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Alteration of Exploration and the Response to Food Associated Cues after Treatment with Pimozide[1]

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IRWIN, J., T. N. TOMBAUGH, R. M. ZACHARKO AND H. ANISMAN. *Alteration of exploration and the response to food associated cues after treatment with Pimozide*. PHARMACOL BIOCHEM BEHAV **18**(2) 235–246, 1983.—A series of experiments assessed the effects of pimozide on spontaneous alternation in a Y- and 8-arm radial maze, and on approach to food or cues that had previously been associated with food. Mice treated with pimozide (0.2, 0.4 and 0.8 mg/kg) displayed a dose dependent reduction of alternation performance, without engendering a perseverative tendency and apparently without affecting the course of habituation. When food deprived mice entered an arm of the maze that was baited with a food pellet they consumed the food and remained in the vicinity of the food cup. Moreover, upon retesting in the non-drug state mice still exhibited a preference for cues that had been associated with food. It seems that although pimozide at the doses tested produced a haphazard pattern of exploration, the drug did not alter the rewarding value of secondary reinforcers. Contrary to an anhedonic hypothesis, it is suggested that higher doses of pimozide may actually increase, rather than decrease, the saliency of biologically significant stimuli.

Pimozide Exploratory behavior Food associated cues Spontaneous alternation

IT has been suggested that pharmacological agents, such as pimozide, which block post-synaptic dopamine (DA) receptors will diminish or eliminate the rewarding value of a primary reinforcing stimulus or cues associated with the primary reinforcer [33, 34, 35]. Originally, it was demonstrated that rats pretreated with pimozide and continuously reinforced (CRF) with food displayed behavior similar to vehicle injected animals subjected to extinction (non-reward) conditions [33,34]. Subsequent experiments have demonstrated comparable CRF results using a variety of different rewarding stimuli including saccharine [34], water [16], and self-administration of amphetamine and cocaine [13, 36, 37]. However, several investigators using identical doses and species have reported that a parallel relationship between the effects of pimozide and extinction does not occur in all situations [17, 24, 28]. For example, the resistance to extinction seen after partial reinforcement training is not paralleled by a comparable degree of response suppression induced by pimozide. Regardless of the type of intermittent reward schedule employed, pimozide induced a more rapid and marked attenuation of operant responding [28]. To account for such results, Wise [35] has argued that pimozide not only attenuates the rewarding value of the primary reinforcer (food), but also diminishes the rewarding properties attributable to secondary reinforcers (incentive motivators) that ordinarily may sustain responding in extinction.

As an alternative to the reward hypothesis it has been suggested that DA receptor blockade either disrupts response initiation [15,25], response maintenance [3,32], or interferes with a sensory-motor interface [22,32]. In fact, it has been shown that the presence of strong exteroceptive stimuli may limit pimozide-induced response suppression [31,32] as well as attenuate the degree to which pimozide alters response distributions [26]. Moreover, even when pimozide-induced decreases in responding occur in appetitively motivated discrimination tasks, they are not accompanied by decreased accuracy of responding [27,30]. Findings such as these have led to the suggestion that the effects of pimozide may largely be attributable to initiation/maintenance deficits that could be attenuated upon presentation of biologically significant and arousing stimuli. Moreover, variations in attention might interact with motoric actions of the drug thereby provoking reduced levels of responding in the absence of strong stimulus control.

The present investigation was undertaken to examine in greater detail the behavioral effects of pimozide, and wherever appropriate relate the findings to the theoretical proposition that pimozide reduces or eliminates the primary and/or secondary reinforcing properties of environmental stimuli. Specifically, the following series of experiments was designed to assess the degree to which pimozide influences [1] patterns of exploratory behavior and [2] responding to

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environmental cues associated with food (secondary reinforcers).

