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Enhancement of Freezing Behaviour by Metoclopramide: Implications for Neuroleptic-Induced Avoidance Deficits[1]

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BLACKBURN, J. R. AND A. G. PHILLIPS. *Enhancement of freezing behaviour by metoclopramide: Implications for neuroleptic-induced avoidance deficits.* PHARMACOL BIOCHEM BEHAV **35**(3) 685–691, 1990.—Administration of the neuroleptic drug metoclopramide (5.0 mg/kg) potentiated freezing responses of rats following 1.0 mA footshock, but did not produce any freezing prior to shock onset. To determine if inappropriate freezing responses to shock could contribute to deficits in active avoidance produced by metoclopramide, drugged and undrugged rats received unavoidable footshock prior to each of ten one-way avoidance trials, or in a separate apparatus prior to the avoidance session (Experiment 2). In neither case was the performance of control rats affected adversely, but in each case the performance of metoclopramide-treated rats was significantly disrupted. Experiment 3 demonstrated that the avoidance performance of metoclopramide-treated rats was disrupted by presentation of an additional conditional stimulus previously paired with shock, whereas the performance of saline-treated rats was enhanced by this procedure. It was concluded that the enhancement of freezing by neuroleptic drugs contributes to the deficit in avoidance responding produced by dopamine receptor antagonists.

Metoclopramide Neuroleptic drugs Dopamine Freezing behaviour Avoidance behaviour

FREEZING behaviour is now recognized as an important component of the defensive repertoire of rodents. Rather than being perceived as a failure to respond, freezing is identified as a highly structured species-specific defense reaction (19, 20, 36). Freezing is an adaptive response that appears to have evolved in order to limit the visibility of animals to nearby predators (18). It is, perhaps, the dominant defensive response of the rat (29). These considerations have been at the forefront of recent developments in the study of defensive behaviour. However, with notable exceptions [e.g., (28)], the interaction between drugs and freezing behaviour is still poorly understood in the context of neurochemical and pharmacological analyses of neural substates of defensive behaviour.

The first experiment of the present study investigated the involvement of brain dopamine systems in freezing behaviour by examining the effects of the dopamine receptor antagonist metoclopramide on freezing responses. Additional experiments examined whether alterations in freezing behaviour may account for some of the perturbation in active avoidance produced by this and other neuroleptic drugs. Previous experiments in our laboratory (7–9) have established that the substituted benzamide, metoclopramide and the classical neuroleptic haloperidol have similar profiles of action in the disruption of one-way avoidance behaviour. These effects differed markedly from those of the atypical neuroleptics, clozapine and thioridazine. Therefore, the disruption of active avoidance by neuroleptics is associated with the potential for producing extrapyramidal side effects, which in turn may reflect striatal actions of classical neuroleptics and metoclopramide. Metoclopramide was studied here because of its more selective effects on the striatum (13) and to permit direct comparison with our earlier finding that metoclopramide in the dose range of 5.0–7.5 mg/kg completely blocked the acquisition of one-way avoidance (8).

EXPERIMENT 1

Freezing can be reliably elicited by shock. Even a single 1-sec, 1.3-mA footshock can increase levels of freezing throughout a 3-hr period (14). Freezing has been identified as a response of rats to a single footshock [e.g., (14, 16, 17, 25, 27)], as well as to a series of shocks [e.g., (14, 22, 27)]. The present study examined the effects of metoclopramide on freezing responses of rats after they had received 1, 2, and a series of 7 footshocks.

METHOD

Subjects

Male hooded rats obtained from Charles River Laboratories of Canada were used. All rats weighed 360–540 g at the start of the experiment and were experimentally naive. Rats were housed in single wire cages at least one week prior to the beginning of testing and were handled at least three times prior to testing. The climatically controlled colony room was on a standard 12-hr light-dark cycle (lights on at 0800 hr). Each experimental session occurred between 0900 and 1300 hr.

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Apparatus

Testing was conducted in a Plexiglas chamber, 26 × 30 × 40 cm high. A hinged ceiling was also constructed of Plexiglas. The grid floor could be electrified by a scrambled 1.0 mA DC current (BRS/LVE shock generator). A 2900 Hz tone generator (Sonalert) was centered 8 cm above the shock grid, and a 3.3-ca cue light (not used in this experiment) was mounted above the tone generator, near the top of the same wall, centered 37 cm above the grid.

