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Chlorpromazine Effects on Behavior Under Escape and Fixed-Time Delivery of Shock

JAMES CLEARY,[1] FREDERICK GAULT AND ROBERT SEWELL

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

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CLEARY, J., F. GAULT AND R. SEWELL. *Chlorpromazine effects on behavior under escape and fixed-time delivery of shock.* PHARMAC. BIOCHEM. BEHAV. **15**(1) 43–47, 1981.—Chlorpromazine has typically been found to reduce responding maintained by negative reinforcement. In squirrel monkeys, however, it has been shown to increase manipulative responses that occur just prior to shock presented under a fixed-time schedule. The present study compared chlorpromazine effects on behavior of rats under a fixed-time schedule of shock delivery and a schedule involving escape from shock. In all conditions, shock was delivered to the tail of rats held in partial restraint, and the response measured was displacement of a panel positioned directly in front of the rat's nose. The escape and fixed-time schedules generated similar temporal patterns and rates of responding under both schedules, and had no differential effect on the temporal distribution of responses within the shock-shock interval.

Chlorpromazine Nose press Escape Fixed-time Restraint Anticipatory responding Rats

INTEREST in chlorpromazine (CPZ) has been maintained by its distinctive effects on behavior, both clinically and in the laboratory. As early as 1957 CPZ was found to reduce avoidance responding at doses that had no effect on escape responding [4]. Although CPZ may induce catalepsy at high doses and generally reduces responding for positive reinforcers [2], its "selective" effect on avoidance argues against the notion that CPZ's primary action is sedative or that it acts as a motor depressant. In addition, the response reduction seen on positive reinforcement schedules argues against CPZ's effect being one of "fear" or "anxiety" reduction. CPZ has also been shown to affect responses which occur just after an aversive event differently than it affects responses that occur in other temporal locations relative to the aversive event [3]. In the above study, response rates in animals displaying post-shock bursts on avoidance schedules were less affected by CPZ than were rates in animals that did not show this response pattern, suggesting that post-shock response bursts were behaviorally similar to escape responses [3]. Thus CPZ's inability to block escape responses at doses that suppress avoidance may be related to its behavioral inactivity on post-shock response bursts.

In addition to response-contingent schedules, complex patterns of responding may also be generated in situations which lack a response contingency, as a direct effect of the aversive stimulus itself [8]. When an aversive stimulus, such as electric shock, is repeatedly delivered in a regular temporal pattern, response sequences may become quite regular [10]. Specific behaviors that occur may include sensory scanning, manual manipulative, and locomotor sequences [9]. Other studies have recently demonstrated that both rates and patterns of lever pressing, by squirrel monkeys, were similar under fixed-time (FT) and fixed-interval (FI) schedules of electric shock delivery when these schedules were alternated as components of a multiple schedule [12]. They reported that the FI schedule maintained a higher rate of responding than did the FT schedule when the schedules were presented singly over long periods of time.

Under schedules of FT shock delivery, monkeys have also been shown to produce patterns of biting, lever pressing, and chain pulling, similar to those characteristically produced by escape-avoidance schedules [10]. However, few comparisons of drug effects on similar patterns of behavior maintained by aversive stimuli delivered under response-dependent and response-independent schedules have been reported.

In an investigation of drug effects on biting attack and manual motor reaction, CPZ (0.06–1.0 mg/kg) was administered to squirrel monkeys that were receiving response-independent shock every four minutes [5]. These investigators found that CPZ significantly increased pre-shock lever pressing but decreased the biting that regularly followed shock. Since biting predominately occurred just after shock and lever pressing just before, the authors suggested that one action of CPZ may be to shift response tendencies from post-shock aggression toward pre-shock anticipatory

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responding. Such anticipatory responding may be a requisite for an effective behavioral repertoire in humans and nonhumans [5].

The present study was designed to investigate, in rats, the effects of CPZ on responses maintained by fixed-time presentation of shock, with and without an escape contingency. This design allows assessment of both response rate and pattern similarities between the schedules as well as CPZ effects. Dependent variables compared in drug and nondrug sessions were post-shock response latencies, number of post-shock response bursts, alterations in the temporal pattern of responding, and rates of responding.

METHOD

Subjects

Six male Sprague-Dawley rats, obtained through the Upjohn Company colony, Kalamazoo, MI, were individually housed and given free access to food and water in the home cage. The subjects were approximately 150 days old at the start of the study and were experimentally naive. A twelve hour light-dark cycle was maintained in the colony room throughout the experiment.