EXPERIMENT 1

An initial experiment was undertaken simply to determine whether treatment with pimozide would influence spontaneous alternation behavior. When mice or rats are placed in a symmetrical Y-maze they display a characteristic pattern of exploration such that they tend to enter sequentially the least recently visited arm of the maze [18,19]. This alternation performance is sensitive to variations in the novelty of the test environment and is believed to be reflective of habituation, as well as attention [21].

METHOD

Subjects

Sixty-four naive male CD-1 mice served as subjects. Mice were obtained from the Canadian Breeding Farms, Laprairie, Quebec, at 50–55 days of age and were acclimatized to the laboratory environment for 7–10 days before being used in the experiment. During this time animals were housed in groups of five and were permitted continuous access to food and water.

Apparatus

Testing was conducted in four identical black Plexiglas symmetrical Y-mazes, with each arm measuring 18.5×9.2×16.2 cm. The floor consisted of 0.32 cm stainless steel rods spaced 1.0 cm apart (center to center) and the roof was composed of 0.63 cm red Plexiglas which reduced illumination. Each arm of the Y-maze was separated from the others by a horizonatally-movable stainless steel gate located 3.5 cm from the central choice point. The solenoid-controlled stainless steel gates allowed access to the other arms through an 8.0×7.0 cm space. Situated on either side of the gate (2.9 and 6.0 cm from the choice point, respectively) were two infrared photodetection units. The photodetectors were wired such that when the mouse successively interrupted photocells located on either side of a gate leading to a particular alley the cell would trigger and an arm entry would be recorded. An arm entry would not be recorded if an animal simply poked its head through the entrance to the arm. The four Y-mazes, located in separate sound attenuated chambers, were controlled by a microcomputer system constructed at Carleton University Science Workshops.

Procedure

Mice received intraperitoneal (IP) injections of either pimozide (0.2, 0.4, or 0.8 mg/kg) or its vehicle (N = 16/group) and were placed in individual holding cages. Pimozide was dissolved in glacial acetic acid and the final volume made up with 5.5% dextrose. All doses of the drug and vehicle were administered in a volume of 10 ml/kg. The doses of pimozide selected were predicated on earlier studies indicating that these doses did not influence escape performance in a traditional escape task but appreciably influenced performance when the task necessitated sustained active responding [3]. Moreover, these doses were shown to severely retard avoidance acquisition and response maintenance in tasks varying in degree of motor difficulty. Indeed, at the highest dose level (0.8 mg/kg) pimozide had been found to disrupt avoidance even in relatively well trained mice. It might be added that doses of 0.5 mg/kg or less reduced avoidance performance in rats by at least 50% [4, 5, 11], while doses of 0.4 and 0.8 mg/kg in mice provoked reductions in excess of 50%. Doses ranging from 0.3 to 0.6 mg/kg also have been reported to produce an 80% response reduction in appetitive reward situations employing pigeons and rats [27,30]. Three hours after injection mice were individually placed in the choice area (center) of the Y-maze. After 10 sec the doors to all arms opened and animals were permitted to explore the maze freely. Testing continued for 15 minutes during which time the number and sequence of arm entries were recorded.

RESULTS AND DISCUSSION

Behavioral Scoring

An arm entry was recorded when a mouse entered an arm, passing through the first set of photodetectors and breaking the beam of the second cell. If an animal entered the choice area and immediately re-entered the arm just vacated, an arm entry was recorded but it was not included in alternation scoring. A response sequence in which animals entered the least recently visited arm was scored as an alternation (e.g., a sequence of entries such as 1, 2, 3 or 1, 3, 2). If upon leaving an arm the animal returned to the most recently visited arm (e.g., 1–2–1 or 2–3–2) this was recorded as a non-alternation. The proportion of alternation responses was calculated for each animal by dividing the number of alternations by the total number of alternations plus non-alternations. Thus, a score greater than 0.5 indicates that animals tended to alternate. Locomotion and alternation data were analyzed in this, as well as in subsequent studies, through analyses of variance and Newman-Keuls multiple comparisons of group means. In addition, χ^2 analyses of the group proportions were calculated to determine whether the levels of alternation differed from chance.

