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Effects of Chlorpromazine on Rats' Acquisition of Lever-Press Responding with Immediate and Delayed Reinforcement

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BYRNE, T., M. G. LESAGE AND A. POLING. *Effects of chlorpromazine on rats' acquisition of lever-press responding with immediate and delayed reinforcement.* PHARMACOL BIOCHEM BEHAV **58**(1) 31–35, 1997.—The effects of chlorpromazine (0, 2, 6, and 10 mg/kg) on the acquisition of lever-press responding by rats were examined under conditions where reinforcement (water delivery) was immediate or delayed. Under the immediate reinforcement condition, water-deprived rats were exposed during 8-h sessions to a fixed-ratio 1 (FR 1) schedule of water delivery without prior autoshaping or hand shaping. Under the delayed reinforcement condition, similar rats were exposed to a tandem FR 1 fixed-time 8-s schedule of water delivery. A different squad of eight rats was exposed to each delay condition and drug dose. For all subjects, responses on one lever produced water and responses on a second lever had no programmed consequences. Regardless of whether reinforcement was immediate or delayed, chlorpromazine reduced in dose-dependent fashion the mean number of operative-lever responses emitted, which suggests that the drug interfered with learning. At all chlorpromazine doses except 10 mg/kg, substantially more operative-lever than inoperative-lever responding occurred, indicating that the operant response was acquired. Chlorpromazine at 2 and 6 mg/kg disrupted the acquisition of stimulus control by the operative lever when reinforcement was delayed, but not when it was immediate. At 10 mg/kg, most subjects did not acquire lever-pressing regardless of whether they were exposed to the immediate or delayed reinforcement procedure. Procedures similar to those used in the present study appear to provide a reasonable assay for examining how drugs affect the initial behavioral effects of immediate and delayed reinforcement, and may merit further investigation. © 1997 Elsevier Science Inc.

Rats Delayed reinforcement Response acquisition Lever press Chlorpromazine

TWENTY-FIVE years ago, Stolerman (32,33) described a novel procedure for studying the initial acquisition of lever-press responding in rats and the effects of drugs thereon. In this procedure, rats that had learned to eat from a food magazine were exposed to a fixed-ratio 1 (FR 1) schedule of food delivery, under which each lever-press produced a food pellet. Lever-press responding was not hand shaped or autoshaped, but substantial levels of responding nevertheless developed relatively quickly in rats not given drug. Both chlorpromazine (2 mg/kg) and chlordiazepoxide (25 mg/kg) substantially reduced responding during acquisition. For unknown reasons, subsequent pharmacological investigations using similar procedures have not appeared.

Recently, however, procedures quite similar to those used by Stolerman have been used to demonstrate that rats and pigeons can acquire designated responses (e.g., lever presses and key pecks) under conditions where shaping is not arranged and the reinforcer is delayed relative to the response that produces it. Prior to a 1990 study by Lattal and Gleeson (12), researchers who attempted to demonstrate response acquisition with delayed reinforcement either inadvertently arranged an immediate consequence for responding or failed to provide critical procedural details [e.g., (8,16,29,30)]. Neither of these problems was evident in the work of Lattal and Gleeson (12), who convincingly demonstrated the acquisition of key pecks in pigeons and lever presses in rats when delayed and unsignaled food deliveries were the consequences of these behaviors. Neither hand shaping nor autoshaping was arranged, but responding nonetheless occurred and was maintained under both resetting and nonresetting delay procedures. This did not occur in the absence of a response–food dependency (i.e., when food was not delivered or was delivered independently of respond-

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ing). Subsequent studies (3,5,13,15,27,38,39) have confirmed in nonhumans the acquisition of operant responding with delayed reinforcement.

It is generally acknowledged that learning occurs less readily when reinforcement is delayed than when it is immediate [e.g., (11,18,31)]. Given this, and the characteristic observation that poorly learned behaviors are more easily disrupted by drugs than are better-learned behaviors (24,25), it is reasonable to expect that a given drug and dose would interfere with the initial acquisition of operant behavior to a greater extent when reinforcement is delayed than when it is immediate. A recent study (15) found, however, that *d*-amphetamine (1, 5.6, and 10 mg/kg) did not obviously interfere with response acquisition in rats exposed to procedures in which water delivery was delayed by 0, 8, or 16 s relative to the response that produced it.

