducted per test day and the daily means were used in the data analyses.

TRD

The TRD task was identical to that previously described for rats (2) and to that used in the NCTR operant test battery (see Refs. 3 and 4 for details). Here, the left lever was extended (the right lever was retracted) and the stimulus light above it

was on. Subjects were required to hold the lever in the depressed position for a minimum of 10 s but no longer than 14 s. Releasing the lever within this 4 s window resulted in reinforcer delivery; releasing the lever too early or too late ended the ongoing trial, after which the subject could immediately begin another trial. The maximum number of reinforcers allowed during any TRD session was 120. The TRD task ended if subjects obtained the maximum number of reinforcers or 40 min had elapsed.

PR

The PR task was identical to that previously used in rats (2) and to that used in the NCTR operant test battery (see Refs. 3 and 4 for details). Here, the right lever was extended (the left lever was retracted) and the stimulus light above it was on. Initially, one or two lever presses (depending upon the individual subject but the same for each subject every test day) resulted in reinforcer delivery. The number of responses required for the next reinforcer was increased by the initial number of lever presses required for the first reinforcer. Thus, if two lever presses were required for the initial reinforcer, four lever presses were required for the next, then six, eight, and so forth. The ratio increments were chosen such that marked periods of pausing generally occurred during each baseline or vehicle PR session. The PR task began immediately after the TRD task and lasted 10 min. Subjects rarely earned more than 30 reinforcers during any PR session (maximum number of reinforcers allowed during any PR session was 120).

Drug and Dosing Procedure

Beginning on PND 251, each subject was injected intraperitoneally (IP) with physiological saline on Tuesdays, Thursdays, and Fridays 15 min prior to operant testing as a control for chlorpromazine injections. Beginning on PND 380, each subject was similarly injected with the vehicle for diazepam [propylene glycol 40%, EtOH 10%, benzyl alcohol 1.5%, benzoic acid in water (0.015 mg/ml) 48.5%] on Tuesdays, Thursdays, and Fridays 15 min prior to operant testing as a control for diazepam injections. Drug (chlorpromazine or diazepam) injections were given 15 min prior to operant testing on Tuesdays and/or Fridays while vehicle injections were given on Tuesdays, Thursdays, and/or Fridays. Testing without prior injection was conducted on Mondays and Wednesdays. The chlorpromazine portion of the study was completed prior to beginning the diazepam portion of the study.

Chlorpromazine (Sigma Chemical, St. Louis, MO) was dissolved in saline so that the final injection volume was 1.0 ml/kg. Doses of chlorpromazine (0.03, 0.1, 0.3, 1.0, 3.0, and 5.6 mg/kg) were injected IP and administered in a randomized order and all doses were given twice. After the last dose, subjects continued to receive IP injections of saline on Tuesdays, Thursdays, and Fridays for 2 weeks.

Diazepam (Elkins-Sinn, Inc., Cherry Hill, NJ) was diluted with vehicle such that the final injection volume was 1.0 ml/kg. Doses of diazepam (0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg) were injected IP and administered in a randomized order and all doses were given twice. After the last diazepam dose, subjects continued to receive IP injections of vehicle on Tuesdays, Thursdays, and Fridays for 2 weeks.

Behavioral Endpoints

Endpoints measured in the operant tasks were identical to those used in the NCTR OTB (3,4) and included: percent task completed (PTC), response rate (RR), accuracy (TRD only), duration of lever hold (TRD only), and breakpoint (PR only).

PTC. The PTC data were measures of a predetermined performance criteria and are functions of both RR and response accuracy (ACC). The PTC measure for each task was calculated by dividing the total number of reinforcers delivered by 120 (the maximum number of reinforcers possible for each task) and multiplying this quotient by 100. The PTC endpoint is a convenient and comprehensive measure showing intra-animal stability in rhesus monkeys and has proven useful for comparing drug effects on performance across tasks (14).

RR. RRs were calculated by dividing the total number of lever presses by the total task time (in seconds).

ACC. ACCs were calculated for the TRD task by dividing the total number of correct lever holds by the total number of lever holds and multiplying this quotient by 100. ACC was not applicable for the PR task (i.e., no incorrect responses were possible).

Duration of lever hold. Duration of lever hold was calculated for the TRD task by dividing the cumulative duration of lever holds (in seconds) by the total number of lever presses.

Breakpoint. For the PR task, breakpoint was defined as the number of lever presses made for the last reinforcer earned.