Locomotor Activity

The mean proportion of alternation sequences and total number of arm entries are shown in Table 1. Pimozide treatment produced a dose dependent reduction in number of arm entries, $F(3,60)=26.45$, $p<0.001$. Newman-Keuls multiple comparisons ($\alpha=0.05$) confirmed that each of the doses reduced the number of entries, with the greatest reduction of locomotor activity occurring in the highest dose group relative to the vehicle condition. This is consistent with other data showing that neuroleptics reduce activity and exploratory behavior [1].

Alternation

An analysis of variance of the proportion of alternation responses revealed that performance varied as a function of the Drug Treatment, $F(3,60)=3.42$, $p<0.05$. Newman-Keuls multiple comparions ($\alpha=0.05$) revealed that the 0.4 mg/kg and 0.8 mg/kg doses of the drug significantly reduced alternation levels. The 0.2 mg/kg dosage also reduced alternation, but this difference was not statistically significant. χ^2 analyses revealed that vehicle treated mice alternated at levels which exceeded chance, $\chi^2(1)=6.72$, $p<0.01$, whereas chance levels of alternation were seen in the three pimozide groups, χ^2's $(1)=1.42$, 0.78, and 0.03 for the 0.2, 0.4 and 0.8 mg/kg groups, respectively p's >0.10. In conclusion, pimozide was found to reduce both total number of arm entries and alternation behavior. Previous research conducted under similar conditions revealed that alternation

TABLE 1

NUMBER OF ARM ENTRIES AND PROPORTION OF ALTERNATION RESPONSES AS A FUNCTION OF DRUG TREATMENT (EXPERIMENT 1)

	Mean Number of Arm Entries	Mean Proportion of Alternation Responses
Vehicle	52.31 ± 4.49	0.63 ± 0.02
0.2 mg/kg Pimozide	37.05 ± 2.25*	0.56 ± 0.02
0.4 mg/kg Pimozide	26.25 ± 1.94*	0.55 ± 0.03
0.8 mg/kg Pimozide	18.44 ± 1.90*	0.51 ± 0.03

*$p<0.05$ relative to vehicle control.

TABLE 2

NUMBER OF ARM ENTRIES AND PROPORTION OF ALTERNATION RESPONSES AS A FUNCTION OF DRUG TREATMENT ON DAY 1 (EXPERIMENT 2)

	Mean Number of Arm Entries		Mean Proportion of Alternation Responses	
Day 1 Drug	Test Day 1 (Drug)	Test Day 2 (Drug-free)	Test Day 1 (Drug)	Test Day 2 (Drug-free)
Vehicle	77.00 ± 5.69	57.08 ± 4.81	0.64 ± 0.01	0.59 ± 0.03
Pimozide (0.8 mg/kg)	32.08 ± 3.08*	63.75 ± 3.83	0.54 ± 0.03	0.59 ± 0.03

*$p<0.05$ relative to vehicle control.

scores were independent of levels of locomtor activity [2,18]. Accordingly, it is unlikely that the observed deficit of alternation in the present investigation was related to changes in motor activity induced by the pimozide treatment.

EXPERIMENT 2

It is clear from the above that treatment with pimozide reduces the alternation tendency seen among naive animals. It is also well documented that anticholinergic agents disrupt normal alternation behavior in a similar fashion, presumably because they attenuate or impede habituation to environmental stimuli [8,21]. The effects of pimozide on alternation behavior may reflect a similar disruption/modification of habituation processes. For example, alternation typically declines within a session as well as between sessions in drug free animals. However, if mice are pre-treated with an anticholinergic drug immediately prior to an initial exposure to a maze, thereby preventing habituation, high levels of alternation are observed when animals are re-tested in the non-drug state [19]. The behavior of these animals is essentially indistinguishable from naive animals tested for the first time. Thus, if pimozide, either directly or indirectly, affects habituation processes, alternation levels should approach those of naive animals when re-tested in a drug-free state.