The present study further examined whether reinforcement delay modulates drug effects on learning by examining the effects of chlorpromazine (Thorazine) on rats' acquisition of lever pressing with immediate and delayed reinforcement. Chlorpromazine was chosen for study to determine whether Stolerman's (32,33) findings could be replicated using similar, but not identical, procedures, and because the effects of the drug on learning remain unclear, despite a substantial literature on the topic. A third reason for using the drug was that its effects are relatively long lasting (4), which makes it an appropriate choice for study during the long sessions characteristically used to investigate response acquisition with delayed reinforcement.

Although the study was designed to provide some information about the behavioral effects of chlorpromazine, the primary intent was to use the drug as a tool to study the relative strength of behavior under the control of immediate and delayed reinforcement. There is no generally accepted single index of response strength, but Nevin [e.g., (19,20)] has proposed that the sensitivity of behavior to disruption by various perturbations, including drugs, is a useful measure of it. Specifically, response strength increases with resistance to disruption. Given the usual assumption that delayed reinforcement is less effective in strengthening behavior than is immediate reinforcement (11,18,31), we hypothesized that the drug would interfere with acquisition under both procedures, but would produce greater disruption when reinforcement was delayed.

METHODS

Subjects

Sixty-four experimentally naive Sprague–Dawley rats approximately 60 days of age were used as subjects. The rats were water deprived as described below prior to dipper-training and response-acquisition sessions. They were housed individually with unlimited access to food in a colony area with a 12 L:12 D cycle. Lights were on from 0700 to 1900 h, and behavioral testing occurred during the dark part of the cycle.

Apparatus

Eight MED Associates (St. Albans, VT, USA) operant test chambers were used. The chambers were 28 cm long by 21 cm wide by 21 cm high. During response-acquisition sessions, two response levers separated by 8.5 cm were mounted on the front panel 7 cm above the chamber floor. The levers were removed during dipper-training sessions. A minimum force of 0.14 N was required to operate the levers. A receptacle located in the center of the front panel 3 cm above the chamber floor allowed access to a dipper filled with 0.1 ml of tap water. Chambers were illuminated by a 7-W white bulb located on the ceiling. An exhaust fan in each chamber masked extraneous noise and provided ventilation. Programming of experimental events and data recording were controlled by an IBM-compatible microcomputer equipped with MED-PC software.

Procedure

All subjects were given one dipper-training session. Prior to this session, they were water deprived for 24 h. Dipper-training sessions were conducted at 0800 h and lasted for 90 min, during which the chamber was illuminated and both levers were removed. Water was delivered under a variable-time 60-s schedule for dipper training. Under this schedule, 4-s dipper presentations occurred aperiodically on average once every 60 s, regardless of the subject's behavior. All rats were observed to drink from the dipper by the end of the session. At the end of dipper-training sessions, subjects were given 20 min of access to water in their home cages. After this time, subjects were water deprived.

All response-acquisition sessions were conducted 24 h after dipper-training sessions ended and lasted for 480 min, during which the chamber was illuminated and both levers were present. Two response-acquisition procedures were arranged. Four groups of eight rats, selected at random, were exposed to an immediate-reinforcement procedure. Under this procedure, an FR 1 schedule was arranged for presses of one lever (the left for half of the subjects in each group, the right for the remainder). Here, a 4-s water delivery immediately followed each press of the operative lever. Presses of the inoperative lever were recorded but had no programmed consequences.

The remaining rats, randomly assigned to four groups of eight, were exposed to a delayed-reinforcement procedure. Under this procedure, a tandem FR 1 fixed-time 8-s schedule was arranged for presses of one lever (the left for half of the subjects in each group, the right for the remainder). Here, a 4-s water delivery occurred 8-s after a press of the operative lever. Operative-lever presses during the delay interval (i.e., for 8 s after a press that produced water) had no programmed consequences. Regardless of when they occurred, presses of the inoperative lever were recorded but had no programmed consequences.

For both the immediate and delayed reinforcement procedures, groups differed with respect to the dose of chlorpromazine that subjects received, either 0, 2, 6, or 10 mg/kg. Chlorpromazine hydrochloride (Sigma, St. Louis, MO, USA) was dissolved in an isotonic saline solution to a 1-ml/kg injection volume and injected intraperitoneally 30 min before experimental testing. Subjects were placed in darkened chambers 25 min after injection; chambers were lighted and sessions began 5 min later.