Grip strength. Forelimb and hindlimb grip strengths (in kg) were averaged over the three trials/test day, providing a single forelimb and single hindlimb measurement/test day.

Statistical Analysis

Between the end of the chlorpromazine portion of the study and the beginning of the diazepam portion of the study, one subject died of unrelated causes. Another subject died of unrelated causes after receiving only one of each of the test doses of diazepam. Data for those test sessions for this animal were similar to those of other subjects receiving the same dose; thus, these data (one test session/dose, rather than two) were included in the analyses.

Separate repeated measures analyses of variance (ANOVAs) were conducted for the chlorpromazine and diazepam portions of the study. Data from the two drug sessions at each dose were pooled and the mean of these two sessions was used in statistical analyses. All rats exhibited stable preexposure baselines for the TRD and PR tasks and for grip strength assessments. As in previous monkey studies, stable performance was defined as that having a standard error of less than 15% of the mean for saline or vehicle sessions. For TRD data to be included in the accuracy analyses, a minimum of three trials (i.e., three lever presses) must have been completed. For each behavioral endpoint in each task, the overall effect of drug treatment on performance was determined using a one-way repeated measures ANOVA. Thus, for the chlorpromazine portion of the study, there were 10 separate repeated measures ANOVA (TRD PTC, PR PTC, TRD ACC, PR RR, etc.). If overall significance was evident ($p < 0.05$), then performance at each dose was compared to vehicle performance using a Bonferroni correction (12).

RESULTS

Overall Effect of Control Injections

When compared to baseline (noninjection) data, vehicle injections during both the chlorpromazine and diazepam portions of the study produced no statistically significant effects on any of the endpoints examined.

TRD Task

Chlorpromazine effects. Chlorpromazine produced significant decreases in TRD performance at doses of 3.0 and 5.6 mg/kg in PTC, RR, accuracy, and mean duration of lever hold (see Table 1 and Fig. 1). Doses lower than 3.0 mg/kg had no significant effects on any TRD measure.

Diazepam effects. Diazepam produced a significant dose-dependent decrease in PTC at the 2.0 mg/kg dose; performance at 4.0 mg/kg was also decreased but increased variability at this dose prevented demonstration of a significant effect (see Table 2 and Fig. 3). RR was unaffected at any dose. Accuracy and mean duration of lever press were decreased at 4.0 mg/kg; however, increased variability at this dose also prevented the demonstration of significant effects.

PR Task

Chlorpromazine effects. Chlorpromazine produced significant dose-dependent decreases in PTC at doses of 1.0, 3.0, and 5.6 mg/kg (see Table 1). RR and breakpoint were also significantly decreased at doses of 3.0 and 5.6 mg/kg.

Diazepam effects. PTC, RR, and breakpoint were not significantly affected by any dose of diazepam tested (see Table 2).

Grip Strength

Chlorpromazine effects. Both forelimb and hindlimb grip strengths were dose-dependently decreased by chlorpromazine. This effect was significant at the highest dose of 5.6 mg/kg (see Table 1).

Diazepam effects. At 4.0 mg/kg, diazepam significantly decreased forelimb grip strength; hindlimb grip strength was unaffected by any dose tested (see Table 2).

Comparison to Monkey Data

Vehicle data from the corresponding monkey studies (3,27) are reprinted in Figs. 2 and 4 and Tables 1 and 2 for the sake of comparison.

DISCUSSION

Rat performance of two tasks contained in the NCTR OTB after acute administration of chlorpromazine or diazepam was assessed and compared with data from earlier studies of performance on identical tasks by rhesus monkeys. In the TRD task that which is thought to model time estimation, baseline performance of rats was very similar to that of well-trained rhesus monkeys. In the PR task that is thought to model motivation to work for food reinforcers, baseline RRs and breakpoints for rats were similar to those of adolescent monkeys but less than half those of adult monkeys. Acute administration of chlorpromazine or diazepam produced significant alterations in rat TRD and PR behavior. The order of sensitivity across these two tasks was similar in the rat and monkey models for diazepam administration; specifically, TRD performance was more sensitive to disruption than was PR performance. In the rat, chlorpromazine administration appeared to affect PR performance at a lower dose than that which altered TRD performance. Fore- and hindlimb grip strength assessments demonstrated that alterations in operant behavior occurred at doses lower than those causing grip strength decreases.