Apparatus

Three restraint tubes previously described, but with several modifications, were used [1]. They consisted of three separate parts: a baseplate, a restraint tube, and a removable cap to which was affixed the response manipulandum.

The baseplate was constructed of 12 mm clear plastic and was 20 cm by 42 cm. It served to mount the restraint tube firmly and to support the electrodes that delivered shock to the tail of the animal. The tube snapped onto the baseplate such that the subject's tail was positioned beneath two aluminum shock electrodes (12 cm×1 cm×1 cm), mounted on a stockade affixed to the baseplate. The electrodes swung down to lightly make contact with the subject's tail. The electrode placements were 2.5 cm apart.

The restraint tube was 0.5 cm clear plastic stock, 23 cm long and 10 cm in diameter. A horizontal floor, consisting of a clear plastic plate (6 cm×23 cm×0.5 cm), was cemented to the bottom of the tube's interior. A longitudinal slit 2.5 cm wide, ran the entire length of the tube's dorsal surface to allow for 'threading' of the animal's tail. The posterior end of the tube was permanently closed by a clear plastic plate (12 cm×15 cm×0.5 cm). This plate had a vertical slit, 3 cm wide, that allowed the rat's tail to extend outside the tube where it could be secured to a plastic bar by cloth-backed surgical tape.

Once the animal was threaded into the tube and its tail secured, a 12.5 cm×17 cm×2.5 cm plastic cap, to which the manipulandum was attached, was affixed to the anterior end of the tube. The manipulandum was a 0.5 cm thick clear plastic plate hinged to the cap at the level of the restraint tube floor. The plate was 8 cm in diameter and closely fit the interior of the tube. The manipulandum was hinged so that it hung into the tube at an angle of 10 degrees from the vertical. The animal's nose could displace this plate, closing a microswitch and counting as a response. Approximately 0.03 Newtons of force were required to close the microswitch.

The experimental sessions were conducted in three force-ventilated chambers into which the entire apparatus was placed. Each chamber was equipped with a viewing window and forty-watt incandescent house light. White noise and a ventilating fan combined to produce approximately 80 dB of masking noise within the chamber.

Procedure

Experimental sessions were conducted five days each week. Two groups of three rats were used. Each group received a 2 milliampere shock every 3.5 minutes. There were sixteen shocks each session. Shock-shock intervals were timed from the termination of the previous shock and a 3.5 minute shock-free period ended each session. For the FT group, responses had no effect: these animals received 0.5 seconds of shock every 3.5 minutes regardless of their behavior. For the escape group (ESC), a response in the presence of a shock terminated that shock. If no response occurred the shock was terminated by the experimenter after 10 seconds. All other responses had no programmed consequences. Animals in each group were prepared similarly and tested simultaneously.

Prior to each session, each animal's tail was cleansed with isopropyl alcohol, and Electro-sol EKG Cream (Scientific Instruments, Rochester, NY) rubbed into the skin at the electrode site. The cream was used to prevent skin damage and reduce skin electrical resistance. Electrodes then swung into position and resistance through the tail was measured across the two electrodes. If the tail resistance was not in the range of 10,000 to 20,000 ohms, more EKG cream was rubbed into the tail. This procedure was repeated until the resistance was within the above range.

Since certain characteristic response patterns seen on fixed-time scheudules with shock develop slowly [8], a baseline of approximately ninety sessions preceeded drug administration for both groups.

Drug Preparation and Schedule of Administration

Chlorpromazine hydrochloride was purchased as Thorazine (Smith, Kline, and French Corp., Philadelphia, PA). To reduce measurement error, the commercially available concentration of 25 mg/ml was decreased to 12.5 mg/ml by mixing with an equal amount of physiological saline (0.9%). This solution was prepared weekly. All injections were given subcutaneously, and all doses refer to the commercial hydrochloride salt. Four doses of CPZ were given: 1 mg/kg, 2 mg/kg, 3 mg/kg, and 4 mg/kg. All saline control injections were 0.2 ml.

Chlorpromazine was usually given on Wednesday of each week, thirty minutes before the session began. Saline injections were given thirty minutes pre-session on all other days. Sessions on Mondays and Tuesdays served as baseline for the particular dosage level given on Wednesday. Doses were given in an irregular order. Each dose was given to each animal twice.

