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Acute Effects of Chlorpromazine in a Monkey Operant Behavioral Test Battery

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FERGUSON, S. A. AND M. G. PAULE. *Acute effects of chlorpromazine in a monkey operant behavioral test battery.* PHARMACOL BIOCHEM BEHAV **42**(2) 333-341, 1992.—The effects of acute chlorpromazine treatment were assessed using a complex operant test battery (OTB) containing five tasks thought to depend upon processes associated with short-term memory and attention [delayed-matching-to-sample (DMTS)], color and position discrimination [conditioned position responding (CPR)], motivation [progressive ratio (PR)], time perception [temporal response differentiation (TRD)], and learning [incremental repeated acquisition (IRA)]. Adult male rhesus monkeys were tested 15 min after IV injection of saline or chlorpromazine (0.010, 0.030, 0.100, or 0.175 mg/kg). Behavioral endpoints measured included percent task completed, response rate or latency, and response accuracy. The order of task sensitivity to disruption by chlorpromazine was TRD = PR = IRA = DMTS = CPR in which sensitivity was defined as a significant alteration in any aspect of task performance. Chlorpromazine slowed response rates in all tasks except TRD but did decrease accuracy in that task. These effects were similar to those noted in previous studies of acute chlorpromazine treatment. Specific motoric effects suggested decreased task initiation at doses that left general motor ability intact. This finding is similar to that noted in parkinsonism caused by chronic chlorpromazine treatment.

Chlorpromazine Monkey Operant behavior Learning Short-term memory Time perception Motivation Color and position discrimination

THE phenothiazine chlorpromazine (Thorazine®) has been widely prescribed as an antipsychotic since the early 1950s. Its efficacy as a neuroleptic, as well as that of other phenothiazines, is closely related to its ability to block D_2 and, to a lesser extent, D_1 dopamine receptors (12,13,42). As treatments for the symptoms of schizophrenia, the phenothiazines have unique therapeutic effects that markedly distinguish them from other psychoactive agents, such an the anxiolytics [reviewed by (43)].

Clinically, the major interest concerning the use of the phenothiazines surrounds their chronic effects since such treatment is essential in the control of the symptoms of schizophrenia. Long-term administration can sometimes result in the development of either tardive dyskinesia or parkinsonian-like symptoms such as bradykinesia. Similar motor dysfunctions have been modeled in rhesus monkeys by chronic chlorpromazine treatment (23) and by selective destruction of dopaminergic neurons with *n*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (NMPTP) (5).

From a psychopharmacological perspective, the acute behavioral effects of chlorpromazine have proven interesting. A well-established effect of chlorpromazine has ben demonstrated utilizing the conditioned avoidance response (CAR) paradigm. Single doses of chlorpromazine can virtually abolish avoidance responding with few significant effects on escape responding (10,11,18,25). This suppression of avoidance responding is not due to nonspecific sedation or a locomotor deficit (21) but rather to a delay in the initiation of the avoidance response (35). Chlorpromazine has also been shown to alter behaviors in animals and humans such as discrimination learning (9), reaction times (46), motor activity (17), sexual behaviors (8), and social interactions (44).

Such studies indicate that acute chlorpromazine administration can affect a variety of behaviors. Most investigations concerning the acute effects of chlorpromazine, however, evaluated its effects on a single complex behavior rather than on several behaviors in the same subjects. Such an assessment on multiple behaviors is desirable for formulating a more comprehensive profile of the effects of chlorpromazine and determining the relative sensitivities of each behavior to presumed dopaminergic blockade.

In this laboratory, a complex operant test battery (OTB), consisting of five"cognitive" tasks, has been used to evaluate the neurobehavioral effects of several psychoactive compounds in monkeys including marijuana smoke (37), Δ-9-tetrahydrocannabinol (THC) (38), diazepam (41), atropine

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(30), *d*-amphetamine (39), physostigmine (32), phencyclidine (27), pentobarbital (31), and morphine (40). The current study is one in a series designed to validate the use of this test battery as a tool in neurobehavioral pharmacology and toxicology. The approach used in this process has involved the study of relatively well-characterized, reversibly acting reference compounds. Neurobehavioral profiles (i.e., selective behavioral effects) can then be generated for each prototypic compound and, when appropriate data exist, compared to their known effects in humans and animals. Such behavioral profiles can then be compared with those produced by compounds with uncertain mechanisms of action in the hope of shedding some light on their mechanisms.

Further validation of this OTB is in progress using children as subjects (28) where it has been shown that, in general, the OTB performance of well-trained rhesus monkeys is indistinguishable from that of children (29). Such observations strengthen the case for using OTB performance in monkeys as a model of complex behavioral performance in humans.

