Psychopharmacologia 3, 361—373 (1962)

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An Analysis of Chlorpromazine-Induced Suppression of the Avoidance Response*

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(Received March 1, 1962)

Chlorpromazine, one of the phenothiazine derivatives, suppresses the avoidance response at doses which neither produce ataxia nor impair the performance of an escape response (COOK et al.; MILLER et al., 1957a; MAFFII). The avoidance response suppression is a property of most, if not all, phenothiazine derivatives (FELLOWS & COOK; IRVIN; STONE; COOK & KELLEHER), and can be manifested during acquisition and extinction (ADER & CLINK; MILLER et al., 1957a, 1957b), as well as maintenance, of the response (COOK & WEIDLEY; VERHAVE et al.). The avoidance-suppressing property of the phenothiazine derivatives may be related to the drugs' action in relieving psychotic disorders, because a rank order relation has been demonstrated between the dose at which any one phenothiazine derivative suppresses the avoidance response and its relative potency in psychotic relief (COOK & KELLEHER). However, some nonataractic compounds, including morphine and belladonna alkaloids such as atropine and scopolamine, also specifically suppress the avoidance response (MIKHELSON et al. cited by BERGER; MAFFII; PASKAL & VANDERWOLF). A more detailed discussion can be found in HERZ's review of drug-induced avoidance response suppression.

The three experiments reported here form part of a systematic search for the factors underlying the specific suppression of the avoidance response by chlorpromazine. Two separate conclusions have been reached to explain chlorpromazine-induced avoidance response suppression. Some investigators (e.g., ADER & CLINK; MILLER et al., 1957a; TORRES) have suggested that chlorpromazine reduces "fear" or "anxiety" the presence of which is believed necessary for the reinforcement of the avoidance response. The "fear reduction" suggestion has an intuitive plausibility to it because of the drug's therapeutic effect, but other investigators (e.g., KILLAM & KILLAM; BRADLEY; KEY) have concluded that chlorpromazine produces an impairment of "sensory-arousal" functions, an impairment which could suppress the avoidance response by inhibiting

* This research was supported by Grant No. APT-36 from the National Research Council of Canada to Dr. D. BINDRA. Chlorpromazine was supplied free of charge, as *Largactil*®, by Poulenc Ltd., Montreal. While conducting the experiments, the author held a Bursary from the National Research Council of Canada.

cue functions or arousal functions or both. From an examination of the results of the present and previous experiments, an alternative conclusion is reached here.

In Experiment 1, an attempt was made to partially overcome chlorpromazine's decremental effect on the avoidance response by manipulating selected parameters of the avoidance situation. Partly because increasing the preshock interval was the only manipulation which improved avoidance response performance under the drug, it was suggested that chlorpromazine induced a locomotor deficit. In order to see whether the locomotor deficit was one of motor performance (as opposed to one attributable to fear reduction), Experiment 2 was planned to investigate chlorpromazine's effect on avoidance learning as measured by later, undrugged, performance. In Experiment 3, the relations between avoidance response suppression and chlorpromazine's effect on selected component acts of the avoidance response were investigated.

Methods and Results

Subjects. Fifty-seven naive male hooded rats of the Long-Evans strain, obtained from the Royal Victoria Hospital colony, served as subjects. At the start of the experiments, the animals were about 110 days old. During the experiments, they were housed two to a cage in which food and water were continuously available.

Apparatus and Materials. The avoidance apparatus used in all experiments was a wooden box, 106.7 cm long, 14.6 cm wide and 50.8 cm deep. The walls of one half of the box were painted black and the walls of the other half white; the color of the walls divided the box into two equal-sized compartments with no structural separation between them. The floor of the apparatus was a grid of 0.16 cm steel rods set about 1.25 cm apart. The grid floor of the black compartment could be electrically charged with a shock "scrambled" through 15 separate output leads; the nonelectrified white compartment was the goal compartment.