RESULTS

Chlorpromazine reduced total nose press responses for all animals at all dose levels. Mean response rate per session across doses for each group is shown in Fig. 1 as a percentage of the baseline rate. For the FT group, mean rates were decreased to 72%, 37.5%, 33.3%, and 26.2% of baseline at CPZ doses of 1 mg/kg, 2 mg/kg, 3 mg/kg, and 4 mg/kg respectively. Mean ESC group rates were decreased to 60.3%, 62.8%, 46.0%, and 46.2% of baseline at the same respective doses. Mean rates for both groups, at all doses of CPZ, were significantly different from the baseline condition ($p<0.05$,

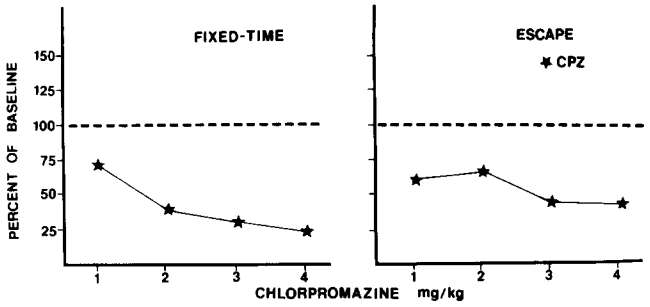

FIG. 1. Mean response rate per session as a percentage of baseline across doses of CPZ. The standard errors of the mean, expressed as a percentage of the baseline mean, were ±4.02% for the FT group and ±5.06% for the ESC group.

Fisher's Protected Least Square Difference). Mean response rates for individual subjects are shown in Fig. 2. At the most effective dose, CPZ appeared to reduce responding to a minimum level of approximately 25 responses per session.

Since total rate was generally decreased by CPZ, a change in the distribution of responses within shock-shock intervals is best expressed, for each 30 second bin, as a percentage of the total rate. In this way a shift in response distribution due to CPZ can be assessed even though the total rates for CPZ are reduced compared to baseline. Mean baseline rates and mean drug rates across bins are shown in Fig. 3 as a percentage of total responses. As can be seen from Fig. 3, the distribution of responses within the shock-shock interval was little affected at any dose of CPZ. Chlorpromazine appeared to increase slightly the proportion of responses in the immediate post-shock period (Bin 1) for both groups, although the absolute number of responses in all bins was decreased. The percentage of responses occurring in the immediate pre-shock period (Bin 7) was not significantly increased at any dose. At the highest dose, responding in the immediate pre-shock period was completely eliminated.

Post-shock response bursts were defined as responses which occurred during the 5 second period following shock offset. The mean number of post-shock response bursts per session were decreased with respect to mean baseline bursts across all doses for both groups (Fig. 4). This effect closely parallels the overall rate-decreasing effect of CPZ (Fig. 1).

Table 1 shows the effect of CPZ on mean post-shock response latencies. Mean baseline latencies for the FT group were more variable (Range=0.18–173.1 seconds) than were the mean baseline latencies for the ESC group (Range =0.15–0.71 seconds). The FT group also showed considerably longer mean baseline latencies. The mean latencies were increased for both groups at all doses of CPZ. Latencies for the FT group were more greatly affected by CPZ than were latencies for the ESC group.