Three walls of this compartment were lined with brown shelf paper making them translucent. One wall remained transparent to permit viewing. A video camera, stationed approximately 50 cm from the compartment, recorded behaviour during test sessions. A title generator affixed to the video camera presented trial time to an accuracy of 0.1 sec.

Metoclopramide-HCl (Sigma Chemical Co., St. Louis, MO) was dissolved as 5.0 mg of the salt weight in 1.0 ml of saline.

Procedure

Rats were assigned randomly to one of two groups (n = 7 per group). Rats of Group Sal were administered saline, rats of Group Met were administered 5.0 mg/kg metoclopramide. Sixty to ninety minutes after injection, a single rat was placed in the Plexiglas compartment. No shocks or other events occurred in the first 10 minutes that the rat was in the compartment. At the end of this habituation period the rat received a 1.0-sec, 1.0-mA footshock. A second shock was presented 2 min after the first. A series of five additional shocks began 2 min after the second, on a variable-time (VT) 60-sec schedule.

Reactions to shock were scored from the videotape using a time sampling technique adapted from Bolles and Collier (21). Behaviours were scored (a) in a baseline period comprising the 2 min prior to the first shock, (b) in the 2 min following the first shock, (c) in the 2 min following the second shock, and (d) in the 2 min after the rat had experienced the final shock. Every 5 sec, timed from shock onset (or from 2 min prior to the first shock), the behaviour of the rat was classified into one of four exhaustive categories: Freezing (immobile except for breathing and movements related to heartbeat, typically accompanied by conspicuous muscle rigidity and laying back of the ears); Active (locomoting, moving body axis or limbs, or sniffing accompanied by head movements); Grooming (stereotyped face washing or self-directed oral actions); or Inactive (absence of marked body axis or head movements, but presence of sniffing or oral activity, with the ears in their normal, upright position. Transitory periods of immobility between actions were classified as Inactive.)

Data Analysis

Only freezing responses were analyzed statistically. In order to maximize the relevance of the analysis to the reactions of rats to shock during avoidance training the analysis was restricted to responses of the rats in a 60-sec interval beginning 30 sec after the onset of each of the four 2-min periods. The pattern of results was virtually identical during this middle minute as it was over the entire 2-min period.

The percentage of freezing responses during the periods before the first shock (baseline), after the first shock, after the second shock, and after the final shock were analyzed using a two-way (Group × Period) ANOVA. Significant effects were further examined using Newman-Keul's post hoc test at 0.05 level of significance.

RESULTS

The percentage of freezing responses recorded in each of the four observation periods are illustrated in Fig. 1. The ANOVA conducted on the freezing scores indicated that there was a significant main effect of Group, $F(1,12) = 7.59$, $p < 0.05$, a significant effect of Period, $F(3,36) = 33.26$, $p < 0.001$, and a significant Group × Period interaction, $F(3,36) = 2.83$, $p < 0.05$.

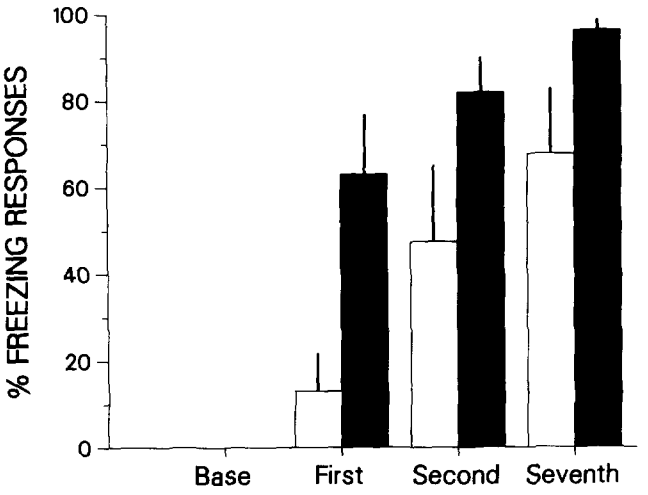

FIG. 1. Percentage of freezing responses by rats 30–90 sec after footshock (mean ± s.e.m.). Behaviours were scored during the baseline period, in the period after the first shock, in the period after the second shock, and after a series of five additional shocks. Light bars represent group injected with saline, dark bars represent group treated with 5.0 mg/kg metoclopramide.