METHOD

Subjects and Apparatus

Twenty-four naive CD-1 male mice served as subjects as described in Experiment 1. The apparatus consisted of a symmetrical black Plexiglas Y-maze with arms measuring 19.0×6.0×7.0 cm, with a black Plexiglas floor and covered with a clear Plexiglas roof. Unlike the apparatus of Experiment 1, the Y-maze was not equipped with a photodetection system.

Procedure

Mice received IP injections of either pimozide (0.8 mg/kg) or its vehicle and were then placed in individual holding cages. The 0.8 mg/kg dose was selected on the basis of results obtained in Experiment 1 where the 66% decrease in number of arm entries demonstrated its behavioral effectivenss. Higher doses were not employed because further reductions in exploratory behavior would produce floor effects prohibiting valid estimates of choice behavior. Three hours after injection mice were individually placed in one arm of the Y-maze. As in Experiment 1, the number and sequence of arm entries were recorded for a 15 min period. In this case an arm entry was recorded when an animal placed all four legs across the area dividing an arm from the choice area. Animals were returned to the holding cages at the end of the session. Twenty-four hours later they were again tested in the Y-maze. Animals were not injected with drug prior to re-test.

RESULTS AND DISCUSSION

Locomotor Activity

An analysis of variance of the total number of arm entries (Table 2) revealed a significant Drug Treatment×Test Day

interaction, $F(1,22)=42.94$, $p<0.001$. Newman-Keuls multiple comparisons ($\alpha=0.05$) indicated that during the first test animals treated with pimozide made significantly fewer arm entries than did the vehicle treated animals. However, during re-test members of the vehicle group made significantly fewer arm entries than emitted during the first test, whereas an increase in the number of arm entries was seen among mice initially tested with pimozide and re-tested in the non-drug state. On the second day of testing the two treatment groups did not differ significantly from one another.

Alternation

Analysis of variance of the mean proportion of alternation scores revealed a statistically significant Drug Treatment × Test Day interaction, $F(1,22)=5.91$, $p<0.05$. Pairwise comparisons ($\alpha=0.05$) between the means comprising this interaction (see Table 2) revealed that on day 1 the alternation performance of animals treated with pimozide was significantly lower than that of animals that received vehicle. Among mice initially treated with vehicle alternation levels declined somewhat between days ($0.05<p<0.10$), while a small increase of alternation was seen among mice initially tested with pimozide. As a result comparable levels of alternation were seen among the two treatment groups on the second test day. χ^2 analyses of the mean proportion of alternation scores indicated that among animals treated with vehicle, alternation significantly exceeded chance during the first test session, $\chi^2(1)=8.21$, $p<0.001$, but not during the retest, $\chi^2=2.94$, $p>0.05$. The alternation performance of animals treated with pimozide did not exceed chance during either the first or second test sessions, χ^2's $(1)=0.54, 2.94$, p's>0.05.

Taken together it appears that treatment with pimozide reduces locomotor activity, as well as spontaneous alternation. When vehicle animals are retested in the absence of drug treatment a small decline in alternation levels is evident. In contrast, an increase in alternation scores is seen among animals initially treated with pimozide. The fact that alternation levels in mice originally treated with pimozide did not differ from those that initially received vehicle suggests that the initial pimozide treatment did not appreciably disrupt the course of habituation (also see [15]). This conclusion is supported by the fact that performance on the second test day among mice previously tested with pimozide did not reach the level seen among vehicle animals when tested in the maze for the first time.