RESULTS

Cumulative responses on the operative and inoperative levers were recorded for each subject in 5-min bins across the entire session. Figure 1 shows cumulative operative-lever responding for all individual subjects and average levels of operative- and inoperative-lever responding for each group. There was considerable variability in responding across subjects in all groups, and the degree of variability generally increased with chlorpromazine dose. At 0 mg/kg chlorpromazine, all subjects under both the immediate and the delayed reinforcement conditions began responding on the operative lever relatively early in the session and soon developed substantial levels of operative-lever responding. As the dose of chlorpromazine increased, the time at which substantial levels of operative-lever

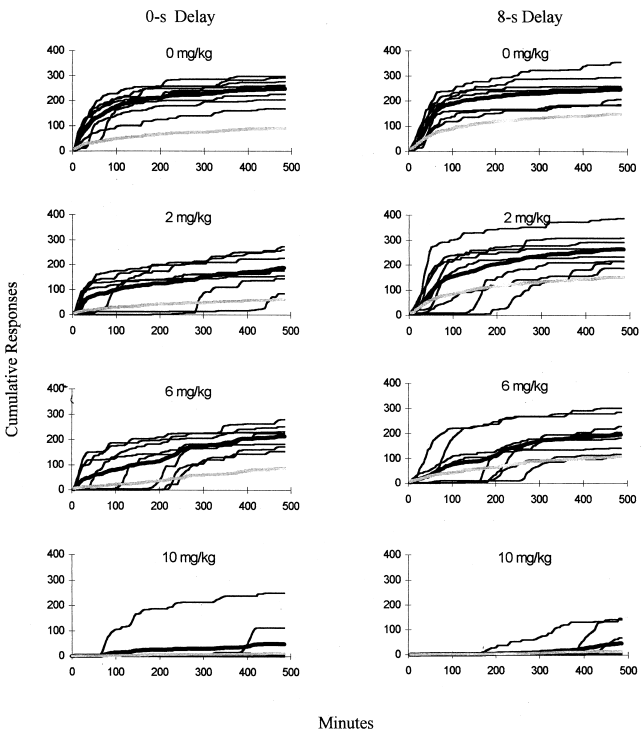

FIG. 1. Cumulative operative-lever responding for all subjects and average operative- and inoperative-lever responding for each group. For each group, thin black lines represent operative-lever responding of individual subjects and the thick black line represents the group average. The gray line represents the group mean level of inoperative-lever responding.

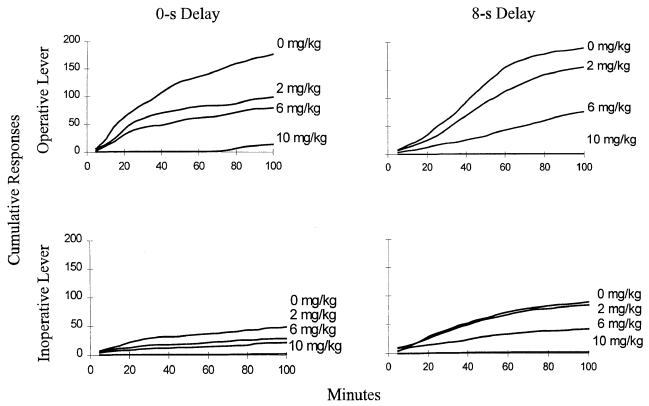

FIG. 2. Mean cumulative operative- and inoperative-lever responding by subjects in the indicated groups across the first 100 min of experimental sessions (n = 8 rats per group).

responding was observed became more variable across subjects, and the number of subjects that began responding early in the session decreased. At 10 mg/kg, most subjects exhibited relatively little operative-lever responding across the course of the 8-h session.

Because two previous studies from our laboratory (15,39) indicated that rats acquired lever-press responding within 100 min under conditions similar to those arranged in the present study and acquisition generally was observed during this period in the present study, data for the first 100 min were analyzed in detail. Figure 2 shows average cumulative operative- and inoperative-lever responses for the first 100 min of the session for all groups. Under both the immediate and delayed reinforcement procedures, the amount of operative-lever responding observed across time was inversely related to chlorpromazine dose. Three-way analysis of variance indicated that there was no significant interaction among the three factors of interest (i.e., drug dose, presence or absence of delay, time) (F = 0.33, $p > 0.05$). Two of the factors alone, dose (F = 282.15, $p <$ 0.01) and time (F = 22.37, $p < 0.01$), did produce significant effects, but the presence vs. absence of reinforcement delay did not (F = 0.19, $p > 0.05$).