Post hoc analysis of the interaction revealed that the percentage of freezing responses by Group Met increased significantly in the first postshock interval, relative to the baseline scores of zero. Further increases occurring after subsequent shocks were not significant. In contrast, the freezing responses of Group Sal did not differ significantly from the Baseline period until after the second shock. Comparing the two groups, Group Met had significantly higher freezing scores than Group Sal after the first and second shocks, but scores did not differ significantly after the final shock.

DISCUSSION

This experiment demonstrated that the freezing responses of rats increased from a baseline of zero to a high level over the course of 1, 3, and then 7 brief footshocks. A moderate dose of metoclopramide enhanced the onset of freezing so that significant freezing occurred after the first shock, whereas in undrugged rats significant freezing was not observed until after the second shock. The absence of significant freezing in saline-treated rats following the first shock was probably due to the short observation time employed; postshock freezing responses have been observed following a single footshock up to 3 hr after the shock (14). However, it should be noted that the percentage of freezing responses by saline-treated rats did show a small, but not statistically significant increase, from the baseline of zero. The finding that a neuroleptic compound had a significant behavioural effect on the first trial after neuroleptic administration, argues strongly against mediation exclusively by some form of learning deficit (3).

The increase in freezing produced by metoclopramide was not limited to the first shock. Freezing responses by drugged rats were significantly more frequent after the second shock as well. After the seventh shock metoclopramide-treated rats were freezing in over 96% of the observation periods. Any facilitation in freezing

responses by this group during this final observation period may have been obscured by ceiling effects.

There are no grounds for attributing the enhancement of freezing by metoclopramide to changes in pain thresholds or to changes in the activity of pain systems. Metoclopramide did not disrupt escape responses elicited by shock presentation in previous studies (7–9).

EXPERIMENT 2

If an animal freezes, it cannot perform an avoidance response. It follows that manipulations that enhance freezing can disrupt avoidance responding (15,46). Lenard and Beer (35) proposed that inappropriate reactions to shock lead to impaired avoidance response maintenance following dopamine-depleting lesions produced by administration of 6-hydroxydopamine (6-OHDA). These authors noted an increase in freezing in the lesion group that was incompatible with avoidance behaviour and that was correlated with the decline in avoidance responses. Although no quantitative data on these incompatible responses were provided, this hypothesis was supported by demonstrating that diazepam, which apparently attenuated freezing during avoidance sessions, alleviated the 6-OHDA-induced deficit even though this anxiolytic had no effect on avoidance by itself (2).

Can a similar analysis by applied to the avoidance deficits observed after administration of neuroleptic drugs? It is well established that such drugs do not disrupt learning about the aversive nature of shock (1, 4, 5, 39). On the other hand, Experiment 1 demonstrated that metoclopramide alters freezing responses in a fearful environment. Thus, the enhanced freezing may interfere with avoidance responding. The following experiment tested this hypothesis by examining the effect of shock administered in the avoidance apparatus at the beginning of an avoidance session and prior to each trial. A separate study determined whether shock administered in a separate compartment, prior to testing, would also disrupt avoidance responding.

Subjects

The rats used were the same strain and from the same supplies as those of Experiment 1, and weighed 340–510 g at the start of the experiment.

Apparatus

The avoidance apparatus consisted of a shuttlebox (25 × 78 × 33 cm deep) divided into two equal halves by a partition. Both halves were painted flat black. The partition could be opened by raising a 13-cm wide guillotine door. A grid floor on one side (the "shock" side) could be electrified by a scrambled 1.0 mA DC current (BRS/LVE shock generator). A 2900 Hz tone generator (Sonalert) was mounted below the grid floor at the end of the shock side, and a 3.3-ca cue light (not used in this experiment) was mounted above the tone generator, near the top of the same wall, centered 34 cm above the grid. Electromechanical relays and timers were used for stimulus control and data collection.

Additional presentations of tone and shock were administered in the separate Plexiglas chamber described in Experiment 1, but all sides of the box were covered with translucent paper.