The compounds used in the experiments were chlorpromazine hydrochloride B.P. and a 0.9% solution of sodium chloride. The fluid contents of commercial vials of the chlorpromazine (5 mg drug/ml water) were mixed with sufficient additional distilled water to attain a concentration (in mg/ml) which was numerically equal to the dose used (in mg/kg). The use of such concentrations kept the volumes of both the drug and the isotonic saline constant at 1 ml/kg. The drug was freshly mixed for each experiment. Administration in all cases was by intraperitoneal injection.

General Procedure. The avoidance response in the present experiments required locomotion from a starting point at the end of the black

compartment into the white compartment. Under "standard conditions", there were no specific warning signals and a 1.2 mA electric shock was administered after a 5 sec preshock interval. In all experiments, the intertrial interval was 30 sec, during which the animal remained in the white compartment. After the intertrial interval, the animal was manually replaced at the starting point and another trial administered. Trials were administered in each session until an animal had performed 9 successful avoidance responses in 10 consecutive trials, with a maximum of 30 trials. The attainment of the 90% criterion or the 30-trial maximum defines a session for all experiments. Avoidance response performance was measured by the total number of shocks received (that is, escape responses) in reaching the 90% criterion or 30-trial maximum. The compounds were injected 30 min. before the start of the appropriate session. "Standard conditions" were used in all training sessions.

Experiment 1

In this experiment, an attempt was made to increase the number of avoidance responses made under the influence of chlorpromazine by increasing, in turn, one of 3 parameters. The 3 manipulated parameters were the magnitude of warning signals, the intensity of electric shock, and the length of the preshock interval.

Procedure. Twenty-six rats were first given 4 sessions of avoidance training, using the "standard conditions" (no specific warning signals, a 1.2 mA shock, and a 5 sec preshock interval). After training, there were 3 Test Phases. No drug was administered during training; 3.0 mg/kg chlorpromazine were injected prior to each Test Phase.

In each Test Phase, the essential plan was to compare the drugged animals' avoidance performance during a session in which the "standard conditions" were used (Standard Session) with the same animals' performance during a session in which the value of one of the 3 parameters was increased (Experimental Session). To this end, the animals used in each Test Phase were assigned to two equal groups which were tested in a counterbalanced order. One group was tested first in an Experimental Session, and then, immediately afterwards, was tested in a Standard Session. The reverse order of Standard and Experimental Sessions was used with the other group. All 26 rats were used in the first Test Phase; 14 of the 26 were selected for the second and third Test Phases. In each Test Phase, one parametric value was increased and all other conditions were held constant.

In the first Test Phase, the magnitude of the warning signals was manipulated (Warning Signals Phase). In the Experimental Session, the warning signals were used; in the Standard Session, no specific warning signals were used. The warning signals comprised a 100 watt

bulb and a 5000 cps. tone of about 70 db., both of which were simultaneously applied when the animal was placed at the starting point, and terminated when the animal entered the white goal compartment. Twelve rats (6 tested first in the Experimental Session and then in the Standard Session, and 6 tested in the reverse order) were tested with the warning signals positioned directly over the entrance to the goal compartment. For the remaining 14 (7 from each of the counterbalanced orders), the warning signals were positioned over the starting point.

In the second Test Phase, the intensity of electric shock was manipulated (Shock Intensity Phase). In the Experimental Session, a 2.8 mA shock was used; in the Standard Session, a 1.2 mA. shock was used.

In the third Test Phase, the length of the preshock interval was manipulated (Preshock Interval Phase). In the Experimental Session, a 15 sec preshock interval was used; in the Standard Session, a 5 sec preshock interval was used.

Results. When the Experimental and the Standard Sessions were pooled, and the differences between first and second sessions only were examined, there were no significant differences between the first and second sessions in either the Warning Signals Phase or the Preshock IntervalPhase. In the Shock Intensity Phase, however, the number of shocks received decreased by a mean value of 2.7 from the first session to the second ($p < .05$; Wilcoxon matched-pairs, signed-ranks test, two-tailed).

Table 1. *Changes between the Standard and Experimental Sessions in the three Test Phases, in mean number of shocks received*

Phase	Changes between sessions		
	Standard session	Experimental session	Change
Warning signals	14.38	13.35	−1.03
Shock intensity	19.28	19.00	−0.28
Preshock interval	19.50	11.21	8.29*

* $p < .01$; Wilcoxon matched-pairs, signed-ranks test, two-tailed.