Rats performed the TRD task under the same parameters and exhibited nearly identical performance as well-trained monkeys. This might imply that performance of this time estimation behavior (i.e., lever press of 10–14 s) is controlled by similar neurological processes in these two species. Acquisition of a shorter, but more precise, time estimation response also appears similar between rats and monkeys. When maintenance of a 1.00–1.27 s bar press was the correct response, rats and monkeys acquired and performed the response similarly (10). In the current study, rats and monkeys also exhibited similar types of errors; that is, both species made very few responses of 2–8 or 14–16 s duration. Most responses were either less than 1 s or in the correct range.

McMillan and Patton (10) described a "least effort" effect displayed by rats performing their very short time discrimination task. Specifically, rat performance was characterized by a mean duration of hold that was only slightly above the required minimum duration of 1.00 s, whereas monkeys averaged a slightly longer hold duration although it was still less than the maximum correct hold of 1.27 s. In the current and previous studies using a 10–14 s discrimination, neither rats nor monkeys exhibited mean durations of hold within the required response range of 10–14 s due to bursts of very short duration lever presses (see Figs. 1–4). If observations are restricted to lever holds within the accurate range (10–14 s), the most frequent responses occurred in the 10–11 s range (see Figs. 1 and 3). This could be interpreted to indicate a similar "least effort" response behavior in rats; however, a similar effect was apparent in monkeys (4).

Unlike TRD performance, PR performance appeared strikingly different between rats and adult rhesus monkeys. In monkeys, a developmental shift in PR performance seems to occur during maturation that may be similar to the cognitive changes that occur at adolescence in humans (6). Alternatively, there may be an effect of PR training history. Specifically, adolescent monkeys do not exhibit the relatively high RRs and breakpoints noted in adult monkeys with a relatively long history of PR responding (15). The data listed in Table 2 were obtained from adolescent monkeys (i.e, 3–6 years of age; 27). Some of those same subjects served in the chlorpromazine study at 6–10 years of age and exhibited adult-type PR performance (see Table 1 and Ref. 3). Thus, PR performance by rats is more similar to that of adolescent monkeys; adult monkeys with a long history of PR performance exhibit much higher RRs and breakpoints.

Task presentation order did not appear to be responsible for the PR performance differences noted between monkeys and rats. PR was the second task presented in the rat OTB, although it was the first task presented in the monkey OTB. However, reinforcers earned on the first task do not seem to have a satiation effect on performance of the following task(s). Additionally, we found that substantial prefeeding 0.25–6 h prior to OTB assessment in rats had no significant effect on performance of either the TRD or PR task (5). Thus, the number of TRD reinforcers earned probably has little effect on PR performance, indicating that task presentation order contributes little to the species differences observed here.

Gross anatomical differences between the rat and the monkey do not seem to affect TRD responding; however, they do appear to influence PR responding. Anecdotal observations of adult monkeys performing under a PR schedule indicate that all four limbs are used to maintain a high rate of responding (i.e., when an arm appears to tire, a foot or the other arm may replace it and responding continues). In addition, monkeys can maintain responding with a foot while retrieving a reinforcer with a hand. Such responding is impossible for the rat in the current apparatus and observations of PR re-

TABLE 1

DOSE OF CHLORPROMAZINE (mg/kg)

	Monkey Saline*	Rat Saline	0.03	0.10	0.30	1.0	3.0	5.6
Temporal response differentiation (n = 6)								
PTC	39.38 ± 1.70†	63.99 ± 5.52	68.05 ± 6.82	67.78 ± 8.17	65.14 ± 7.41	47.99 ± 14.72	18.26 ± 6.36‡	7.99 ± 6.43‡
RR (resp/s)	0.13 ± 0.03	0.09 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	0.07 ± 0.02	0.05 ± 0.01‡	0.01 ± 0.00‡
ACC	38.19 ± 4.83	38.17 ± 3.22	42.60 ± 4.94	39.67 ± 4.12	40.74 ± 5.76	31.43 ± 9.06	16.82 ± 4.63‡	8.65 ± 5.58‡
Mean duration of lever hold (s)	7.11 ± 0.69	7.69 ± 0.54	8.08 ± 0.71	7.77 ± 0.51	7.94 ± 0.67	6.36 ± 1.41	5.07 ± 0.74‡	2.70 ± 0.67‡
Progressive ratio (n = 6)								
PTC	18.75 ± 1.48	20.86 ± 1.82	20.00 ± 1.89	20.42 ± 1.27	20.69 ± 1.62	16.90 ± 2.37‡	13.05 ± 1.31‡	5.07 ± 1.61‡
RR (resp/s)	2.40 ± 0.43	0.93 ± 0.20	0.78 ± 0.22	0.75 ± 0.15	0.78 ± 0.20	0.59 ± 0.22	0.34 ± 0.09‡	0.14 ± 0.09‡
Breakpoint	104.64 ± 16.15	34.38 ± 7.14	33.67 ± 7.88	33.08 ± 6.01	33.92 ± 6.90	28.28 ± 7.26	21.08 ± 4.19‡	9.58 ± 4.01‡
Grip strength (n = 6)								
Forelimb	N/A	0.89 ± 0.06	0.83 ± 0.07	0.91 ± 0.07	0.87 ± 0.08	0.87 ± 0.04	0.80 ± 0.05	0.61 ± 0.05‡
Hindlimb	N/A	0.92 ± 0.07	0.90 ± 0.06	0.91 ± 0.10	0.91 ± 0.07	0.89 ± 0.06	0.82 ± 0.03	0.52 ± 0.05‡

