Pharmacology Biochemistry & Behavior, Vol. 17, pp. 1245–1249, 1982. Printed in the U.S.A.

Avoidance Performance, Cue and Response-Choice Discrimination After Neuroleptic Treatment[1]

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Received 24 May 1982

ANISMAN, H., A. CORRADINI, T. N. TOMBAUGH AND R. M. ZACHARKO. *Avoidance performance, cue and response-choice discrimination after neuroleptic treatment.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1245–1249, 1982.—The effects of pimozide on discriminated avoidance performance in a Y-maze were evaluated in mice. Relatively low doses of pimozide (0.4 mg/kg) retarded acquisition of an active avoidance response. The avoidance deficit induced by this dosage was largely eliminated among mice that had received either 1 or 2 previous avoidance training sessions, but was still evident in mice treated with a higher drug dosage (0.8 mg/kg). If mice were initially trained in the drug condition, the disruptive effects were still evident in a later test conducted in the absence of the drug treatment. In contrast to the avoidance deficits, pimozide did not disrupt the acquisition or the performance of a cue- or response-choice discrimination. That is, once a running response was initiated (on avoidance trials) pimozide treated animals appeared capable of appropriately directing the response. It is suggested that at the dosages used pimozide did not affect S-S learning or learning response-outcome contingencies, but rather hindered performance owing to deficits in response initiation processes. Moreover, within a task involving aversive motivation pimozide did not appear to reduce the reinforcement derived for correct responding.

Neuroleptic treatment Pimozide Avoidance performance Cue discrimination
Response-choice discrimination

THE ability of neuroleptics to impair performance but not escape performance in shuttle avoidance tasks has been repeatedly demonstrated. While the response deficits produced by dopamine (DA) receptor blockers do not appear to be attributable to a failure of the animal to learn the S-S association between a signal and shock [5, 6, 7], it is possible that neuroleptics may disrupt other associative components governing avoidance learning. For example. Beninger and Phillips [5] have suggested that pimozide could alter the mechanism by which learned S-S associations are able to affect instrumental behavior. That is, pimozide disrupts the neural interface necessary for responses to be coupled with relevant environmental stimuli. Consequently, the animal fails to initiate responding in the presence of the conditioned stimulus (CS) even though it serves as a warning stimulus for the impending shock. Moreover, even if animals learn when to initiate the response (e.g., running), it is conceivable that the drug interferes with the organism's ability to learn where to direct this response, or disrupts the association between particular responses and outcomes [1,2]. Consequently, the present series of experiments were undertaken to assess the effect of pimozide on avoidance behavior and to determine if avoidance deficits were accompanied by deficits in associative learning.

EXPERIMENTS 1a-1h

Since the shuttle avoidance task does not distinguish between drug effects on associative and nonassociative processes nor does it differentiate between treatment effects on different types of associative processes [1], the present experiments employed a continuous discriminated Y-maze task. In such a paradigm animals are not only required to learn that a cue is associated with shock, and that an active response is associated with shock offset or avoidance, but the animals must also learn to direct this response appropriately. Thus the task involves evaluation of whether a drug treatment influences avoidance performance (initiation of a response prior to shock onset), as well as discrimination accuracy (i.e., whether on escape and avoidance trials animals direct the response to the correct arm). Consequently, if pimozide influences associative processes, disturbances of avoidance performance should be accompanied by deficits in discrimination accuracy.

In light of the possibility that pimozide might not affect all learning processes in a similar manner, two types of discrimination tasks were evaluated—cue discrimination and response-choice discrimination. The cue discrimination task required that animals learn to run into an illuminated arm

[1]Supported by Grants A9845, U0058, and A7074 from the Natural Sciences and Engineering Council of Canada. Requests for reprints should be addressed to Hymie Anisman, Department of Psychology, Carleton University, Ottawa, Ontario, Canada, K1S 5B6.

upon CS onset. In the response-choice task mice were required to learn that a particular type of response (i.e., turning left or turning right, which is based presumably on interoceptive cues or feedback) is associated with safety. In the continuous Y-maze avoidance task the safe arm of one trial serves as the start arm for the next trial, thus response learning is not confounded by spatial (positional) cues signalling safety. Inasmuch as several experiments have revealed that pimozide does not influence S-S learning, there was no reason to believe that the drug would disrupt cue discrimination performance. However, the potential effects of pimozide on response discrimination learning, uncontaminated by external cues, have not been evaluated.