Comparisons between the Standard and Experimental Sessions for all 3 Test Phases are shown in Table 1. Of the 3 manipulated variables, lengthening the preshock interval was the only manipulation which increased the number of avoidance responses performed under the influence of chlorpromazine ($p < .01$; Wilcoxon matched-pairs, signed-ranks test, two-tailed).

The results from the Warning Signals Phase were also analyzed for the effects of the position of the signals. These results are shown in Table 2. Disregarding the order of presentation of Experimental and Standard Sessions, the warning signals had a tendency to improve avoidance performance when they were positioned over the starting

point, but a tendency to decrease performance when they were positioned over the goal entrance (for both, $p < .05$; Wilcoxon matched-pairs, signed-ranks test, two-tailed).

The behavior of the animals in this experiment was observed closely, and a specific pattern of responding could be observed when an animal made an avoidance response during the 15 sec preshock interval. During the total avoidance response, 3 or 4 separate behavioral "units" or "component acts" could be isolated by pauses between them. First, the animal typically executed an orienting movement, turning its head to one side or, often, turning completely around to face the white compartment. Orienting tended to occur rapidly. Second, there was a considerable pause, following which the animal quickly moved towards the white compartment. Third, some animals paused just before entering the white compartment, frequently sustaining a shock during the pause. Fourth, many animals also paused just after entering the white compartment, after which they would typically continue to the far end of the compartment. For purposes of convenient description, I have used the term *segmentation* to describe this pattern of motion and pauses because the total response appears segmented into various bits or component acts. Complete segmentation, that is, all 3 pauses in the same trial, was seen only about a dozen times, but each pause was observed at least twice in all animals which made any response. The first pause, between orienting and the initial locomotion, was by far the most frequent; this pause occurred on almost every trial.

Table 2. *Changes between the Standard and Experimental Sessions of the Warning Signals Phase, in relation to the position of the warning signals. Scores represent mean number of shocks received*

Position of warning signals	Changes between sessions		
	Standard session	Experimental session	Change
Goal entrance	6.83	10.08	3.25*
Starting point	20.71	16.14	−4.57*

* $p < .05$; Wilcoxon matched-pairs, signed-ranks test, two-tailed.

Experiment 2

Rats were first given two sessions of avoidance training while under the influence of chlorpromazine. Then, in a third session, they were tested, undrugged, in order to see if the avoidance response had been acquired.

Procedure. Twenty-two rats were first randomly assigned to either a Chlorpromazine Group ($n = 12$) or a Saline Group ($n = 10$). Then all animals received 3 sessions of avoidance training in all of which

the "standard conditions" were used. The Saline Group received isotonic saline prior to all 3 sessions. The Chlorpromazine Group received injections of 2.5 mg/kg chlorpromazine prior to the first two sessions; for the third session, this group also received injections of isotonic saline.

Table 3. *Mean number of shocks received by the Saline and Chlorpromazine Groups in learning the avoidance response. In the 3rd session, both groups received only saline*

Session	Group	
	Saline	Chlorpromazine
1st	7.4	16.5*
2nd	1.6	13.1*
3rd	0.8	1.3**

* Greater than the Saline Group in the same session ($p < .002$; Mann-Whitney U test, two-tailed).

** Less than the Saline Group in the 1st session ($p < .002$; Mann-Whitney U test, two-tailed).

Results. The results of the experiment are shown in Table 3. In the first two sessions, the Chlorpromazine Group received more shocks than the Saline Group ($p < .002$; Mann-Whitney U test, two-tailed). In the third session, however, when only saline was administered to both groups, all animals received about the same number of shocks. The mean improvement in performance from the first to the second session was about the same for both groups. The performance of the Chlorpromazine Group in the third session was superior to the performance of the Saline Group in the first session ($p < .002$; Mann-Whitney U test, two-tailed).