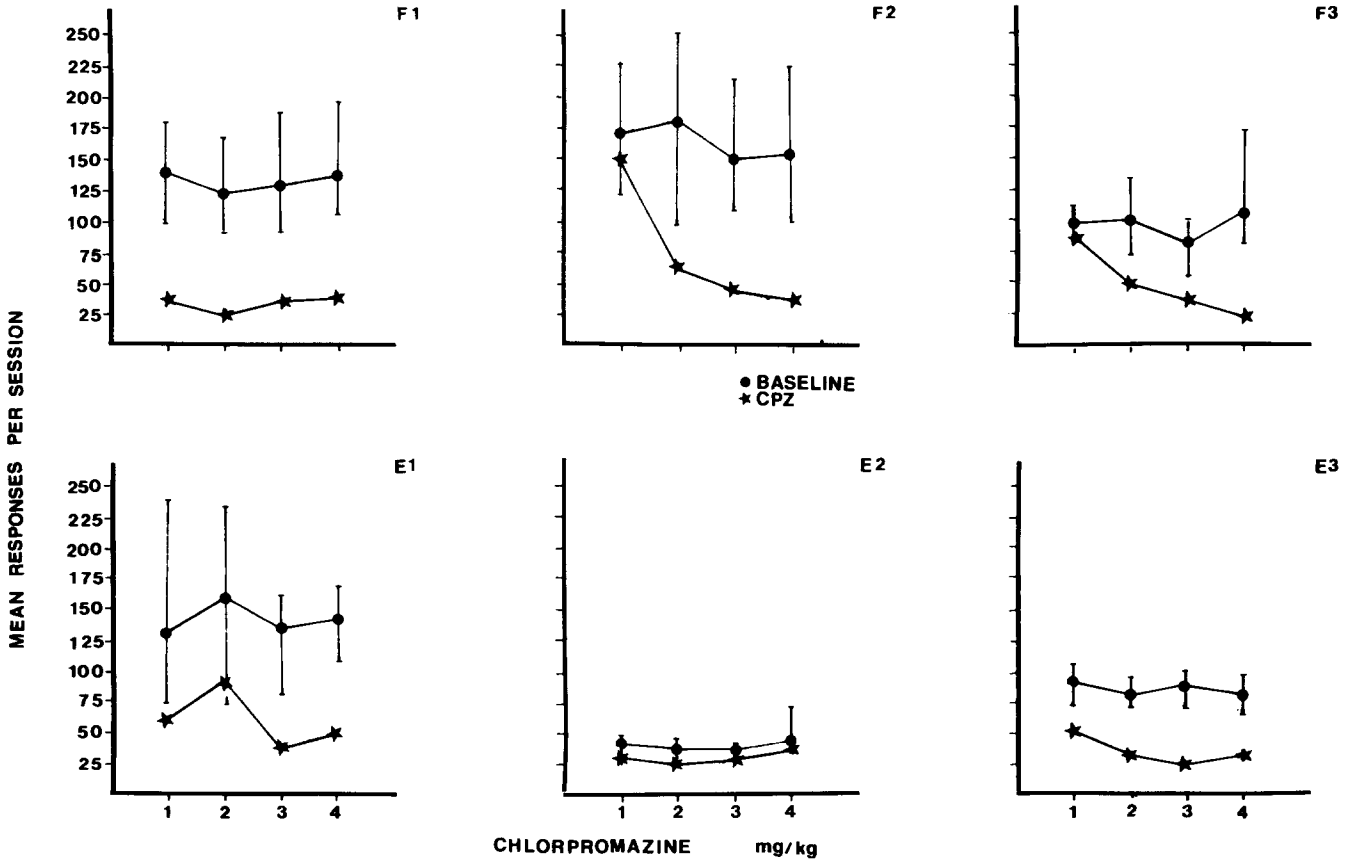

FIG. 2. Individual mean response rates across doses of CPZ. Baseline rates are means of the two sessions prior to each drug administration (total of 4 sessions). F1, F2, and F3 are the Fixed-time group; E1, E2, and E3 are the Escape group. Vertical lines enclose the range.

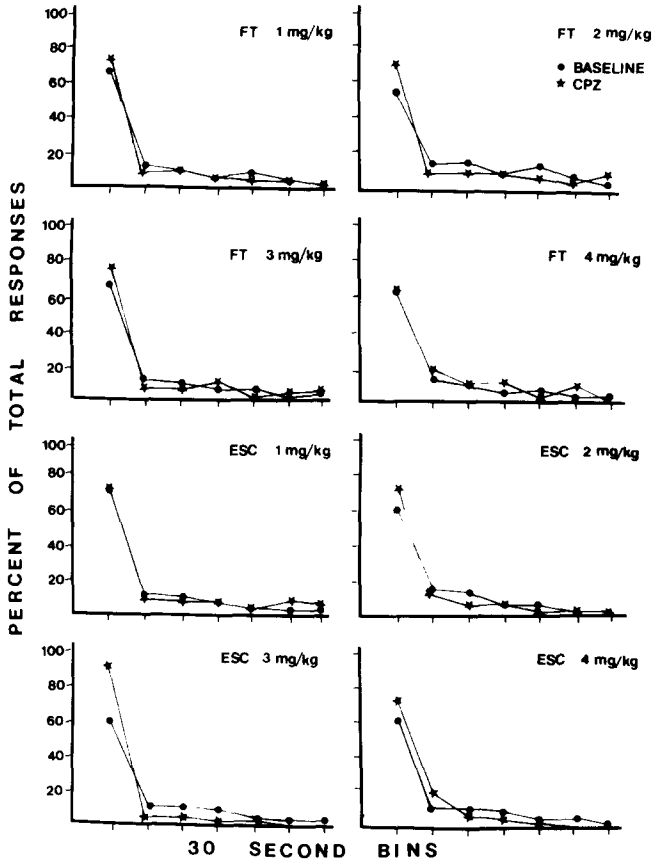

FIG. 3. Individual mean response rates, as a percentage of total responses across 30 sec bins and doses of CPZ.