The present experiment was specifically designed to measure the acute effects of chlorpromazine on performance in the tasks contained in the OTB in rhesus monkeys. The doses used (0.01–0.30 mg/kg, IV) were chosen based on the findings of a previous study in squirrel monkeys (15) and on the criteria that the highest dose grossly affected most behavioral endpoints and the lowest dose was without significant effects. The behavioral tasks contained in the test battery include delayed-matching-to-sample (DMTS), conditioned position responding (CPR), progressive ratio (PR), temporal response differentiation (TRD), and incremental repeated acquisition (IRA). Performance of these tasks is thought to depend upon processes associated with short-term memory and attention, color and position discrimination, motivation, time perception, and learning, respectively. Previous studies have demonstrated that these tasks are differentially sensitive to the effects of a variety of psychotropic compounds (26). Chlorpromazine was chosen for study because of its relatively well-characterized mechanism of action (1), allowing it to serve as a reversibly acting prototypic dopamine antagonist.

METHOD

Subjects

Seven adult, male rhesus monkeys (*Macaca mulatta*) between 6 and 10 years of age and weighing from 6–10 kg served as subjects. All monkeys had previously been trained under the schedules in the OTB for several years and had been used as subjects in previous studies on the acute effects of several psychoactive compounds (27,30–32,37–41). Animal housing, feeding, etc. were as previously described (37). Briefly, each monkey was individually housed and fed its daily allotment of food immediately after each test session. Water was available ad lib. Animal care and procedures were in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines and approved by the Institutional Animal Care and Use Committee of the NCTR.

Apparatus

The apparatus have been described in detail elsewhere (37) and consisted of portable primate restraint chairs, sound-attenuated behavioral chambers, operant panels, and computer consoles. The operant panels were equipped with three rear-projection press plates, four retractable levers, six serial position indicator lights, and correct and incorrect response indicator lights. The press plates, levers, and indicator lights were aligned horizontally, with the press plates and serial position indicator lights located above the levers. Symbols and colors were projected onto the press plates from the rear and, when pressed, each effected a switch closure. Serial position and correct and incorrect indicator lights were illuminated from behind the panel with various colors. A trough for reinforcer (190 mg banana-flavored food pellet) delivery was centered below the levers.

Operant Schedules

The use and description of the tasks contained in the OTB have been reported in detail elsewhere (26,37) and a diagram of the behavioral test panel is shown in Paule et al. (34). A brief description of each task follows.

DMTS. For the DMTS task, only the three press-plate manipulanda were used (levers were retracted). At the start of each trial, one of seven geometric symbols (the "sample") was projected onto the center plate in a random fashion (side press-plates were dark). To continue the trial, each monkey was required to make an "observing" response (a press) to the center plate. After the observing response was made, the center plate was extinguished for one of six time delays (i.e., 2, 4, 8, 16, 32, and 48 s, presented pseudorandomly) during which all three press-plates were dark. After the time delay, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the "match" resulted in reinforcer delivery and initiation of a new trial with another sample stimulus (presented randomly). A nonmatching response was followed by a 10-s time-out period (all plates darkened) and then initiation of a new trial.

CPR. For the CPR task, only the three press-plates were used (levers were retracted). At the start of each trial, the center plate was illuminated with either a solid red, yellow, blue, or green (side press-plates were dark). The monkey continued the trial by making an observing response (a press) to the center plate, after which it was extinguished and the two side plates were immediately illuminated white. If the center plate color had been either blue or green, a response to the right press-plate (white) resulted in reinforcer delivery and initiation of a new trial. If the center press-plate had been either red or yellow, a response to the left press-plate (white) resulted in reinforcer delivery and initiation of a new trial. Responding to the incorrect position initiated a 10-s time-out period followed by the initiation of a new trial. The sequence of color presentation was random.

PR. For the PR task, only the far right retractable lever was extended. Each monkey was required to increase the number of lever presses required for each subsequent reinforcer. Initially, one or two lever presses (depending upon the individual monkey 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, etc. The ratio increments were chosen so that marked periods of pausing or cessation of responding generally occurred during each baseline or vehicle PR session.

TRD. For the TRD task, only the far left retractable lever was extended. 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 current trial, after which the monkey could immediately start another trial.

IRA. For the IRA task, all four retractable levers were extended and the serial position indicator lights were used. Subjects were required to acquire or learn a new sequence of lever presses each test session. The IRA task began with the presentation of a one-lever response sequence (IRA1). Each response on the correct one of the four levers resulted in reinforcer delivery and after 20 correct response sequences (criterion performance) a 1-min time-out period was followed by the presentation of an "incremented" two-lever sequence (IRA2) in which a response on a different lever was required before a response on the original (IRA1) lever produced a reinforcer. After 20 errorless two-lever sequences (i.e., no errors were made between the first and last correct lever presses of the required sequence), the task was incremented to a three-lever sequence and so on, up to a six-lever sequence or until the allotted task time elapsed. The serial position indicator lights signalled position in the response sequence, indicating the number of correct responses necessary for reinforcer delivery. Incorrect responses were followed by a 2 s time-out but did not reset the response requirement; thus, error correction was permitted. Correct responses were followed by illumination of the appropriate serial position indicator light.