EXPERIMENT 3

Typically animals tested in a Y-maze alternation task exhibit approximately equal numbers of entries to each of the arms and spend an equivalent amount of time in each of the arms. It would be expected that if mice are food deprived and one maze arm is baited with food pellets, animals will spend a larger proportion of time in the food associated arm and/or would exhibit a greater number of entries to this arm relative to the other non-baited arms. If pimozide reduces the reward value of food [35] then the time spent in the food baited arm should decrease relative to the duration of time spent in the remaining arms. Experiment 3 evaluated the immediate effects of pimozide on alternation behavior and on the amount of time spent in an arm where food was presented. In this experiment animals were subsequently re-tested in a non-deprived and non-drugged state to determine whether carryover effects of the initial treatment would be evident.

METHOD

Subjects and Apparatus

A total of 16 naive CD-1 male mice aged 60–70 days, served as subjects. All subjects and apparatus specifications were the same as those of Experiment 2.

Procedure

Following 20 hours of food deprivation all mice were presented in the home cage with a white plastic cup (4.4 cm) containing two 45 mg Noyes food pellets. This was repeated at hourly intervals four times during the day in order to familiarize animals with the type of food which would be used in the maze. After animals had consumed the last Noyes food pellet, Purina food pellets were placed in the cage hopper for two hours. Following a twenty-one hour interval mice received IP injections of either 0.8 mg/kg pimozide or its vehicle as previously described. Three hours after injections mice were individually placed in the Y-maze for 15 minutes. A plastic dish located at the end of one arm of the Y-maze contained two Noyes pellets. In addition to recording the sequence of arm entries, the proportion of time spent in the "food arm" was noted. At the end of the test session all animals were allowed ad lib access to food and water. Twenty-four hours after the initial session animals were given a second 15 min test. On this occasion mice did not receive any injections and the plastic dish did not contain any food. Again the number and sequence of arm entries, as well as the proportion of time spent in the food-cup arm were recorded.

RESULTS AND DISCUSSION

Locomotor Activity

Consistent with the results of Experiment 2, an analysis of variance of the total number of arm entries yielded a significant Drug Treatment × Test Day interaction, $F(1,14)=4.89$, $p<0.05$ (see Table 3). Pairwise comparisons ($\alpha=0.05$) indicated that during the first test session pimozide treated animals made significantly fewer arm entries than did the vehicle treated animals. While pimozide treated animals exhibited a significant increase in the number of arm entries between the first and second test sessions, vehicle treated animals did not significantly differ in activity between the two test sessions. Finally, the two treatment groups did not differ significantly from one another on the second day of testing.

Spontaneous Alternation

An analysis of variance of the mean proportion of alternation responses indicated that neither Drug Treatment nor the Drug Treatment × Test Day interaction was significant, F's<1. It seems that the administration of pimozide to food deprived animals did not substantially reduce alternation relative to vehicle treated mice (see Table 3). Although a slight reduction of alternation scores for vehicle subjects was seen in this experiment relative to that seen in Experiments 1 and 2, the levels of alternation of the pimozide treated animals were higher than those previously observed. When animals were re-tested 24 hours later drug-free (without food deprivation or arms baited with food) levels of alternation

TABLE 3

NUMBER OF ARM ENTRIES AND PROPORTION OF ALTERNATION RESPONSES AS A FUNCTION OF DRUG TREATMENT (EXPERIMENT 3)

	Mean Number of Arm Entries		Mean Proportion of Alternation Responses	
Day 1 Drug	Test Day 1 (Deprived Drug)	Test Day 2 (Non-deprived Drug-free)	Test Day 1 (Deprived Drug)	Test Day 2 (Non-deprived Drug-free)
Vehicle	63.38 ± 6.8	65.13 ± 4.8	0.59 ± 0.03	0.60 ± 0.02
Pimozide (0.8 mg/kg)	30.00 ± 5.5*	58.25 ± 5.5	0.58 ± 0.04	0.61 ± 0.02

*$p<0.05$ relative to vehicle controls.

did not differ from that seen on the first test day, $F(1,14)<1$, and alternation scores for vehicle and pimozide groups exceeded chance levels, χ^2 s(1)=3.76 and 4.92, respectively, p's<0.05). These results confirm our earlier supposition that pimozide induced variations in alternation were unrelated to levels of locomotor activity. That is, although a substantial reduction of arm entries was seen in the pimozide treated group, the alternation scores were seemingly unaffected. Previous experiments [14,20] have revealed that making the arms of the maze distinct from one another will either increase alternation scores or limit the reductions of alternation ordinarily provoked by drug treatments. Whether the increase in alternation in the present experiment was due to the deprivation procedure, the availability of food in the test situation, or the presence of the dish containing food in the arm, cannot be determined from the results of Experiment 3, but will be addressed later in this paper.