*Data exhibited by adult monkeys (Ref. 3) (n = 4 for the TRD task and n = 7 for the PR task) (see discussion for explanation of adolescent vs. adult monkey PR performance).

†The TRD PTC measure was calculated by dividing the total number of reinforcers delivered by 120 (the maximum number of reinforcers possible) and multiplying this quotient by 100. Because the duration of the TRD task for the monkey is one-half the length as that in the rat (monkey TRD 20 min, rat TRD 40 min), the apparent difference in PTC is due primarily to the difference in task length.

‡Significant differences from saline controls ($p < 0.05$).

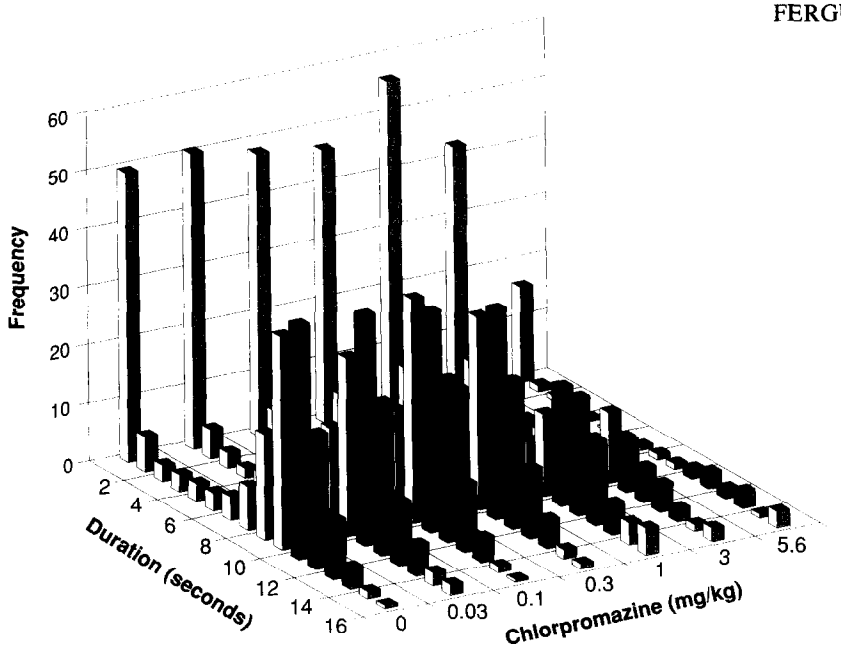

FIG. 1. Effect of chlorpromazine on mean duration of lever hold of rats in the temporal response differentiation (TRD) task. The first bar represents the frequency of lever holds with a duration of 0.1–0.9 s, the second bar represents the frequency of lever holds with a duration of 1.0–1.9 s, and so forth. Darkened bars represent those responses within the correct range (10–14 s).

sponding indicate that only the rat's forepaws are used. Additionally, a short pause in responding occurs after reinforcer delivery during which rats retrieve and consume the food pellet. Such differences might explain the disparity in RRs between the rat and the adult monkey.