METHOD

Subjects

One hundred and sixty male CD-1 mice, obtained from the Canadian Breeding Farms, Laprairie, Quebec, at 50–55 days of age, were housed in groups of 5 in standard polypropylene cages. Mice received at least 14 days of acclimatization to the laboratory prior to being used as experimental subjects.

Apparatus

Avoidance training was conducted in 4 symmetrical black Plexiglas Y-mazes with arms 22.0×9.0×15.0 cm. Within each arm, situated 3 cm from the triangular choice area was a stainless steel wall partially made up of a solenoid-controlled horizontally movable gate. In the open-gate position a 7.0×8.2 cm space permitted entry/exit from each arm. Two sets of photocells, mounted 1.0 cm on either side of the gate at a height of 2.0 and 4.0 cm above the grid floor, monitored the position of the animal and determined when correct or incorrect responses were emitted. The photodetector cells were wired such that crossing the beam on both sides of the gate simultaneously (as would occur when the mouse was half-way into the safe arm) would not trigger the cells. When the mouse crossed the beam in the safe arm, without concurrently crossing the beam just outside the gate, the cell was triggered, resulting in gate closing and trial termination. An additional set of photodetector cells was located 2.5 cm from the end wall of each arm at a height of 2.0 cm above the grid floor. If a mouse did not trigger a cell at the start of the arm, as might occur if the mouse jumped over the cells, the latter cells were invariably triggered.

The floor of each arm consisted of 0.32 cm stainless steel bars spaced 1.0 cm apart (center to center). The triangular choice area was formed by a series of independent bars, 1.0 cm apart, mounted from beneath the maze. The grid bars were connected in series by neon bulbs such that each arm and the triangular choice area could be electrified independently. Footshock was delivered to the grid floor through a 3000 volt source, thereby providing relatively constant current. Centered 2.0 cm from the top of each of the end walls of the arms, which were covered by a thin stainless steel sheet connected in series with the grid floor, was a 1.5 cm diameter opaque disc, through which light from a 14 W bulb projected. Also mounted at the center of the red Plexiglas roof of the maze was a 3 inch speaker. The tone provided by the speaker and illumination of the arms could be presented either independently or in combination. The mazes were individually housed in sound attenuated chambers. The time and sequencing of discrimination trials, as well as recording of correct and incorrect responses and their latencies, were determined by a microcomputer system.

Procedure

A series of 8 independent experiments were conducted to evaluate the effects of pimozide on avoidance in the cue- and response-choice discrimination tasks. The procedures of the two tasks were essentially the same across experiments, differing only with respect to drug dosage and amount of training mice received prior to the drug tests. Mice (n=10/group in each experiment) were individually placed in the mazes, 60 sec after which avoidance training commenced. In the cue discrimination task a trial commenced with all gates opening, coupled with onset of the tone and illumination of the lamp in the safe arm. Essentially the tone served as the signal of impending shock, while the cue light served both to signal impending shock and to designate the response required of the animal. If a response was not made within 10 sec of CS onset, footshock (150 μA, AC) was delivered to the start arm, the triangular choice area and to the incorrect arm. The trial terminated when a correct response was made, or within 26 sec of UCS onset on those infrequent occasions where an appropriate response was not emitted. If the mouse entered the correct arm within 10 sec of CS onset the trial terminated immediately. An incorrect arm entry within 10 sec of CS onset resulted in the grid being electrified until the animal entered the correct arm. Using this procedure the safe arm of one trial served as the start arm of the next trial. When a successful escape/avoidance response was not made within 26 sec of shock onset the start arm for the next trial was determined by the location of the animal at the time of shock offset. Within a session mice received 50 avoidance trials, at intervals of 60 sec between trials. The sequence of correct arms was based on a predetermined random sequence.