Behavioral Testing Procedure

Behavioral test sessions were conducted daily (Monday–Friday) and lasted approximately 50 min. Monkeys were rotated through nine identical behavioral test chambers so that, in general, no monkey was placed in the same chamber on 2 consecutive test days. Behavioral schedules alternated daily. For example, PR (10 min), IRA (35 min), and CPR (5 min) were presented on 1 test day; TRD (20 min) and DMTS (30 min) were presented the next test day.

Drug and Dosing Procedure

Chlorpromazine (Sigma Chemical Co., St. Louis, MO) was dissolved in saline so that the final injection volume was 0.1 ml/kg. The purity of the chlorpromazine was determined to be 99% by in-house high-performance liquid chromatography (HPLC) analysis using a UV detector set at 230 nm. Doses of chlorpromazine (0.010, 0.030, 0.100, 0.175, and 0.300 mg/kg, IV) were administered in a randomized order. Chlorpromazine injections were given 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. Due to the daily alternation of behavioral tasks, all chlorpromazine doses were given twice to provide dose–response data for each operant task. Approximately 15 min after injection, each monkey was placed into an operant chamber and the behavioral session began 1 min later.

Behavioral Endpoints

The endpoints measured in each task have been described in detail elsewhere (37). Three fundamental measures were monitored for most tasks: percent task completed, response rate or latency, and response accuracy.

Percent task completed. The percent task completed data are measures of a predetermined performance criteria and are functions of both response rate and response accuracy. The percent task completed measure is calculated by dividing the total number of reinforcers earned in a given session by the total number of reinforcers possible for a given session and multiplying this quotient by 100. The total number of reinforcers possible for a given task was chosen arbitrarily based upon the length and difficulty of the task. The percent task completed endpoint is a convenient and comprehensive measure showing intraanimal stability and is useful for comparing drug effects on performance across tasks.

Response rate and latency. Response rates for each of the PR and TRD tasks were calculated by dividing the total number of lever presses by the total task time (in seconds). Response rates for each of the CPR, DMTS, and IRA tasks were calculated by dividing the total number of responses by the total task time minus time-out and any delay periods (in seconds). For the DMTS and CPR tasks, mean response latencies also were calculated for both observing and choice responses.

Response accuracy. Response accuracy for each of the CPR and DMTS tasks was calculated by dividing the number of correct responses by the total number of trials in a given session and multiplying this quotient by 100. For the TRD and IRA tasks, response accuracy was calculated by dividing the total number of correct lever presses by the total number of lever presses in a given session and then multiplying this quotient by 100. Response accuracy is not applicable for the PR task.

Other measures. For the TRD task, mean duration of lever hold and for the PR task, the breakpoint (the magnitude of the last ratio completed for which the monkey earned a reinforcer) were also measured.

Statistical Analysis

Only those monkeys exhibiting stable performance for the measure of percent task completed after saline (control) injections were included in the statistical analyses. Stable performance was defined as that having a standard error of less than 15% of the mean for saline (control) sessions. During the current study, all seven monkeys exhibited stable preexposure baselines for the IRA, PR, and CPR schedules, five exhibited stable preexposure baselines for the DMTS schedule, and four exhibited stable preexposure baselines for the TRD schedule. Thus, results from the DMTS task are based on data from five monkeys and results from the TRD task are based on data from four monkeys. For an animal's data to be included in the TRD and CPR accuracy analyses, a minimum of three trials must have been completed. For inclusion in the DMTS and IRA accuracy analyses, a monkey must have completed a minimum of 10 trials. For each behavioral endpoint in each task, the overall effect of drug treatment on performance was determined using a one-way repeated-measures analysis of variance (ANOVA). If overall significance was evident ($p < 0.05$), then performance at each dose was compared to saline control performance using a Bonferroni correction (24).

RESULTS

Overall Effect of Saline Vehicle

When compared to baseline data, saline vehicle injections produced no statistically significant group effects on any of the endpoints examined. Baseline and saline performance are separately represented in each figure.

DMTS

Percent task completed. Chlorpromazine produced a dose-dependent decrease in the percent task completed (Fig. 1A) that was significantly different from saline vehicle (control) performance at doses of 0.100, 0.175, and 0.300 mg/kg.

Response rate. Response rates were significantly decreased from 0.35/s for control to 0.01, 0.04, and 0.02/s at doses of 0.100, 0.175, and 0.300 mg/kg, respectively (Fig. 1B).