In general, the behavioral effects of chlorpromazine and diazepam were similar across the two species (3,27). This similarity is interesting because there were some significant differences in methodologies. The route of administration differed across the two species [IP in the rat and intravenously (IV) in the monkey] and this probably partially accounts for the differences in doses required to produce significant behavioral

TABLE 2

DOSE OF DIAZEPAM (mg/kg)

	Monkey Vehicle*	Rat Vehicle	0.25	0.50	1.0	2.0	4.0
Temporal response differentiation (n = 5)							
PTC	19.07 ± 6.22†	54.57 ± 8.48	46.67 ± 9.20	47.00 ± 9.99	37.42 ± 8.23	23.83 ± 7.77‡	27.00 ± 13.41‡
RR (resp/s)	0.08 ± 0.01	0.08 ± 0.01	0.09 ± 0.02	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.06 ± 0.01
ACC	30.36 ± 6.44	35.48 ± 6.21	28.50 ± 5.07	34.57 ± 8.64	23.04 ± 4.47	16.84 ± 6.66	20.02 ± 10.16
Mean duration of lever hold (s)	6.91 ± 1.19	7.56 ± 0.64	7.16 ± 0.78	6.47 ± 1.01	5.81 ± 0.48	6.46 ± 0.54	5.03 ± 1.65
Progressive ratio (n = 5)							
PTC	11.59 ± 2.09	16.97 ± 1.65	16.42 ± 3.69	15.50 ± 2.61	16.50 ± 2.21	21.00 ± 2.26	16.25 ± 1.57
RR (resp/s)	0.33 ± 0.10	0.59 ± 0.17	0.65 ± 0.27	0.53 ± 0.15	0.58 ± 0.16	0.87 ± 0.28	0.55 ± 0.16
Breakpoint	17.97 ± 3.57	29.12 ± 6.66	29.50 ± 9.39	26.90 ± 6.91	29.00 ± 7.31	36.20 ± 8.63	28.00 ± 6.50
Grip strength (n = 5)							
Forelimb	N/A	0.78 ± 0.06	0.66 ± 0.05	0.76 ± 0.10	0.71 ± 0.06	0.63 ± 0.10	0.62 ± 0.05‡
Hindlimb	N/A	0.85 ± 0.05	0.75 ± 0.03	0.86 ± 0.05	0.81 ± 0.05	0.76 ± 0.06	0.87 ± 0.07

*Data exhibited by adolescent monkeys (Ref. 27) (n = 4 for the TRD task and n = 9 for the PR task) (see discussion for explanation of adolescent vs. adult monkey PR performance).

†The TRD PTC measure was calculated by dividing the total number of reinforcers delivered by 120 (the maximum number of reinforcers possible) and multiplying this quotient by 100. Because the TRD task for the monkey is one-half the length as in the rat (monkey TRD 20 min, rat TRD 40 min), the apparent difference in PTC is due primarily to the difference in task length.

‡Significant differences from vehicle controls ($p < 0.05$).

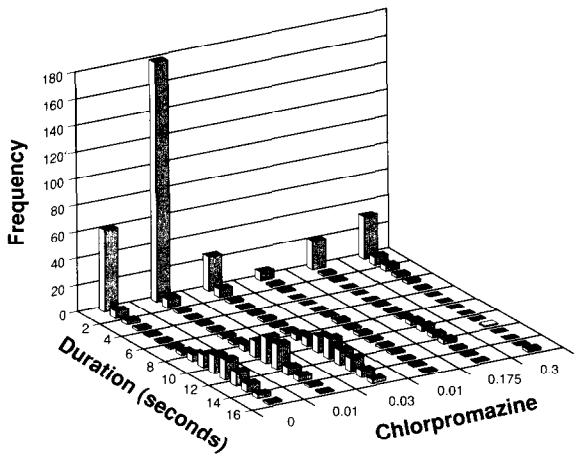

FIG. 2. Effect of chlorpromazine on mean duration of lever hold of monkeys in the temporal response differentiation (TRD) task. The first bar represents the frequency of lever holds with a duration of 0.1–0.9 s, the second bar represents the frequency of lever holds with a duration of 1.0–1.9 s, and so forth. Data from Ferguson & Paule, 1992 (Ref. 2).

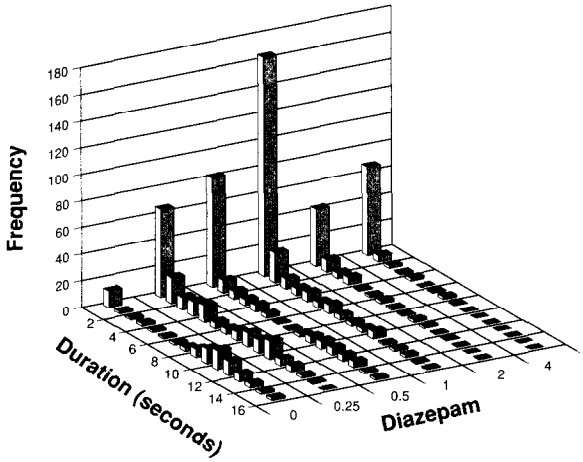

FIG. 4. Effect of diazepam on mean duration of lever hold of monkeys in the temporal response differentiation (TRD) task. The first bar represents the frequency of lever holds with a duration of 0.1–0.9 s, the second bar represents the frequency of lever holds with a duration of 1.0–1.9 s, and so forth. Data from Schulze et al., 1989 (Ref. 27).

alterations. Maximum TRD task session length differed between the two species (40 min in the rat and 20 min in the monkey). Additionally, the monkeys performing the NCTR OTB were trained on five tasks and the TRD and PR tasks were presented on alternate test days. In the current study, rats were trained to perform only the TRD and PR tasks and these two tasks were presented each test day.