In the response-choice discrimination task only the tone signalled impending shock. For half the animals successful avoidance or escape responding required that they always turn right, while for the remaining animals correct responding necessitated a left turn at the choice point. In all other respects the procedure was the same as that employed in the cue discrimination task.

Experiments 1a-1b: Acquisition. The initial two studies were undertaken to assess the effects of a relatively low dose of pimozide on acquisition of the discriminated avoidance response. Mice received intraperitoneal (IP) injection of either pimozide (0.4 mg/kg) in a volume of 10 ml/kg or its vehicle, and were maintained in a holding cage for 3 hr, after which mice were tested either in the cue- or response-choice task. Pimozide was dissolved in a few drops of glacial acetic acid, to which dextrose (5.5%) was added and the solution was heated and stirred vigorously (pH=5.5). The dosage of pimozide selected was based on a series of preliminary studies which indicated that this dosage would disrupt avoidance performance in a shuttle task, and would hinder escape behavior in a task that was motorically demanding [4,8].

Experiments 1c-1h: Performance. These experiments examined the effects of pimozide on performance in mice that had received prior avoidance training (Experiments 1c and 1d=50 trials; Experiments 1e and 1f=100 trials) in either the cue- or response-choice tasks. Twenty four hours following drug-free training, mice received an IP injection of either pimozide (0.4 mg/kg) or vehicle and 3 hr later were tested in the task in which they had previously been trained. Finally,