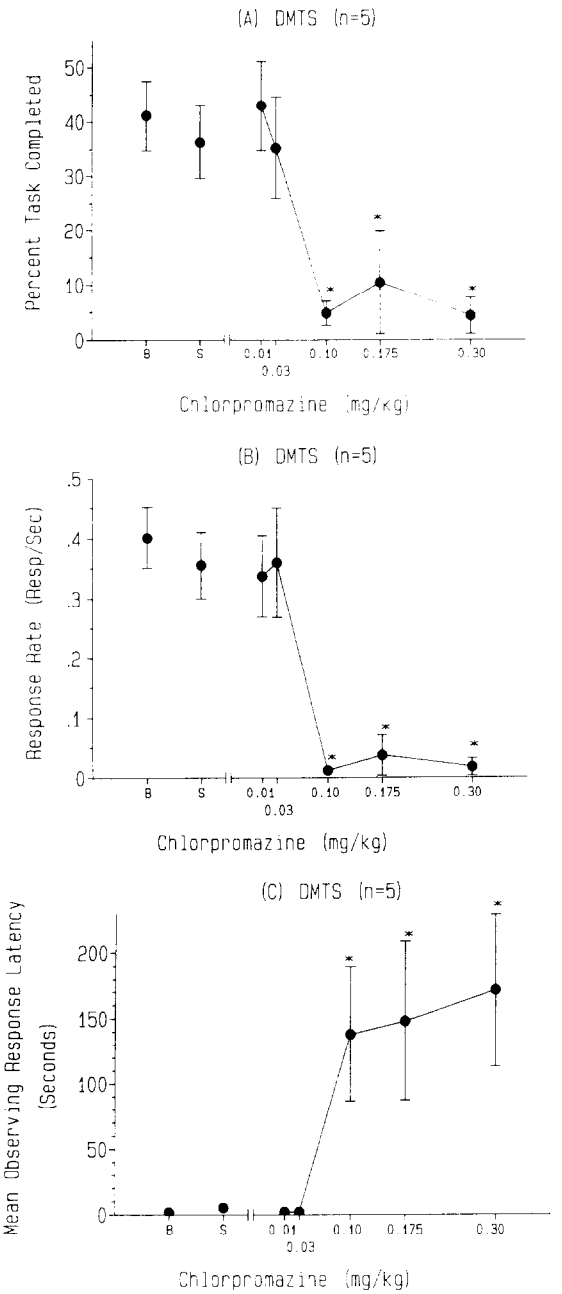

FIG. 1. Effects of chlorpromazine on delayed-matching-to-sample (DMTS) (A) percent task completed, (B) mean response rate, and (C) mean observing response latency. Each point represents the mean ± SE. On the abscissa, B represents the preexposure baseline of performance and S represents saline control performance. Asterisks represent significant differences from saline controls as determined by Fisher's (LSD) *t*-test ($p < 0.05$).

Response latencies. Observing response latencies for the DMTS task were significantly increased from 5.2 s for control to 137.6, 147.5, and 170.7 s at 0.100, 0.175, and 0.300 mg/kg, respectively (Fig. 1C). Choice response latency was only marginally affected by chlorpromazine ($p < 0.06$) and this was not affected by time delay (data not shown). Latency of correct choices was no more affected by chlorpromazine than was latency to make incorrect choices (data not shown).

Response accuracy. As expected, accuracy decreased as the time delay increased. For control performance, mean accuracy at the shortest delay was 79%, which decreased to 55% at the longest delay. The overall factor of dose was significant in the ANOVA, $F(6, 89) = 3.30$, $p < 0.04$; however, control accuracy was not significantly different from that after any of the five chlorpromazine doses nor did chlorpromazine preferentially affect accuracy at any specific delay (data not shown).

CPR

Percent task completed. Chlorpromazine significantly decreased percent task completed at 0.175 and 0.300 mg/kg (Fig. 2A).

Response rate. Response rates were significantly decreased from 1.43/s for control to 0.89, 0.145, and 0.026/s at 0.100, 0.175, and 0.300 mg/kg, respectively (Fig. 2B).

Response latencies. Chlorpromazine produced dose-dependent increases in observing response latencies, which were significant at 0.175 and 0.300 mg/kg (Fig. 2C). Mean observing response latency increased from 3.0 s for control to 134.2 and 237.1 s for the two higher doses. Choice response latency increased somewhat in a dose-related manner but was not significantly different from control (Fig. 2D). Latency to make correct choices was no more affected by chlorpromazine than was latency to make incorrect choices (data not shown).

Response accuracy. Accuracy in the CPR task was not significantly affected by chlorpromazine (data not shown).

PR

Percent task completed. Percent of the PR task completed was significantly decreased by chlorpromazine at 0.100, 0.175, and 0.300 mg/kg (Fig. 3A).

Response rate. Mean response rates were significantly decreased from 2.40/s for control to 1.25, 0.41, and 0.01/s at doses of 0.100, 0.175, and 0.300 mg/kg, respectively (Fig. 3B).

Breakpoint. Breakpoint (the magnitude of the last ratio completed for which each monkey earned a reinforcer) was significantly decreased from 104.6 for control to 66.4, 32.7, and 1.7 lever presses at 0.100, 0.175, and 0.300 mg/kg, respectively (data not shown).

TRD

Percent task completed. Percent of the TRD task completed was significantly decreased at doses of 0.100, 0.175, and 0.300 mg/kg (Fig. 4A).