Analysis of variance for operative-lever data revealed a significant overall drug effect under both the immediate (F = 10.00, $p < 0.01$) and delayed (F = 10.00, $p < 0.01$) reinforcement conditions. Multiple comparisons (Tukey's HSD) for the immediate reinforcement groups revealed that significantly ($p < 0.05$) less responding occurred in the groups that received 6 and 10 mg/kg than in the group that received 0 mg/kg. The difference in operative-lever responding between the 0- and 2-mg/kg groups approached, but did not reach, statistical significance ($p > 0.05$). Multiple comparisons for the delayed reinforcement groups indicated that the groups that received 6 and 10 mg/kg emitted significantly fewer responses ($p < 0.05$) than the group that received 0 mg/kg. The difference in operative-lever responding between the 0- and 2-mg/kg groups was small and did not approach significance ($p > 0.05$).

Although the mean level of inoperative-lever responding under both the immediate and delayed reinforcement procedures was inversely related to chlorpromazine dose, for all groups there was substantial variability across subjects in inoperative-lever responding. Analysis of variance for the inoperative-lever data in Fig. 2 indicates that there was a significant effect of chlorpromazine under both the immediate (F = 7.23, $p < 0.01$) and the delayed (F = 6.25, $p < 0.01$) reinforcement procedures. Multiple comparisons indicated that under the immediate reinforcement procedures, there was significantly less ($p < 0.05$) inoperative-lever responding in the 6- and 10-mg/kg groups than in the 0-mg/kg group. The difference in inoperative-lever responding between the 0- and 2-mg/kg groups was not significant ($p > 0.05$) under this procedure. Among delayed reinforcement groups, only the 10-mg/kg group responded significantly less than the 0-mg/kg group. Although the mean level of cumulative inoperative-lever responding in the 6-mg/kg group was substantially below the level observed in the 0-mg/kg group, variability in the former group was extreme. Therefore, the difference between the groups was not significant.

Figure 3 shows the proportion of total responses emitted on the inoperative lever across the first 100 min of the session. Data for all groups, except those that received 10 mg/kg chlorpromazine, are depicted. Subjects that received 10 mg/kg emitted too few responses during this period to allow for meaningful analysis. In this figure, values decline as stimulus control of responding develops and greater proportions of total responding are allocated to the operative lever. A value of 1.0 indicates equal responding on both levers, and a value of 0.5 indicates twice as many responses on the operative lever as on the inoperative lever.

With immediate reinforcement, a substantial majority of responses occurred on the operative lever within the first 20 min of the session, regardless of whether subjects received 0, 2, or 6 mg/kg chlorpromazine. Stimulus control of responding developed more slowly with delayed reinforcement, but none-

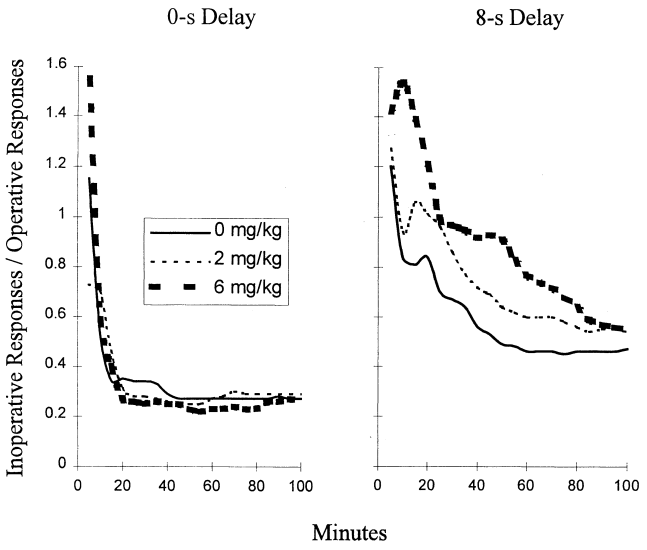

FIG. 3. Ratio of the mean number of total inoperative-lever responses to the mean number of total operative-lever responses across the first 100 min of experimental sessions by subjects in the indicated experimental groups (n = 8 rats per group). Declining values indicate progressively more responding on the operative lever, which is indicative of the development of stimulus control by the operative lever.

theless was evident in subjects that received 0, 2, or 6 mg/kg chlorpromazine. To analyze statistically the development of stimulus control, mean discrimination ratios (inoperative responses/operative responses) across the first 100 min were compared as a function of drug dose. There was a significant drug effect when reinforcement was delayed ($F = 7.78$, $p < 0.01$) but not when it was immediate ($F = 0.29$, $p > 0.05$). Planned comparisons indicated that, when reinforcement was delayed, mean discrimination ratios in the 0-mg/kg group were significantly lower than those in the 6-mg/kg group ($p < 0.01$) but not those in the 2-mg/kg group ($p > 0.05$).