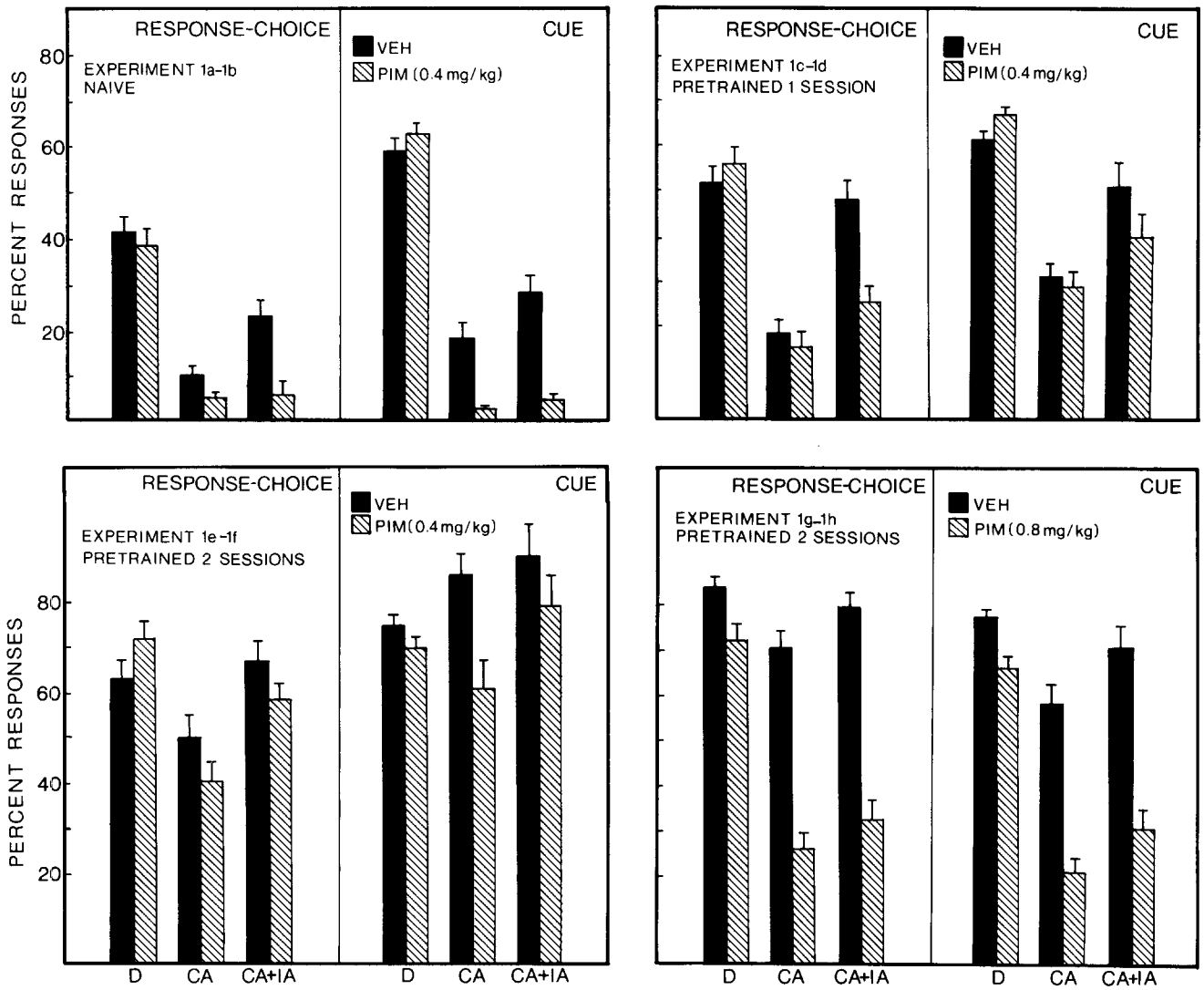

FIG. 1. Mean percentage (±S.E.M.) correct discrimination responses (D), correct avoidance responses (CA), and correct plus incorrect avoidance responses (CA+IA) in the cue- and response-choice tasks. Performance of naive mice treated with vehicle or the 0.4 mg/kg dose of pimozide is shown in the top left hand panels. The performance of mice that received 1 and 2 previous training days and were tested with the 0.4 mg/kg dose are shown in the top right and lower left hand panels, respectively. Finally, the lower right hand panels depict the performance of mice that received vehicle or 0.8 mg/kg of pimozide after two training days.

in Experiments 1g and 1h mice also received two days of training (100 trials) and were tested after treatment with 0.8 mg/kg of pimozide or its vehicle. The latter two experiments were undertaken to determine if high dosages of pimozide would produce disturbances in either discrimination performance or active avoidance.

RESULTS AND DISCUSSION

The mean number of correct and correct plus incorrect avoidance responses, as well as the number of correct discriminations for Experiments 1a-1h are shown in Fig. 1.

Experiments 1a-1b Acquisition

Analysis of variance revealed that in the cue-discrimination task (Experiment 1a) pimozide (0.4 mg/kg) retarded the acquisition of correct and correct plus incorrect avoidance responses, $F's(1,18)=10.30, 9.33$, $p's < 0.05$, respectively. Although pimozide also reduced somewhat the number of avoidance responses in the response-choice task this reduction was not statistically significant, $F's(1,18)=2.01$ and 3.01, $p's=0.174$, and 0.100, respectively. As seen in Fig. 1, fewer avoidance responses were emitted in the response-choice than in the cue-discrimination task, and it is possible that the low levels of performance precluded detection of a significant drug effect. With respect to performance on the discrimination components of the tasks, the analysis of variance revealed that pimozide did not significantly affect performance in either the cue- or response-choice tasks.

Experiments 1c-1h: Performance

As shown in Fig. 1, if mice had received either a single

TABLE 1
PERCENT CORRECT DISCRIMINATION, CORRECT AVOIDANCES, AND CORRECT AND INCORRECT AVOIDANCES

	Correct Discrimination		Correct Avoidance		Correct and Incorrect Avoidances	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Response-choice						
Vehicle	43.4 ± 3.46	59.6 ± 3.37	18.4 ± 2.82	38.6 ± 3.96	30.80 ± 3.84	62.0 ± 4.50
Pimozide	54.6 ± 4.05	75.8 ± 2.76	2.6 ± 1.02*	24.40 ± 3.33*	4.60 ± 1.94*	33.4 ± 4.24*
Cue						
Vehicle	58.2 ± 2.05	60.0 ± 2.37	7.40 ± 1.83	22.0 ± 3.09	11.80 ± 2.79	31.6 ± 4.40
Pimozide	60.8 ± 2.40	69.6 ± 1.94	3.40 ± 1.27*	9.60 ± 1.89*	5.00 ± 1.72*	12.80 ± 2.27*