Response rate. The overall factor of dose was significant in the ANOVA, $F(6, 74) = 2.77$, $p < 0.05$; however, control response rates were not significantly different from those after any of the five chlorpromazine doses (data not shown).

Response Accuracy. Accuracy in the TRD task was significantly decreased from 38.2% for control to 13.1% an 7.2% at 0.100 and 0.175 mg/kg, respectively (Fig. 4B).

Duration of lever hold. Mean duration of lever hold, which averaged 7.11 s for control sessions, was not significantly affected by chlorpromazine (data not shown). Since accuracy was decreased, it might appear that duration of lever hold must necessarily be altered. However, at 0.100 mg/kg two of the four monkeys decreased their duration of lever hold and the remaining two were relatively unaffected (mean lever hold duration at 0.100 mg/kg = 4.56 s). At 0.175 mg/kg, two of the four monkeys increased their duration of lever hold from control levels, one decreased its lever hold duration, and one

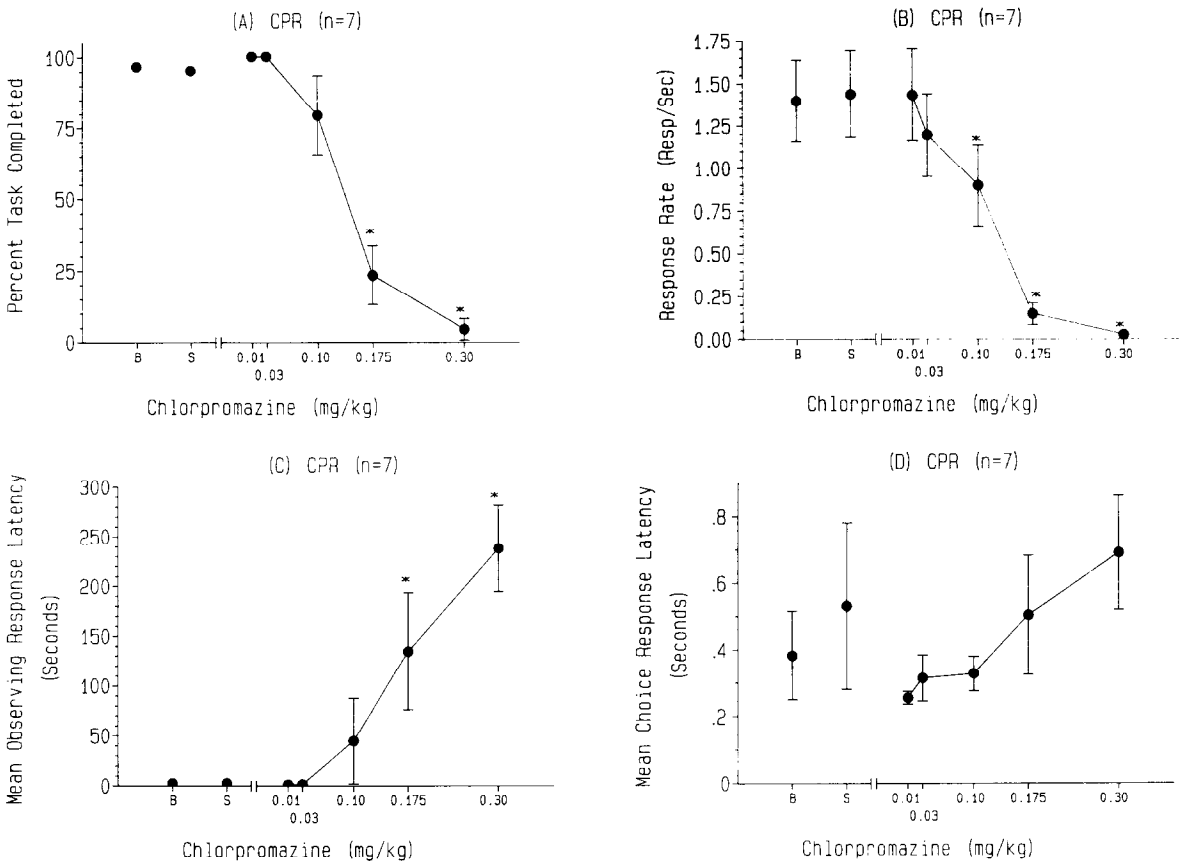

FIG. 2. Effects of chlorpromazine on conditioned position responding (CPR) (A) percent task completed, (B) mean response rate, (C) mean observing response latency, and (D) mean choice response latency. Data presented as in Fig. 1.

was unaffected (mean lever hold duration at 0.175 mg/kg = 8.29 s). Thus, accuracy decreased but lever hold duration fluctuated across animals and doses such that the average hold duration did not significantly differ from control.

IRA

Percent task completed. The percent IRA task completed was significantly decreased by chlorpromazine at 0.100, 0.175, and 0.300 mg/kg (Fig. 5A).