Experiment 3

This experiment represents an attempt to specify more precisely the effect of chlorpromazine on the avoidance response by differentiating the drug's effect upon locomotor initiation and upon the running time after initiation. An attempt was also made to relate the severity of segmentation to the degree of avoidance response suppression induced by the drug.

Procedure. Nine rats were first given 3 sessions of avoidance training, using "standard conditions", followed by two Test Phases. Prior to the first Test Phase, each animal received isotonic saline (Control Phase). Prior to the second Phase, each animal received 2.5 mg/kg chlorpromazine (Chlorpromazine Phase). In all other respects the two Test Phases were identical.

Paired comparisons on each animal were made between the two Test Phases. First, in both Test Phases, a regular session of trials was administered (that is, with the 90% criterion and 30-trial maximum), using the "standard conditions". During the regular session, the total number of *shocks received* was noted for each animal.

Then, immediately following the regular session, the shock was discontinued and 10 additional trials were administered. On the odd-

numbered nonshock trials, the time between placing the animal at the starting point and its subsequent initiation of locomotion was recorded; this was called the *locomotor initiation latency.* If an animal did not move within 30 sec, it was manually placed in the white compartment and assigned a latency of 30 sec for that trial. On the even-numbered nonshock trials, the time between the locomotor initiation and the subsequent entry into the goal compartment was recorded; this was called the *running time.* If an animal initiated locomotion, but paused before entering the goal compartment, the trial was discounted and another was immediately administered in its place. Both the locomotor initiation latency and the running time were measured with a manually operated stopwatch.

Results. Means of the 5 locomotor initiation latencies and of the 5 running times were computed for each animal, for both Test Phases.

Table 4. *Comparisons of mean group scores between the Control Phase and the Chlorpromazine Phase*

	Measure	Test phase	
		Control	Chlorpromazine
Regular session	Number of shocks received	1.55	5.66*
Nonshock trials	Locomotor initiation latency (in sec)	0.68	3.32*
	Running time (in sec)	0.85	0.82

* Greater than the same measure in the Control Phase ($p < .01$; Wilcoxon matched-pairs, signed-ranks test, two-tailed).

Table 4 shows group means for all 3 measures in both Test Phases. Under the influence of chlorpromazine, the animals received more shocks and had longer locomotor initiation latencies than without the drug (for both, $p < .01$; Wilcoxon matched-pairs, signed-ranks test, two-tailed). However, the drug did not alter the running time.

Table 5
Product-moment correlation coefficients among the three measures, during the Chlorpromazine Phase

	Number of shocks received	Running time
Locomotor initiation latency	0.94***	−0.65*
Running time	−0.69**	—

* $p < .05$, two-tailed test.
** $p = .02$, two-tailed test.
*** $p < .01$, two-tailed test.

Using the results of the Chlorpromazine Phase only, product-moment correlation coefficients were computed among the 3 measures. The coefficients are shown in Table 5. The locomotor initiation latency under chlorpromazine was highly and positively correlated with the number of shocks received under the drug ($p < .01$, two-tailed). The

running time was negatively correlated with the number of shocks received ($p = .02$, two-tailed) to about the same degree and in the same direction that the running time was correlated with the locomotor initiation latency ($p < .05$, two-tailed).

In this experiment, another phenomenon was observed, which had been noted but disregarding previously. In the Chlorpromazine Phase, four rats had a tendency to shriek while sitting on the grid, when no shock was being applied. This conditioned vocalization (VANDERWOLF) was not the squealing associated with placing an animal at the starting point nor picking up the animal from the grid. For the four animals, conditioned vocalization occurred on 10% to 75% of the trials in the Chlorpromazine Phase, primarily during the nonshock trials. The animals which showed conditioned vocalization made fewer avoidance responses than the other animals, but within the group of four conditioned vocalizers there did not seem to be a rank order relation between the number of shocks received and the number of conditioned vocalizations.

Discussion

The results of Experiment 1 suggested that chlorpromazine induced a locomotor deficit in suppressing the avoidance response. The locomotor deficit was specifically suggested by the finding that lengthening the preshock interval from 5 sec to 15 sec increased the number of avoidance responses made under chlorpromazine. It appeared that the drugged rats could make the avoidance response, but merely required more time. The failure of both introducing warning signals and increasing the shock intensity to increase the number of avoidance responses suggested that the locomotor deficit could not be attributed to sensory deficits.