Procedure

Rats were assigned randomly to one of four groups (n = 6 per group). On the day prior to avoidance training rats of each group received 10 noncontingent pairings of tone and scrambled footshock in the Plexiglas compartment. This procedure has been found to facilitate subsequent acquisition of avoidance behavior when the tone is used as the warning signal (WS) for shock onset (1, 7, 9).

Each avoidance session began by putting a rat into the "safe" (nonelectrified) side of the shuttlebox. After 30 sec the rat was placed on the shock side facing away from the guillotine door. The trial began with onset of the tone WS and the opening of the door. If the rat moved into the safe side during the 10-sec tone period the tone was turned off, the door was lowered, and an *avoidance* response was recorded. If the rat failed to avoid during the 10-sec tone period, the offset of the tone was continguous with the onset of the footshock. Movement into the safe side was followed by lowering the door, and an *escape* response was recorded. In either case the *response latency* was defined as the time from WS onset until the rat passed into the safe side. If no response occurring within 10 sec following shock onset, the rat was pushed gently into the safe side and the response latency was recorded as 20 sec. Entry into the safe side always initiated the next 30-sec intertrial interval.

On the training day each rat received 5 avoidance training trials. This amount of training was selected to provide an intermediate level of acquisition of the response, based on earlier studies (7,9). There were no significant between-group differences on the training day (all $Fs < 1$).

On the test day rats of each group were given 10 avoidance trials. Two groups of rats, the noncontingent footshock (NCF) groups, received a 3.0-sec footshock in the shock side of the avoidance apparatus prior to the first trial. In addition, these rats received a 1.0-sec footshock on each trial after being placed in the shock side of the compartment, prior to the onset of the WS. Rats of the two Control groups did not receive the noncontingent footshock. One NCF group (NCF-Met) and one Control group (Control-Met) received a 5.0 mg/kg metoclopramide prior to testing, while the other groups (NCF-Sal and Control-Sal) received saline injections.

The procedure described above was replicated with four additional groups (N = 8 per group), with the following change. On the test day, rats in the shock groups received three noncontingent, 1.5-sec, 1.0-mA footshocks (1S1 = 30 sec) in a separate Plexiglas chamber.

Statistical Analysis

The number of avoidances were analyzed using a two-way (Drug treatment × Shock treatment) ANOVA. Latency scores were analyzed with a three-way (Drug × Shock × Trial) ANOVA. In each case, significant effects were further analyzed using Newman-Keul's post hoc test at a 0.05 level of significance.

RESULTS

The number of avoidances on the test day are illustrated in the top panel of Fig. 2. Noncontingent footshock disrupted the performance of the rats that had received metoclopramide, but it did not disrupt the performance of the rats that had received saline. Drug administration alone produced a minor deficit (6.9/10 correct responses vs. 9.0/10 for Control rats). This deficit was markedly exacerbated by administering noncontingent shocks to the drug-treated rats prior to each trial (reducing Group NSF-Met to 3.8/10), a procedure that had no effect on undrugged rats (9.2/10 for Group NCF-Sal). These impressions were confirmed by the ANOVA. There was a significant effect of Drug, $F(1,20) = 43.83$, $p < 0.001$, a significant effect of Shock, $F(1,20) = 6.26$, $p < 0.05$, and a significant Drug × Shock interaction, $F(1,20) = 7.81$, $p < 0.05$. Post hoc testing indicated that of the two groups that received metoclopramide, the one that received noncontingent