Sequence completion and progression. Completion of the initial one-lever sequence (IRA1) represents 16.7% task completed. Completion of IRA2, IRA3, and IRA4 represent 33, 50, and 66.7% respectively. The two lowest doses of 0.01 and 0.03 mg/kg did not interfere with the performance of IRA1 nor the succeeding IRA2 as all seven monkeys were able to successfully complete the 20 correct response sequences. In the following three-lever sequence (IRA3), one monkey did not reach criterion after 0.01 mg/kg and a different monkey failed to reach criterion after 0.03 mg/kg. Higher doses more clearly interfered with completion of the IRA sequences; however, at 0.10 mg/kg four of the seven monkeys were able to complete through the IRA3 sequence. At the highest dose (0.300 mg/kg), only one monkey responded and it did not complete IRA1.

Response rate. Mean response rates were significantly decreased from 1.44/s for controls to 0.67, 0.04, and 0.01/s at 0.100, 0.175, and 0.300 mg/kg, respectively (Fig. 5B).

Response accuracy. Overall accuracy was significantly decreased only at the 0.175 mg/kg dose. Accuracy decreased from a control value of 62.9 to 44.6% at 0.175 mg/kg (data not shown). At 0.300 mg/kg, only one monkey responded and its performance was not significantly different from control.

DISCUSSION

The order of OTB task sensitivity to disruption by chlorpromazine was TRD = PR = IRA = DMTS = CPR, in which "sensitivity" refers to a significant alteration in any aspect of task performance (percent task completed, response rate or latency, or accuracy) at doses lower than those affecting performance of the other tasks. Thus, behaviors thought to be dependent upon processes associated with time perception (TRD), short-term memory and attention (DMTS), motivation (PR), learning (IRA), and color and position discrimination (CPR) were equally sensitive to presumed dopaminergic blockade. The primary effect of chlorpromazine was to slow response rates in all but the TRD task, where instead accuracy was decreased. These effects are consistent with those of previous human (46) and animal studies (6,15,22, 36,47) concerning the effects of acute chlorpromazine treatment. However, use of the OTB further extends the profile of effects caused by acute chlorpromazine administration by assessing behaviors in five different tasks in the same subjects. The specific motoric effects of chlorpromazine observed in the present study suggest a drug-induced decrease in task initi-

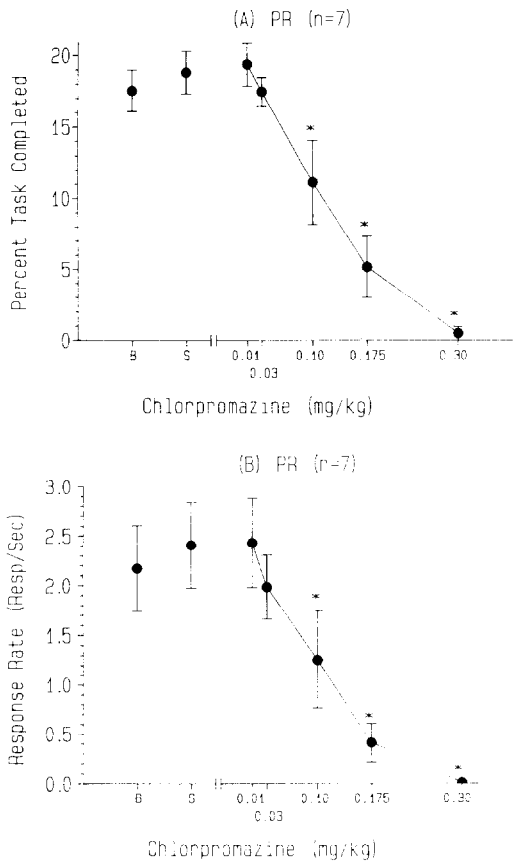

FIG. 3. Effects of chlorpromazine on progressive ratio (PR) (A) percent task completed and (B) mean response rate. Data presented as in Fig. 1.

ation (i.e., increased observing response latencies) at doses that generally leave motor ability intact (i.e., little or no effect on choice response latencies). These particular motoric effects are similar to those noted in the parkinsonism-like effects noted during chronic chlorpromazine treatment (45).

In humans, such neuroleptic-induced parkinsonism is characterized by decreased facial and arm movements and rigidity (4), in addition to difficulty in movement initiation (45). This difficulty in initiating movement has been modeled in monkeys treated acutely with chlorpromazine in which movement initiation time or the time between stimulus onset and arm movement was increased much more than was motor response time or the time between initiation of arm movement and the completed response (36). MPTP-treated monkeys also display a delay in initiation of motor movements, an apparent result of destruction of neurons in the nigrostriatal dopaminergic system (2). This initiation delay, as modeled in MPTP-treated rats, was shown not to be the result of inattention to stimuli (7).