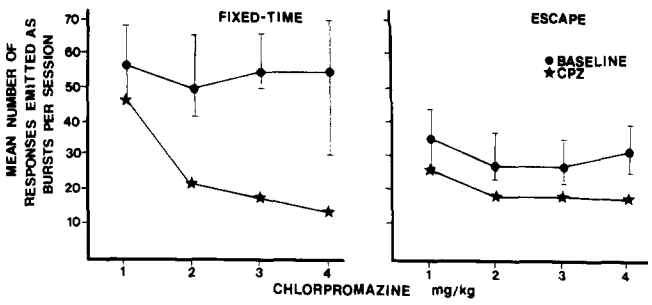

FIG. 4. Mean responses educed as post-shock response bursts per session, for baseline and all doses of CPZ. Vertical lines enclose the range.

TABLE 1

MEAN POST-SHOCK RESPONSE LATENCIES

Group and Dose	Baseline (Seconds)	Drug (Seconds)
Fixed-time 1 mg/kg	0.90	4.56
Fixed-time 2 mg/kg	1.87	36.57
Fixed-time 3 mg/kg	1.39	56.64
Fixed-time 4 mg/kg	2.33	33.28
Escape 1 mg/kg	0.17	0.27
Escape 2 mg/kg	0.20	0.31
Escape 3 mg/kg	0.26	0.70
Escape 4 mg/kg	0.19	0.36

DISCUSSION

A comparison of baseline rates of responding between the fixed-time group and the escape group show several similarities. The two schedules generated comparable rates of responding, with the FT shock schedule actually producing a slightly higher rate. The temporal distribution of responses within the shock-shock interval was almost identical for the two groups, as were the total responses emitted as post-shock bursts. These findings are in agreement with the contention that complex patterns of responding can be produced as a direct result of the response-independent presentation of an aversive event, and that these patterns can resemble those produced under response-dependent schedules [8]. Differences in the baseline behavior of the 2 groups that can be attributed to the effect of the escape contingency is best shown in the post-shock response latencies.

The overall rate-reducing effects of CPZ seen under fixed-time shock schedules are comparable to those typically observed under avoidance schedules in a variety of species [6,13]. The rate reduction is, however, in contrast with the effects of CPZ reported for squirrel monkeys receiving fixed-time shock, where the response consisted of pressing an ineffective lever [5]. In that study, overall lever pressing rates were increased by CPZ.

Several differences between the above experiment [5] and the present one could account for this dissimilarity in drug effects. In addition to differences in species, apparatus, and response topography, the monkeys receiving fixed-time shock in the above experiment had an alternate response option available (biting); this was not the case in the present study. Further, temporal patterns of responding differed in the two experiments. The authors indicated that lever pressing occurred primarily in the pre-shock period and that CPZ acted upon this response class, increasing the rate [5]. In the present study, baseline rates were low in the immediate pre-shock period and CPZ had little effect on or decreased responding in this portion of the shock-shock interval. Thus the present study does not suggest that CPZ increases anticipatory responding. However, the failure of rats to develop appreciable pre-shock responding during baseline

could have precluded the strengthening of this response class by CPZ. Also, a "freezing" response may occur in the pre-shock period [11]. This freezing response may be of more strength and longer duration in the rat than in the squirrel monkey.

To clarify the possible role of the factors discussed above, studies using a variety of species and parameters would have to be undertaken. Through such studies, the importance of response topography, sequential response patterning, and general species characteristics as determinants of drug effects on behaviors maintained under both response-independent and response-dependent schedules, might be discovered.

Chlorpromazine had little effect on the distribution of responses throughout the shock-shock interval. The slight increase in the proportion of responding during the immediate post-shock period appears to be due to CPZ's effect on responses educed as post-shock bursts. Although these bursts were decreased by CPZ at all doses, they were reduced proportionately less than were the total responses. Similar findings have been reported under avoidance schedules [3]. The apparent insensitivity of responses occurring as post-shock bursts may account for CPZ's 'selective' ability to decrease avoidance responding at doses that do not affect escape [3]. Other authors have likened responses that occur just after an aversive event to escape responses [8]. The between group similarities in rate of responses educed as bursts, as well as the effect of CPZ on this response class, support this analysis.

Many reports of responding under escape schedules report only whether a response occures in the presence of the aversive stimulus. Under these conditions low doses of CPZ often show no effect. In the present study, responding occurred throughout the shock-shock interval under both response-dependent and response-independent schedules and was decreased by CPZ. Total responses under the escape schedule were reduced less, proportional to their baseline, than were total responses under the fixed-time schedule. That this difference between the groups is neither large nor totally consistent across doses suggests that the presentation of the shock itself exerts considerable control over behavior. In addition, the similarities in both rate and temporal patten of responding between the response-dependent and the response-independent groups, attest to potent control by the stimulus.

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