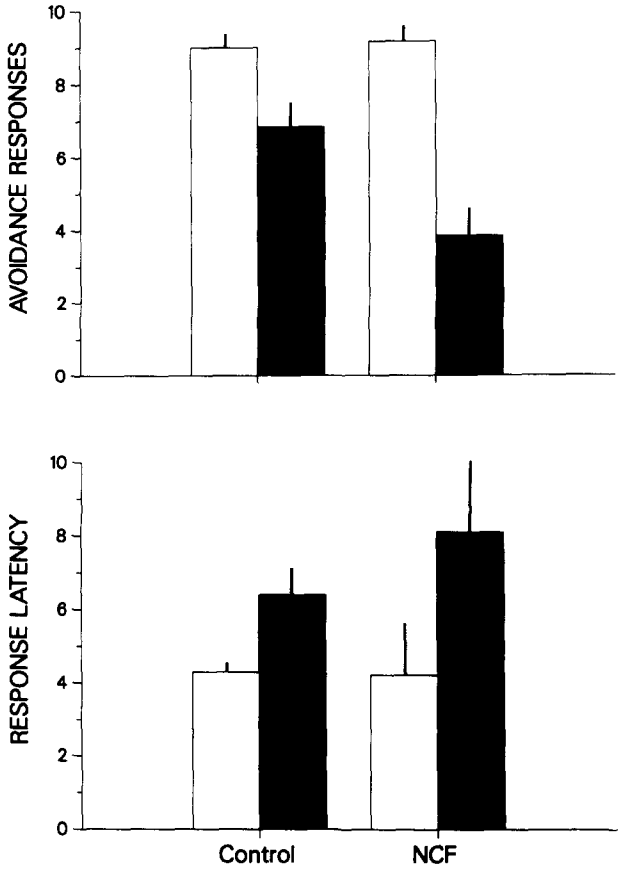

FIG. 2. Top panel indicates mean (±s.e.m.) number of avoidances executed on the test day. Bottom panel indicates mean (±s.e.m.) response latencies. All rats received 5 avoidance training trials. On the test day NCF Groups received noncontingent shock prior to each trial. Control Groups did not. Light bars represent Sal Groups, dark bars are Met Groups received 5.0 mg/kg metoclopramide.

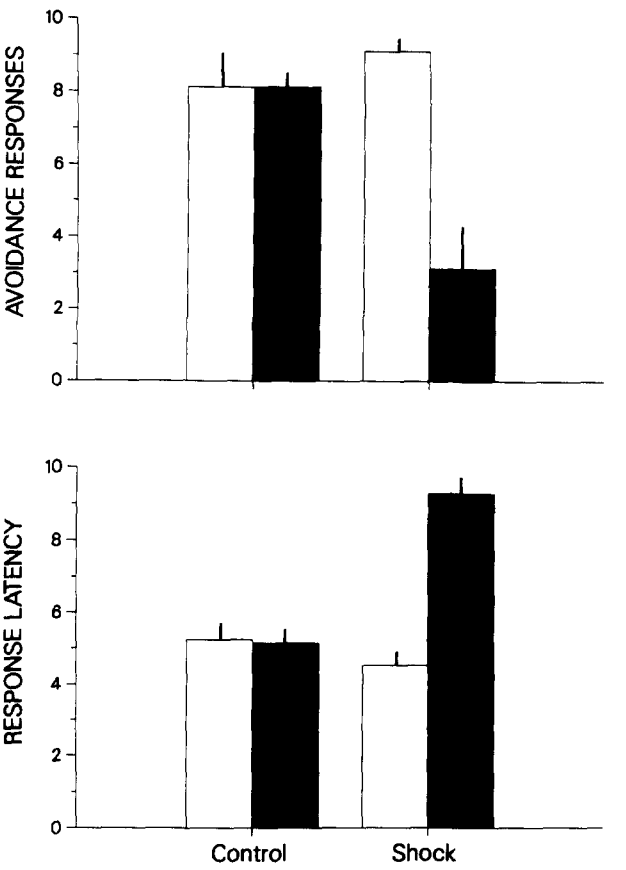

FIG. 3. Top panel indicates mean (±s.e.m.) number of avoidances executed on the test day. Bottom panel indicates mean (±s.e.m.) response latencies. All rats received 5 avoidance training trials. On the test day the Shock Groups received three 1.5-sec footshocks in a separate compartment prior to the first avoidance trial. Light bars represent Sal Groups, dark bars are Met Groups.

shocks (NCF-Met) performed worse than the no-shock group (Control-Met). In contrast, the performance of the two groups that received saline did not differ. Thus, there was a synergistic effect of metoclopramide and noncontingent shock.

Examination of the latency scores (bottom panel of Fig. 2) suggests a similar pattern of results. However, because of greater within-group variaiblity, the interaction was not significant. There was a significant effect of drug, $F(1,20) = 19.74$, $p<0.001$, but not a significant effect of Shock, $F(1,20) = 1.49$, $p>0.20$, nor a significant Drug × Shock interaction, $F(1,20) = 1.73$, $p>0.20$.