In the present study, each trial in the DMTS and CPR tasks required two motor responses to press-plate manipulanda (an observing response and a choice response), which were differentially affected by chlorpromazine. Observing response latencies in both tasks were significantly increased at doses that only slightly affected choice response latencies. These chlorpromazine-induced increases in observing response latencies are similar to the noted movement-initiation difficulties characteristic of idiopathic parkinsonism (16) and the motor-initiation delays seen in MPTP-treated monkeys and rats (2,7).

Of the choice responses in the two press-plate manipulanda tasks, those in the CPR task were much less affected by chlorpromazine than were those in the DMTS task. Choice responses in the CPR task appear almost to be a continuation of the observing response motor movement since monkeys will immediately move their hands from the observing response press-plate to the choice response press-plate. Since there is no time delay imposed between the observing response and presentation of the choice stimuli in the CPR task, choice response latencies average about 0.5 s. In contrast, the DMTS task has imposed delays of up to 64 s between the observing response to the sample stimulus and the presentation of choice stimuli. Monkeys appear to make separate movements for these two responses: They make an observing response to the sample press-plate after which their hands are usually removed from the operant panel and a separate movement brings the hand back to the panel after the choice stimuli are presented. Thus, choice response latencies in the DMTS task average 1–4 s. That the DMTS task appears to require two "separate" motor movements may explain the marginally significant effects of chlorpromazine on choice response latencies in that task but not in the CPR task.

Within any given OTB task, response rate and percent task

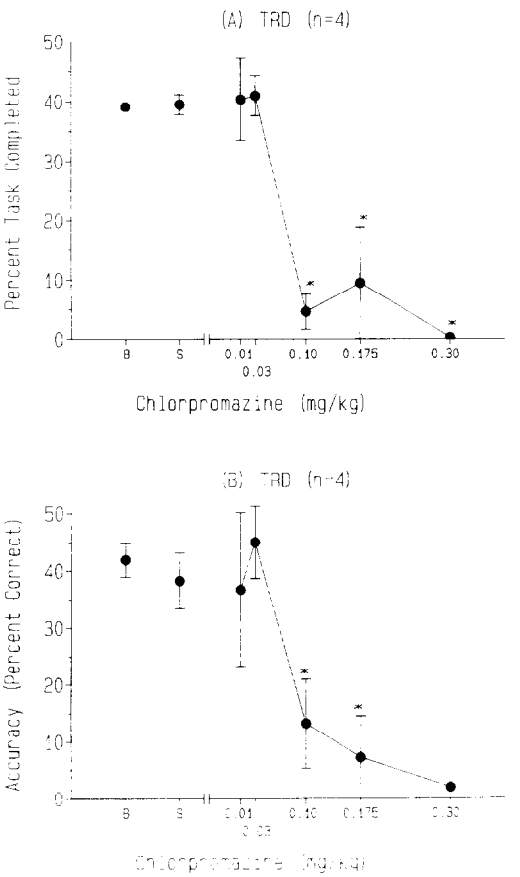

FIG. 4. Effects of chlorpromazine on temporal response differentiation (TRD) (A) percent task completed and (B) accuracy. Data presented as in Fig. 1.

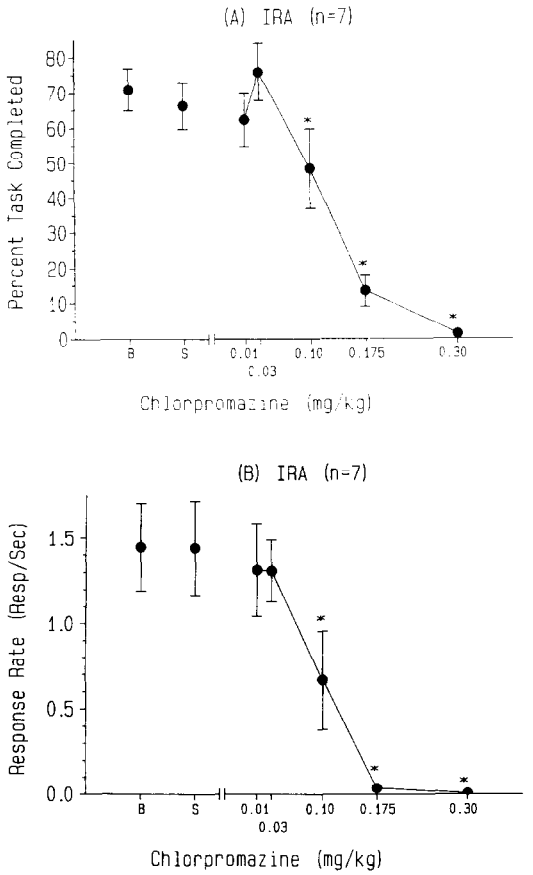

FIG. 5. Effects of chlorpromazine on incremental repeated acquisition (IRA) (A) percent task completed and (B) response rate. Data presented as in Fig. 1.

completed were generally equisensitive to the acute effects of chlorpromazine and were the first measures to be disrupted; accuracy was generally not as sensitive. DMTS and CPR accuracies were unaffected by doses of chlorpromazine that markedly reduced response rates and/or increased observing response latencies. Accuracy on the IRA task was significantly altered only at 0.175 mg/kg; however, this was not a universal finding as one of the four monkeys which responded at this dose exhibited increased accuracy relative to its control performance. Conversely, TRD accuracy was as sensitive to chlorpromazine as was TRD percent task completed. Thus, if an effect on accuracy was used in determining OTB task sensitivity to disruption by chlorpromazine the order would be TRD > IRA = DMTS > CPR (the PR task does not have an accuracy component).