session (Experiments 1c and 1d) or 2 sessions (Experiments 1e and 1f) of avoidance training the pimozide treatment did not significantly affect the rate of correct or correct plus incorrect avoidance responses. Nevertheless, in both tasks somewhat lower rates of avoidance responding were evident among pimozide treated animals than in mice that had received the vehicle treatment. As in the first two experiments, the drug treatment was not found to alter discrimination performance in either of the tasks.

When animals were tested after two training sessions (Experiments 1g and 1h) using the higher dosage of pimozide (0.8 mg/kg) performance in both the cue- and response-choice tasks was modified. Specifically, pimozide reduced the rate of correct avoidance responses and correct plus incorrect avoidances in both the cue discrimination, $F's(1,18)=13.42$, 10.68, $p's<0.01$, respectively and response-choice discrimination tasks, $F's(1,18)=19.51$, 17.45, $p's<0.01$, respectively. Moreover, as in the preceding experiments the drug treatment was not found to affect discrimination performance in either task.

EXPERIMENT 2

The results of Experiment 1 indicated that treatment with pimozide tended to disrupt subsequent avoidance performance without affecting either cue- or response-choice discrimination performance. It was previously reported that if haloperidol treated animals received several sessions of avoidance training [9], or if the response was reflexive or highly prepared [6], then high rates of responding were evident upon drug withdrawal. Experiment 2 was undertaken to evaluate the effects of pimozide on later nondrug performance in an avoidance task that is not well established, and to determine whether carryover effects are evident on either the cue- or response-choice discrimination. Even though pimozide was not found to have immediate effects on discrimination performance, it is possible that the drug would limit the between-days improvement of discrimination performance that would be evident in the absence of any drug treatment.

METHOD

Subjects and Apparatus

Experiments 2a and 2b each involved 40 CD-1 mice. The subject and apparatus specifications were the same as those described in Experiment 1.

Procedure

Mice received IP injection of either pimozide (0.4 mg/kg in a volume of 10 ml/kg) or its vehicle. Three hours later mice of Experiment 2a were tested in the cue-discrimination task, whereas mice of Experiment 2b were tested in the response-choice task. The testing procedures were identical to those of Experiment 1. Immediately after training mice were returned to their home cages and 72 hr later were retested in the avoidance task in the absence of any drug treatment.

RESULTS AND DISCUSSION

Table 1 shows the frequency of correct and correct plus incorrect avoidance responses on each of the test days for Experiments 2a and 2b. Analysis of variance revealed that the frequency of correct and correct plus incorrect avoidance responses increased over days in both the cue-discrimination, $F's(1,18)=13.43$, 12.97, $p's<0.01$, respectively, and response-choice tasks, $F's(1,18)=52.65$, 54.26, $p's<0.01$, respectively. Moreover, treatment with pimozide was found to reduce the frequency of such responses in the response-choice task, $F's(1,18)=6.30$, 10.93, $p's<0.01$, respectively, and to a lesser extent in the cue-discimination task, $F's(1,18)=3.55$, 3.92, $p's=0.076$ and 0.063, respectively. In neither task, however, was the Drug Treatment found to interact with Days. It seems that the avoidance disturbance engendered by the pimozide treatment was not only evident during the initial test session, but was also maintained upon subsequent testing in the nondrug condition.