As can be seen in Fig. 3, prior footshock disrupted the performance of the rats treated with metoclopramide, but did not disrupt the avoidance behaviour of rats treated with saline. All ANOVAs were significant ($p<0.05$) and post hoc tests indicated that Group Shock-Met avoided less often and had longer response latencies on the test day than any other group.

DISCUSSION

The observed disruption of avoidance responding by shock treatment in drugged rats is consistent with the finding of Experiment 1 that metoclopramide-treated rats have an exaggerated freezing response to shock. It is also consistent with the proposal that dopamine disruption causes inappropriate reactions to shock that lead to impaired avoidance responding (35). Together, these findings suggest that at lest some portion of the disruptive effect of neuroleptic drugs on avoidance can be attributed to the enhancement of incompatible freezing responses following shock.

However, an alternative interpretation of these results is possible. Rather than disrupting the performance of metoclopramide-treated rats by interfering with their response capabilities, the noncontingent footshocks may have interfered with the avoidance performance of drugged rats by perturbing their representation of response-outcome contingencies. This is a variant of the "learned helplessness" hypothesis of Overmier and Seligman (38), namely that subjects may learn that responses are independent of shock termination. However, there is no obvious reason why the drug should have produced such a confusion in metoclopramide-treated rats when the undrugged rats were not disrupted.

EXPERIMENT 3

Freezing is a response of rats not only to aversive stimuli such as shock and predators, but also to conditional stimuli that have previously been paired with aversive events [e.g., (14, 21, 23–26, 42)]. The previous experiments in this study demonstrated that shock can disrupt the avoidance behaviour of metoclopramide-treated rats, apparently by increasing incompatible freezing re-

sponses. The present experiments examined whether conditioned responses to shock-related stimuli could also disrupt avoidance responding by metoclopramide-treated rats. In order that a tone could be used as the additional conditional stimulus, the usual tone WS was replaced by illumination of a cue light for this experiment.

METHOD

Subjects and Apparatus

Rats from the same supplier as those of the other experiments (390–500 g) were used, and were tested in the same apparatus as in Experiment 2.

Procedure

Rats were assigned randomly to one of four groups. Two groups of rats (CS+ groups) received 10 noncontingent tone-shock pairings in the separate Plexiglas chambers on each of two days prior to avoidance training. Rats of the other groups (Control groups) were simply placed in the Plexiglas chamber and then removed without having experienced any programmed events. On the next day, rats of all groups received an initial avoidance training session consisting of five avoidance trials. In this training session the WS consisted of illumination of the light mounted on the end wall of the shock side of the box. The ceiling lights in the test room were not illuminated on this day, the only ambient lighting being provided by two dim red incandescent bulbs. Prior testing indicated that this amount of training would provide rats with a moderate amount of protection from the disruptive effects of metoclopramide, as in Experiments 2 and 3. There were no differences between groups on number of avoidances or response latencies on this training day (Fs<1). On the following day rats of each group were given 10 avoidance trials. On the test day the two Control groups were tested using only the cue light WS. However, for the two CS+ groups the tone was activated at the same time as the light WS. One CS+ group (CS+-Met, n=9) and one Control group (Control-Met, n=9) received 5.0 mg/kg metoclopramide prior to testing, while Groups CS+-Sal (n=10) and Control-Sal (n=10) received saline injections.

Statistical Analysis

The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment 2.

RESULTS

The number of avoidances on the test day are illustrated in the top panel of Fig. 4. It is apparent that the conditional stimulus disrupted the performance of the metoclopramide-treated rats. This impression is confirmed by the ANOVA. There was a significant effect of Drug, $F(1,34)=23.33$, $p<0.001$, and a significant Drug × Conditioning interaction, $F(1,34)=11.46$, $p<0.05$, but there was no significant effect of Conditioning ($F<1$). Post hoc tests indicated that Group Control-Sal did not differ from either Group Control-Met or Group CS+-Sal, but that Group CS+-Met performed significantly worse than any other group. Thus, the presence of the additional tone CS+ did not have an adverse effect on the performance of the saline-treated rats (in fact Group CS+-Sal performed nonsignificantly better than Group Control-Sal), but the conditional stimulus had an adverse impact on the performance of metoclopramide-treated rats.