An analysis of variance of the proportion of total time spent in each arm revealed that the amount of time spent in the food arm on day 1 was greater than the amount of time spent in that same arm on the ensuing day when animals were not food deprived, $F(1,14)=7.84$, $p<0.05$. However, neither the effect of Drug Treatment nor the Drug × Block interaction were statistically significant, F's(1,14)<1. Pimozide clearly did not reduce the time animals spent in the food arm, and in fact, a small non-significant increase in the time spent in this arm was exhibited by pimozide treated mice. A separate analysis of the proportion of time spent in the food arm following consumption of the pellets yielded similar results. During initial testing both the drug and vehicle groups spent a significantly greater amount of time in the food arm than might be expected by chance, χ^2's(1)=4.87 and 18.31, respectively, p's<0.05. Upon subsequent re-test in the non-deprived and drug-free state, time spent in the arm previously associated with food did not differ from chance, χ^2's(1)=1.18 and 0.21, p's>0.10.

It would appear that the pimozide treatment did not alter the animal's propensity to remain in the vicinity of the food reinforcement. Previous studies demonstrated that pimozide alters operant responding for food reinforcement [35] as well as the initiation of alimentary behaviors [32]. The latter study, however, suggested that the disruption of the initiation of consummatory behaviors may have been secondary to a motor disturbance, rather than an alteration of the reinforcing value of the food. The present finding that mice pretreated with 0.8 mg/kg spent a greater amount of time in the arm associated with food is essentially consistent with the results of Tombaugh *et al.* [32] which were obtained with rats injected with 1.0 mg/kg.

EXPERIMENT 4

In the Y-maze levels of alternation among naive mice are typically found to be approximately 65%. Since chance alternation is 50%, the limited range of scores may prevent detection of subtle differences in performance between treatment groups. This ceiling effect is avoided with an 8-arm radial maze, which was recently shown to be particularly sensitive to the effects of pharmacological manipulations on exploratory patterns [7]. Alternation behavior can be monitored as in the Y-maze and, in addition, the probability of returning to the 2 or 4 least recently visited arms may be analyzed. Moreover, we have found that mice tested in the 8-arm maze frequently visit immediately adjacent arms. The occurrence of such a response is usually about 40% (chance adjacent alternation being 12.5%), thus permitting more sensitive assessment of the degree to which alternation patterns are disrupted by pimozide.

In view of its potential advantages, an 8-arm radial maze was employed in Experiment 4 to further assess the effects which pimozide exerts on alternation behavior. Three different patterns of alternation were evaluated: (a) 4-arm alternation (the probability of entering one of the four least recently visited arms; chance=50%, the same as in the Y-maze), (b) 2-arm alternation (the probability of entering one of the two least recently visited arms; chance=25%), (c) adjacent alternation (the probability of visiting an immediately adjacent arm; chance=12.5%). Additionally, in this experiment the placement of an empty food dish in one of the arms of the maze permitted further investigation of the effects which distinctive environmental stimuli had on alternation behavior.

METHOD

Subjects

Twenty naive male CD-1 mice were employed as subjects, as described in Experiment 1.