Although the warning signals were ineffective in improving the avoidance response performance under chlorpromazine (Table 1), the same signals acted as aversive stimuli, directing the drugged animals away from the source of stimulation (Table 2). It is clear, from the escape responses to the warning signals, that the drugged animals sensed and attended to the stimuli, and were aroused by them. Therefore, if chlorpromazine had induced a sensory deficit sufficient to suppress the avoidance response, the introduction of the warning signals should have improved the avoidance response performance, because the signals clearly were perceived.

Similarly, if chlorpromazine decreased sensitivity to electric shock, the increase in shock intensity from 1.2 mA to 2.8 mA should have improved avoidance response performance under the drug. Undrugged rats reach an asymptotic minimum in the avoidance response latency at about 1 mA (KIMBLE; BLACK et al.). If chlorpromazine had decreased

the sensitivity to electric shock, the avoidance response latency would not yet have reached its minimum at the lower intensity, and the increase to 2.8 mA would shorten the response latency. For that reason the increased locomotor latency induced by chlorpromazine cannot be attributed to a decreased sensitivity to electric shock.

Although the results of Experiment 1 suggested a locomotor deficit without accompanying sensory impairments, chlorpromazine might have reduced the "fear" or "anxiety" the presence of which is believed necessary for the reinforcement of the avoidance response. The results of Experiment 2, however, demonstrated that the chlorpromazine drugged rats learned the avoidance response as well as the saline control group, as shown by the performance in the third session (Table 3); apparently the drug prevented the performance of the response in the first two sessions. It is difficult to understand how the avoidance response could be acquired under the influence of chlorpromazine if the drug reduced the efficacy of the reinforcer during training to the point where the performance of the response was suppressed. Avoidance training under chlorpromazine results in more rapid extinction than training without drug (ADER & CLINK; MILLER et al., 1957b) and also blocks mediated acquisition of the avoidance response (DAVIS et al.). However, the maintenance of the electric shock in the present Experiment 2 demonstrates rapid avoidance response acquisition under chlorpromazine, even though the ease with which the acquisition can be shown varies with different procedures.

It has thus been concluded that chlorpromazine induces a locomotor deficit without impairing the pertinent sensory or motivational processes. The results of Experiment 3 specify the locomotor deficit more precisely as a deficit in initiation; chlorpromazine delays locomotor initiation without affecting the speed of locomotion after initiation. Applying a variance interpretation (FERGUSON, p. 107) to the correlation coefficient between the length of the locomotor initiation delay and the number of shocks received (Table 5), it can be estimated that over 85% of the avoidance response suppression is attributable to the delay in locomotor initiation. The failure of chlorpromazine to affect the running time supports the conclusion of MILLER et al. (1957a) that the drug does not suppress the avoidance response by producing peripheral muscular inabilities. The negative correlation between the number of shocks received and the running time can be interpreted as further evidence that chlorpromazine does not alter the efficacy of shock and shock termination, that is, the rats which have been shocked more often tend to run faster. Results similar to those obtained in Experiment 3 were also found in an unreported experiment in which the avoidance response required jumping rather than running to the goal.

If chlorpromazine suppresses the avoidance response by delaying the initiation of locomotion, the first segmentation pause (Experiment 1) is understandable. However, the pauses just before and just after entering the goal compartment are not easily understood unless entering the goal and moving to its far end constitute separate locomotor acts the initiation of which chlorpromazine also delays. While training 18 naive undrugged rats in the same apparatus, for another experiment, it was noted that 14 of the animals made pauses during the first training session just like the pauses made by chlorpromazine-drugged rats in the present experiments. Both normal naive rats, during the initial training trials, and chlorpromazine-drugged rats, in later as well as the initial trials, paused between orienting and running, just before entering the goal compartment, and just after the entrance. The rank order frequency of the pauses is the same for both normal naive and chlorpromazine-drugged rats. It thus appears that orienting, approaching the goal, entering the goal, and moving to its far end all constitute separate component acts in the avoidance response. Under normal conditions, continued practice decreases the initiation latencies of the component acts until they become integrated into one smooth response. Chlorpromazine, by delaying the initiation of locomotor acts, reinstates the segmentation (as opposed to integration) observed during normal training, leaving the latency of the nonlocomotor orienting act and the running speed relatively intact.