Examination of the latency scores (bottom panel of Fig. 4) suggests a similar pattern of results. However, the statistical

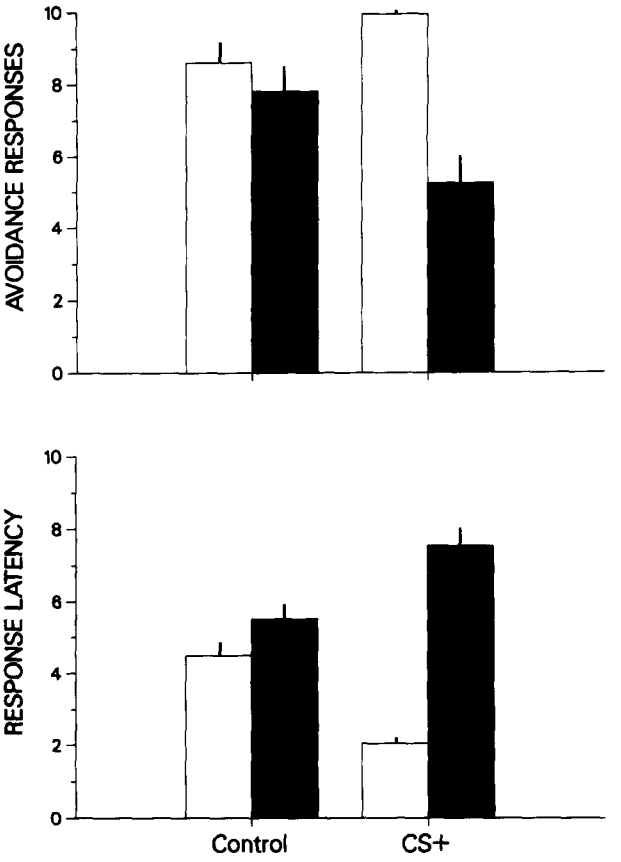

FIG. 4. Top panel indicates mean (±s.e.m.) number of avoidances executed on the test day. Bottom panel indicates mean (±s.e.m.) response latencies. CS+ rats received 20 tone-shock pairings on prior training. All rats received 5 avoidance training trials with a light WS. On the test day a light WS. On the test day the WS was a tone-light compound for the CS+ Groups and was a light for the Control Groups. Light bars represent Sal Groups, dark bars are Met Groups received 5.0 mg/kg metoclopramide.

analysis indicated a slightly different set of effects. There was a significant effect of Drug, $F(1,34)=20.12$, $p<0.001$, and a significant effect Drug × Conditioning interaction, $F(1,34)=9.47$, $p<0.005$, but there was no significant effect of Conditioning ($F<1$). The post hoc tests again indicated that there was no difference between the performance of the saline- and metoclopramide-treated rats that were not exposed to the tone. However, Group CS+-Met did not have significantly longer latencies than did Group Control-Met. Instead, Group CS+-Sal had significantly *lower* latencies than did Group Control-Sal. Thus, the additional conditional stimulus potentiated performance for undrugged rats, as indexed by the latency scores, whereas for drugged rats there was a nonsignificant disruption of performance.

DISCUSSION

The presence of an additional tone conditional stimulus did not have an adverse effect on the performance of saline-treated rats (compare Group CS+-Sal with Group Control-Sal). In fact, the response latencies of the rats that were presented with the conditional stimulus were lower than those of control rats. This finding is consistent with numerous reports that presentation of a classically conditioned stimulus associated with shock can lead to

enhanced avoidance responding [e.g., (31, 37, 40, 41, 43–45, 47)].

In contrast to these effects, the conditional stimulus decreased, rather than increased, the number of avoidances successfully executed by the metoclopramide-treated rats. Metoclopramide by itself had only a minor effect on the performance of control rats, but in combination with the conditional stimulus it produced a substantial disruption in performance. Thus, the disruptive effects of shock and metoclopramide in combination, previously observed in Experiments 2, were replicated with an aversive conditional stimulus in place of an unconditional footshock. These observations suggest that freezing responses following shock are conditioned responses to fear-elicitng stimuli.