In the rat, chlorpromazine affected both PR and TRD responding at about the same doses; at 1.0 mg/kg PR PTC was decreased by approximately 20% whereas TRD PTC was decreased by approximately 25%. In the monkey, PR and TRD responding were also equisensitive to disruption by chlorpromazine (3).

PR behavior was not altered by diazepam at doses up to 4.0 mg/kg in either the rat or the monkey (27). TRD performance, however, was affected by diazepam in both species. In the rat, 2.0 mg/kg diazepam decreased TRD PTC; however, accuracy, RR, and mean duration of lever hold were not significantly affected by doses up to and including 4.0 mg/kg. In the monkey, TRD PTC and RR were not altered but accuracy was decreased at higher doses ($\geq$ 1.0 mg/kg). Thus, TRD behavior is more sensitive than PR behavior to disruption by diazepam in both species.

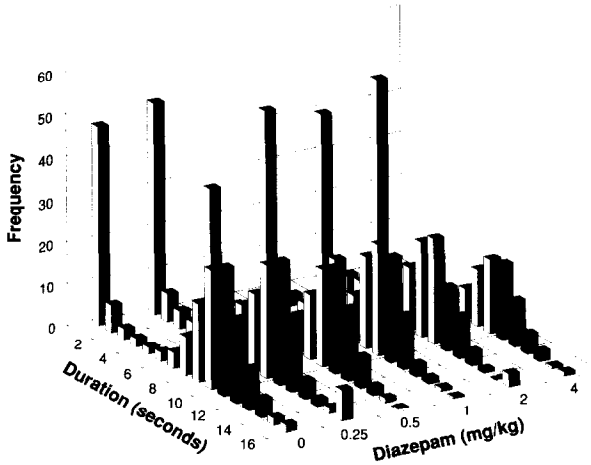

FIG. 3. Effect of diazepam on mean duration of lever hold of rats in the temporal response differentiation (TRD) task. The first bar represents the frequency of lever holds with a duration of 0.1–0.9 s, the second bar represents the frequency of lever holds with a duration of 1.0–1.9 s, and so forth. Darkened bars represent those responses within the correct range (10–14 s).

Grip strength measurements were included in the current study to compare the sensitivity of operant tasks with those related in a more general way to limb motoric function. These assessments indicated that only at relatively high doses of chlorpromazine and diazepam were fore- or hindlimb grip strengths affected. For example, the highest doses of chlorpromazine (5.6 mg/kg) and diazepam (4.0 mg/kg) were necessary to significantly decrease grip strength. The motor performance associated with grip strength is very different from that of lever pressing; however, the effects observed in operant behavior at lower doses are likely due to drug effects on aspects of cognitive performance rather than on general decreases in motor abilities.

Decrements in cognitive performance that occur at doses lower than those required to decrease fore- or hindlimb grip strength indicate the prospective utility of a rat OTB. Previously, we demonstrated that rats can readily acquire and perform the TRD and PR tasks (2). Data from the current study add to evidence showing that rat performance of the TRD task is very similar to that of rhesus monkeys. Furthermore, relative task sensitivity to disruption by chlorpromazine and diazepam is similar in rats and monkeys. Thus, not only is baseline performance nearly identical across these species, but responses to the psychotropic compounds studied here are also comparable.

Continued validation of rat OTB behavior as a model of complex behavior will involve further comparisons of the effects of drugs in rats with those in monkeys and when possible, other species. The NCTR OTB presents an opportunity to develop a phylogenetic analysis of learning sets, with specific reference to these tasks. Data from performance of other Old

World monkeys and New World monkeys, as well as other rodent species and adult humans, would greatly enhance the comparative utility of the OTB (e.g., Ref. 7). Currently, the availability of a rat model will make possible studies, such as neurochemical or neuropathological assessments, that are not likely to be conducted in nonhuman primates.

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