Apparatus

Testing was conducted in an 8 arm radial maze of the type

TABLE 4

MEAN NUMBER OF ARM ENTRIES, PROPORTION OF ENTRIES TO ARM CONTAINING EMPTY FOOD DISH AND PROPORTION OF TIME SPENT IN ARM CONTAINING EMPTY FOOD DISH AS A FUNCTION OF DRUG TREATMENT (EXPERIMENT 4)

	Mean Number of Arm Entries	Proportion of Entries to Arm Containing Empty Food Dish	Proportion of Time Spent in Arm Containing Empty Food Dish
Vehicle (no dish)	60.6 ± 7.47	0.13 ± 0.01	0.14 ± 0.01
Vehicle (with dish)	52.8 ± 3.02	0.12 ± 0.01	0.13 ± 0.01
Pimozide (no dish)	26.60 ± 4.88*	0.10 ± 0.03	0.12 ± 0.04
Pimozide (with dish)	25.00 ± 2.65*	0.14 ± 0.03	0.16 ± 0.03

*$p<0.05$ relative to respective vehicle controls.

TABLE 5

MEAN PROPORTION OF 4-ARM, 2-ARM AND ADJACENT ALTERNATION RESPONSES AND PERSEVERATION RESPONSES AS A FUNCTION OF DRUG TREATMENT AND PRESENCE OF EMPTY FOOD DISH (EXPERIMENT 4)

	4-Arm	2-Arm	Adjacent	Perseveration
Vehicle (no dish)	0.80 ± 0.05	0.56 ± 0.10	0.49 ± 0.11	0.07 ± 0.02
Vehicle (with dish)	0.83 ± 0.03	0.55 ± 0.04	0.54 ± 0.07	0.08 ± 0.02
Pimozide (no dish)	0.66 ± 0.11	0.40 ± 0.12	0.33 ± 0.11	0.12 ± 0.06
Pimozide (with dish)	0.64 ± 0.04	0.32 ± 0.05	0.23 ± 0.07	0.12 ± 0.03

*$p<0.05$ relative to respective vehicle controls.

previously described by Olton [23]. Each arm (55.9×11.4 cm) radiated from a central octogonal area (25.4 cm in diameter) which an animal would have to re-enter before entering another arm. The maze was constructed of wood with surface areas covered in sand-colored plastic.

Procedure

Animals received an IP injection of either pimozide (0.8 mg/kg) or its vehicle and were placed in individual holding cages for three hours. Mice were then individually placed in the center of the 8-arm maze and allowed to explore for 15 minutes. For half the mice in each drug group one end of one arm of the maze contained a small plastic dish and for the other half the plastic dish was absent. The animal's behavior was monitored through a television camera which enabled an observer, situated in an adjacent room, to record the number and sequence of arm entries.

RESULTS AND DISCUSSION

Table 4 shows the mean number of arm entries, proportion of time spent in the arm containing the dish and proportion of entries to the food dish arm. Treatment with pimozide was found to significantly reduce the number of arm entries, $F(1,16)=39.43$, $p<0.01$. Analysis of the proportion of entries into the arm containing the dish for half the animals revealed that neither the drug, the presence of the cup, nor the interaction of the two approached statistical significance, F's<1. A comparable analysis of the proportion of time spent in the food cup arm yielded similar results, F's<1. χ^2 analyses revealed that none of the groups frequented the arm containing the empty food cup at levels which differed from chance, χ^2's<1. Furthermore, the amount of time vehicle and pimozide treated animals spent in this area did not differ from chance, χ^2's<1.

Treatment with pimozide reduced the frequency of alternation responses for all three measures, F's(1,16)=6.28, 6.24 and 6.70, $p<0.05$ for 4-arm, 2-arm and adjacent alternation, respectively (see Table 5). An additional analysis was undertaken to determine whether pimozide induced stimulus perseveration as observed with catecholamine stimulants, such as amphetamine. That is, would animals show a tendency to enter the arm that had just been visited on the preceding trial. This analysis revealed that pimozide did not increase the frequency of such responses, $F(1,16)=1.40$ $p>0.10$, suggesting that the reduction of alternation behavior was not a consequence of a perseverative bias.