The profile of OTB task sensitivity to chlorpromazine is similar to that of phencyclidine in which the TRD, IRA, DMTS, and PR were equally sensitive tasks (27). However, phencyclidine significantly decreased IRA, DMTS, and CPR accuracies, whereas chlorpromazine had no clear effects on these measures. Thus, even though the overall task sensitivity profiles of these two drugs are similar there are substantial differences in their behavioral effects.

The doses of chlorpromazine used in the present study were well below the typical oral doses of 100–400 mg (≈1–6 mg/kg) when prescribed as an antipsychotic (4). Since the bioavailability of orally administered chlorpromazine (relative to intramuscular administration) is approximately 32% (14) and since intramuscular bioavailability is likely to approximate that after IV administration, such oral doses would equate to IV doses of about 0.5–1.9 mg/kg, much higher than those used in the present study. The daily dose for humans, however, is generally given at bedtime to specifically avoid side effects such as "sedation" (4). It is likely that the "sedative" effects of such doses in humans would be significant since single oral doses of 50–75 mg (equivalent to approximately 0.2–0.4 mg/kg in the monkey, IV) have been shown to slow logical reasoning and reaction times (19,46). Thus, assuming equivalent potency in monkeys and humans, the doses of 0.010–0.300 mg/kg used in the present study were likely below those expected to cause excessive sedative effects in monkeys.

Use of the OTB is currently unique to this laboratory; however, other investigators have used similar tasks to investigate the behavioral effects of acute chlorpromazine administration. In general, the effects reported here are comparable with those reported previously. For example, chlorpromazine decreased accuracy in squirrel monkeys performing under a differential reinforcement of low response rate (DRL) schedule (6), a finding that parallels the TRD results of the present study since time perception is also thought to be associated with correct DRL responding. The chlorpromazine-induced decrease in PR response rate reported here is similar to the decreased response rate noted in chlorpromazine-treated rats under a fixed-ratio (FR-30) schedule (22). As in the present study, percent task completed and response rate were decreased, whereas accuracy was not significantly affected, in chlorpromazine-treated rats performing an IRA task (33).

Response latencies in the DMTS and CPR tasks can be considered types of "reaction time" measures and thus a comparison of the effects of chlorpromazine in studies using other reaction time measures is useful. As in the present study, chlorpromazine produced significant increases in the reaction times of squirrel monkeys performing an electric shock discrimination task (15) and increases in choice response latencies in rats performing a brightness discrimination task (47).

Chlorpromazine clearly has neurochemical effects in addition to dopamine antagonism and it could be postulated that the effects in the current study were due at least in part to these nondopaminergic actions. For example, chlorpromazine acts as an anticholinergic and antihistaminic (1) and has high affinity for α_1-adrenoceptors and serotonin receptors (20). However, there is evidence that the decrease in response rate across several tasks is directly related to its dopaminergic effects. Bergman et al. (3) found that the ability of chlorpromazine to block D_2, but not D_1, dopamine receptors was significantly correlated with its ability to decrease response rate in squirrel monkeys working under a fixed-interval schedule. Furthermore, they demonstrated that other nonselective dopamine antagonists, such as SCH23390 and risperidone, as well as the selective D_2 antagonist eticlopride, were similar in their behavioral effects, suggesting that the response rate decreases were due to D_2 dopamine receptor blockade.

In summary, acute chlorpromazine treatment in rhesus monkeys produced significant but relatively nonselective effects in operant tasks thought to depend upon brain functions associated with time perception, short-term memory and attention, motivation, learning, and color and position discrimination. The decreases in response rates and percent task completed

and the decrease in TRD accuracy were comparable to previous findings. Specific motoric effects resembled those of the parkinsonism associated with long-term chlorpromazine treatment, indicating that the classic movement-initiation difficulty associated with chronic treatment may be predicted from the acute effects of that compound. Similar assessments of the acute effects of chlorpromazine in human subjects might also reveal these effects and might discern which individuals may be predisposed to drug-induced parkinsonism relative to the other neuroleptic-induced disorders such as tardive dyskinesia. Multiple comparisons of the acute effects of drugs on several behaviors within the same subjects, which are available when using instruments such as the OTB, allow assessment of drug sensitivities across and within different tasks thought to represent different brain functions and thus allow a relatively comprehensive description of their behavioral effects.

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