Although the nominal reinforcement delay was 8 s, obtained delays were consistently shorter. Across the entire session, the mean obtained reinforcement delay (i.e., the average time elapsed between the last operative-lever response and water delivery) was 5.83, 5.72, 6.45, and 7.79 s for subjects that received 0, 2, 6, and 10 mg/kg chlorpromazine, respectively. Across all animals, there was a significant negative correlation ($r = -0.82$, $p < 0.01$) between mean obtained delays and total operative-lever responses.

DISCUSSION

The behavioral effects of chlorpromazine and related neuroleptics have been studied extensively; several reviews are available [e.g., (1,6,10,28)]. In nonhumans, such drugs generally produce dose-dependent decreases in the rate of occurrence of positively reinforced operants. They reduce spontaneous motor activity and exploratory behavior, while increasing the latency to respond to (but not necessarily the ability to discriminate) various stimuli (1).

The effects of chlorpromazine and related compounds on learning are complex and may depend on how learning is defined and measured (9). There is, however, clear evidence that such drugs can interfere with learning. Under repeated acquisition procedures, for example, chlorpromazine and related compounds increase errors (impair learning) and decrease response rates (7,19,20,21,22,23,26,35). Chlorpromazine also slowed the initial acquisition of operant behavior (i.e., interfered with learning) in prior studies by Stolerman (32,33).

Results of the present study are consistent with those reported by Stolerman (32,33). The present data suggest that chlorpromazine interfered with learning insofar as the drug produced dose-dependent decreases in both operative- and inoperative-lever responding, and the former effect can be construed as learning impairment. At chlorpromazine doses of 0, 2, and 6 mg/kg, however, all subjects acquired operative-lever responding under both the immediate- and delayed-reinforcement procedures. Moreover, such responding appeared at substantial strength and exceeded inoperative-lever responding relatively early in the session (i.e., within less than 100 min). For most subjects under both conditions, response acquisition was not evident at 10 mg/kg chlorpromazine. This is a relatively high dose, and it appeared to suppress all activity in nonselective fashion.

The procedures used in the present study indexed two aspects of learning, however: the response-strengthening effects of water deliveries (reinforcement) and the development of stimulus control by the lever on which responses produced water. Although a nonzero level of lever pressing occurs in rats when lever presses have no programmed consequences, most responding occurs relatively early in the session and there is no substantial increase in the rate of responding over the course of the session (15,36). Sustained increases in the rate of operative-lever responding, when observed, are indicative of the response-strengthening effects of reinforcement and the acquisition of operant responding, which is behavior controlled primarily by its consequences (30,32). By decreasing the rate of operative-lever responding in the present study, chlorpromazine interfered with the acquisition of operant behavior, that is, with learning.

The other index of learning, development of stimulus control, was not influenced by general drug-induced rate decreases. Chlorpromazine nonetheless significantly affected this measure when reinforcement was delayed but not when it was immediate. This finding is interesting in that it demonstrates that reinforcement delay influenced whether the drug disrupted learning. It also is consistent with previous findings, which indicate that many drugs disrupt behavior to a greater extent when stimulus control is weak than when it is relatively strong (14,24,25,36). In the absence of drug, stimulus control of responding in the present study, as indexed by the proportion of responses allocated to the operative lever, developed slower and to a lesser degree under the delayed reinforcement procedure than under the immediate reinforcement procedure.

Nearly three decades ago, Thompson and Schuster (37) proposed two general strategies for behavioral pharmacology. In one, which has become common, behavior is used to provide information about pharmacological variables (e.g., receptor mechanisms). In the other, used in the present study, drugs are used as tools to gain information about behavior. The results, when analyzed in terms of Nevin's model [e.g., (19,20)], suggest that response strength (as indexed by the discrimination ratio, but not by overall operative-lever responding) is weaker during the acquisition of operant behavior with delayed as opposed to immediate reinforcement. This outcome may be of interest to experimental psychologists as well as to behavioral pharmacologists.

Procedures similar to those used by Stolerman (32,33) have rarely been used by behavioral pharmacologists. Moreover, with a few exceptions [e.g., (2,7,17,34)], the role of reinforcement

delay as a potential modulator of drug effects has been ignored. The present results suggest that such procedures provide a reasonable assay for examining how drugs affect the initial behavioral effects of immediate and delayed reinforcement, and may merit further investigation. It should, however, be emphasized that there are several different procedures for arranging delayed reinforcement, all with associated limitations [see (12, 38,39)]. These procedures do not necessarily produce comparable behavioral effects, and it should not be automatically assumed that similar drug effects will be observed across different delay procedures.

ACKNOWLEDGEMENTS

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