Some other experimental results are also pertinent to the conclusions drawn here. Chlorpromazine depresses locomotion in both open field and activity wheel situations (Boyd & Miller; Jasmin & Bois; Janssen et al.), and the amount of locomotor decrement, like the degree of avoidance suppression, is directly related to the dose level (Fellows & Cook; Miller et al., 1957a). Fellows and Cook, as well as Irvin, also found that, within a group of phenothiazine derivatives, the dose at which any one of the compounds suppressed the avoidance response was related to the dose required to depress locomotor activity. Using a time-sample method in which locomotor acts were included, Bindra and Baran found that chlorpromazine decreased the number of activity *changes*, that is, the number of initiations of new acts.

If chlorpromazine delays locomotor initiation, it follows that the drug should not affect the acquisition or maintenance of a response which requires no locomotion. In keeping with this conclusion, Hunt demonstrated that a high dose of chlorpromazine impaired neither the acquisition nor the maintenance of a conditioned emotional response, as measured by the suppression of bar pressing and by defecation. The observation of conditioned vocalization in Experiment 3 seems similar to Hunt's findings, and has similar implications. Moreover,

BLOUGH found that chlorpromazine actually facilitated the acquisition and maintenance of a response which required pigeons to stand still for food reinforcement.

In delaying locomotor initiation, chlorpromazine must selectively affect only certain kinds of locomotor acts, for both escape response initiation and the reaction time to unconditioned stimulation seem unimpaired by the drug. As the evidence suggests a direct motor deficit, the selective action of the drug must be attributed to differences in the locomotor initiation mechanisms among the responses. Assuming a continuum from completely stimulus-bound to completely voluntary responses, chlorpromazine may selectively suppress the initiation of the more voluntary responses, that is, of responses the initiation of which is more dependent upon mediating processes (HEBB, p. 48). The avoidance response is often regarded as a kind of escape response to which classical conditioning has been added, but the implication of a mediating process in the avoidance response requires a more complex mechanism. The more complex mechanism is required, in part, by the evidence that chlorpromazine suppresses the avoidance response while disrupting neither the classical conditioned response (HUNT), nor the escape response (MAFFII), nor the instrumental response (ACETO et al.; BLOUGH).

Conclusion

Chlorpromazine suppresses the avoidance response by delaying the initiation of the more voluntary locomotor acts, and when a number of such acts are components of some integrated response, the initiation of each component act is delayed. The locomotor initiation delay is a motor performance deficit induced through the inhibition of some central nervous system function.

Summary

Three experiments were reported, as part of a search for the factors underlying chlorpromazine-induced suppression of the avoidance response. The avoidance response required moving from the end of one compartment in a two-compartment box into the other compartment. The experiments were conducted upon the hooded rat.

The results of the experiments may be summarized as follows.

1. Lengthening the preshock interval increased the number of avoidance responses made under the influence of chlorpromazine by rats which had been previously trained without drug. Neither intensifying the electric shock nor introducing warning signals affected the number of responses made under the drug. It was concluded that chlorpromazine induces a locomotor deficit which is not attributable to sensory deficits.

2. Chlorpromazine did not impair avoidance response acquisition when the drug was injected just prior to two training sessions and omitted for the third, the test, session. It was concluded that the drug did not alter the efficacy of the avoidance response reinforcer.

3. Chlorpromazine induced a delay in the initiation of locomotion without affecting the running time. The length of the locomotor initiation delay correlated highly with an independent measure of avoidance response suppression. It was concluded that the avoidance suppression was attributable to the inability to initiate locomotion under chlorpromazine, and that the inability resulted from the drug's action upon some central motor function.

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