Fanselow and Lester (29) have suggested that postshock freezing is a conditioned response exhibited by rats in anticipation of future shock that is dependent on the presence of shock-related cues. Rats exhibit much less freezing following shock treatment when moved to a novel compartment than if handled and returned to the shock compartment (14, 21, 25). Furthermore, no freezing is observed in the five minutes following shock if rats are shocked immediately upon being placed in the compartment (17,26). This demonstrates that freezing is not simply a reaction to shock, but rather a response conditioned to cues in the environment. If the rat does not have sufficient exposure to the environment prior to shock onset, no crouching occurs. Therefore, the presentation of shocks or shock-related stimuli in metoclopramide-treated rats leads to enhanced freezing in anticipation of future shock, freezing that may interfere with subsequent avoidance responding.

GENERAL DISCUSSION

Together, the experiments in this study clearly indicate that the avoidance performance of metoclopramide-treated rats is influenced adversely by the noncontingent presentation of aversive footshock. In combination with the finding that metoclopramide enhances freezing responses, it appears that increased freezing by metoclopramide-treated rats can account for this avoidance deficit.

These findings have important implications for the interpretation of deficits in avoidance responding observed following neuroleptic treatment. Such deficits are particularly pronounced during response acquisition (1, 6–9, 30). During acquisition all rats normally experience several shocks before becoming proficient at one-way avoidance responding and these shocks will potentiate the subsequent avoidance responding of undrugged rats. In contrast, shocks can disrupt the responding of metoclopramide-treated rats. Therefore, in subsequent avoidance sessions in shock-related environment, the neuroleptic-treated rats will freeze more and avoid less than controls. This may also account for the gradual onset of disruption of avoidance responding seen after neuroleptic treatment in experienced rats (6–8). Although a drugged rat may respond well in initial sessions, prolonged exposure to shock or shock-associated environmental cues may gradually lead to an increase in freezing and consequently to response inhibition. These effects may also explain why lower doses of neuroleptic drugs are required to impair performance on bar press or shuttle avoidance, tasks in which rats receive many shocks during the course of training, than those required to disrupt performance of a more simple and efficacious response (33).

Although not examined directly in the present study, there is evidence that neuroleptic-treated rats display freezing in the avoidance situation. Posluns (39) reported, in rats given chlorpromazine, a highly significant correlation between the latency to initiate locomotion and the number of shocks received in the session ($r = .94$). In Poslun's study, it is apparent that the rats' failure to initiate locomotion was equivalent to freezing. It should be noted, however, that not all avoidance response failures can be attributed to freezing at the commencement of the trial. Posluns observed that rats frequently paused just before entering the safe compartment. Similar behaviour was seen in the present series of experiments with metoclopramide-treated rats.

As a general model that may assist in the interpretation of these data, it is proposed that specific forebrain systems mediate the elicitation of active avoidance behaviours by distal cues that signal aversive events. These are flight systems. Other neural systems are responsible for autonomic responses and freezing to shcok and shock-related stimuli. For example, conditioned freezing responses involve a projection of the central amygdaloid nucleus to the caudal portion of the central grey region (34). Given the incompatibility between fight and freezing responses, these systems may have reciprocal inhibitory influences on one another (32). Within this framework we propose tht dopaminergic activity facilitates or primes the flight systems in the presence of appropriate environmental stimuli, but does not potentiate freezing. In the absence of normal dopaminergic activity, flight systems can still function in response to a direct aversive stimulus, but have lost the facilitatory input. Nonetheless, in the absence of effective dopaminergic neurotransmission, animals may still recognize cues that signal important events. Thus, even though a rat may be unable to direct prepatory skeletal responses towards appropriate stimuli after treatment with neuroleptics, it can still recognize a tone as a signal for shock. In the absence of an anticipatory flight response, high levels of freezing will be displayed in anticipation of shock. As a result, the animal will experience additional shock which will further enhance the probability of freezing at the expense of flight.

This analysis is consistent with the observed effect of neuroleptic drugs on appetitive behaviours. Neuroleptic-treated rats orient to conditional meal cues, but do not engage in vigourous prepatory approach responses. Nonetheless, such rats do engage in normal consummatory feeding responses when food is presented (10–12). In each case distally directed preparatory responses (avoidance or approach) involve dopamine systems, and are disrupted by neuroleptic treatment, whereas locally directed consummatory responses (freezing or feeding) are dopamine-independent, and are, therefore, resistant to disruption by neuroleptics.

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