Discriminated performance, like avoidance behavior, was found to improve over the two days in both the cue- and response-choice tasks, $F's(1,18)=4.93$, 20.16, $p's<0.05$, respectively. However in contrast to the drug effect on avoidance behavior, treatment with pimozide was not found to disrupt discrimination performance. To the contrary, in both the cue- and response-choice tasks pimozide was actually found to enhance discrimination performance, $F's(1,18)=6.38$, 4.32, $p's=0.019$ and 0.052, respectively. Such an effect was not observed in Experiment 1, and it is certainly possible that the enhanced discrimination performance in Experiment 2 was a spurious result. Nonetheless, these findings certainly serve to emphasize that discrimination performance is not disrupted by treatment with pimozide.

GENERAL DISCUSSION

The data of the present experiments uniformly indicated that pimozide did not disrupt accuracy of responding during acquisition of either the cue- or the response-choice discrimination. Furthermore, once established, the performance of the discrimination was unaffected by the drug treatment. Moreover, when animals were retested in the nondrug condition, the between-days improvement of performance was not disrupted among mice that had previously received pimozide treatment. Thus, although pimozide retarded acquisition of the active avoidance response, once a response was initiated (either prior to or after shock onset), the response was appropriately directed. Clearly, mice were capable of distinguishing cues associated with danger (shock) from those associated with safety (no shock). Likewise, once a response was initiated pimozide treated animals did not appear to suffer deficits in determining where to direct the response even in the absence of exteroceptive (positional) cues. These data provisionally suggest that in a task involving aversive motivation, such as that of the present investigation, pimozide did not disrupt the reinforcement value derived from particular responses, and did not appear to retard the acquisition of the cue-shock association or the association between response-choice and shock. The present report not only confirms the previous contention that pimozide does not influence the S-S association [5,6] or the relationship between responses based on interoceptive cues and shock, but also indicates that the lack of the drug effect is independent of the degree of discrimination training animals had received. Of course, it is possible that with higher doses or reduced levels of shock intensity, or perhaps in some other type of aversive task, discrimination deficits would be evident. However, the data of the present investigation do provide *prima facie* evidence that pimozide does not appreciably alter motivation or the rewarding value associated with avoidance or escape responses.

As observed in previous studies involving neuroleptics [4, 6, 7, 8, 9], treatment with pimozide was found to disrupt active avoidance performance. Moreover, when animals were previously trained in the avoidance task the disruptive influence of pimozide (0.4 mg/kg) was attenuated. With a sufficiently high dosage (0.8 mg/kg) of the drug, however, the avoidance deficits were evident even if animals had previously acquired the avoidance response. As such, these data are consistent with the proposition that deficits in response initiation were responsible for the avoidance disturbances. Once the response requirements of the task have been established, they are less vulnerable to disruption by treatment with pimozide.

The disruptive effects of pimozide on avoidance behavior were not only evident when animals were tested in the drug condition, but were quite pronounced even when animals were tested in the nondrug condition 3 days afterward. As yet unpublished studies from this laboratory suggest that at this time the drug had been metabolized and residual accumulation of drug did not contribute to behavioral change. Apparently, this deficit reflects the fact that, in spite of the evidence showing that pimozide did not disrupt the formation of associations underlying cue- and response-choice discriminations, acquisition of such associations was not sufficient to enhance later avoidance performance. In contrast to this, other studies have reported that prior acquisition of associations in animals treated with pimozide greatly facilitated drug-free performance. For example, using a one-way avoidance task, which is relatively simple to acquire, Fibiger *et al.* [9] reported that avoidance deficits observed with haloperidol treatment were absent when rats were tested in the absence of the drug. In a similar fashion, Beninger *et al.* [6] found that although pimozide disrupted defensive burying in rats, a highly prepared response, performance was unaffected upon later testing in a nondrug state. These results suggest that when a relatively simple task or highly prepared response is employed, associations formed in the presence of pimozide have a high degree of utility in guiding and directing behavior. Yet, in the present situation when the avoidance response was relatively difficult to establish, the formation of prior associations exerted considerably less influence over performance. Whether this reflects simply the cumulative effect of not having experienced the contingency between response-shock avoidance during initial training, or whether pimozide has cognitive effects or actually disrupts the processes subsuming the timing of response-outcome associations remains to be determined.

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