Comparison of the results from the first four experiments indicates that pimozide is at least as effective in disrupting alternation in the 8-arm radial maze as it is in Y-maze. Moreover, the presence of the dish alone or in combination with drug treatments did not influence alternation performance. Evidently the mere presence of the dish was not a sufficiently powerful stimulus to influence the pattern of exploration observed in the 8-arm maze. This is contrasted to previous experimental reports that novel or distinctive environmental stimuli do influence patterns of exploratory behavior [8,20].

EXPERIMENT 5

The purpose of Experiment 5 was twofold. First it was undertaken to determine whether the effects of pimozide on alternation behavior would be altered when food was present in one of the arms of the maze, and as such represents an extension of Experiment 3 and 4. A second purpose was to ascertain if pimozide altered the capacity of environmental cues to acquire secondary reinforcing properties. If pimozide blocks or blunts the rewarding impact of primary reinforcers, as proposed by the anhedonic theory [35], an attenuation in the capacity of food related cues to serve as incentive motivators should be observed. While there is some support for this position [6,12], other experimental data suggest that pimozide does not alter the ability of an animal to either acquire associations between environmental events (S-S learning) or utilize encoded information to guide and direct behavior [27, 29, 30]. The current experiment was designed to determine the effects which pimozide has on associative processes by examining alternation performance in the 8-arm radial maze when food deprived animals are re-tested in the absence of the primary reinforcer. In addition to monitoring patterns of exploration, this experiment, similar to Experiment 3, also evaluated whether the drug treatment influenced the amount of time spent in the arm containing food or the arm that had previously been associated with food.

METHOD

Subjects and Apparatus

A total of 28 naive male CD-1 mice served as subjects. Subject and apparatus characteristics were the same as those of Experiment 4.

Procedure

First test—food present. During the first two days all animals were trained to eat Noyes food pellets in the home cage as described in Experiment 3. At the end of the second training session (Day 2) food was removed from the food hoppers. Twenty-one hours later (Day 3) half the animals received an IP injection of 0.8 mg/kg pimozide while the remaining mice were injected with vehicle. Three hours after injection mice received three, five minute test periods where a food dish containing a single 45 mg Noyes pellet was situated at the end of one arm of the maze. Each test period began with the placement of the mouse in the center of the maze. After five minutes, provided that the food pellet had been eaten, the animal was returned to the home cage for one minute while a new food pellet was placed in the dish. The mouse was then returned to the center of the maze for the next five minute session. In instances where animals did not quickly enter the food arm the duration of the period was extended to a maximum of 10 minutes. If an animal did not consume the food within this time the trial was terminated. In all cases animals were provided with at least two minutes to explore the maze after finding the food. For example, if an animal entered the arm and ate the pellet after four minutes, the trial was terminated after six minutes. If the food was consumed during the first three minutes then the trial block ended at five minutes. In addition to recording the sequence and number of arm entries, latency to eat the pellet and the amount of time spent in the arm containing the food was recorded. For the purpose of calculating locomotor activity (number of arm entries) and alternation performance, only those responses made during the first five minutes of any given block were included.

Second test—food absent. At the end of the first test all mice were returned to their home cages and allowed ad lib access to food and water for the next three days (Days 4, 5, and 6). Food was then removed from the hoppers and 21 hours later (Day 7) half the animals from each of the two groups were injected IP with 0.8 mg/kg of pimozide (Groups Pimozide-Pimozide and Vehicle-Pimozide) and half with its vehicle (Groups Pimozide-Vehicle and Vehicle-Vehicle). Three hours post-injection mice were re-tested in the 8-arm radial maze for a single 15 minute session where the food dish was present but did not contain any food pellets. As in the first test, the number and sequence of arm entries, and amount of time spent in the arm containing the empty food dish were recorded.

RESULTS AND DISCUSSION

Separate analyses were conducted on test day 1 and test day 2 performance due to procedural differences. That is, on test day 1 mice received three successive exposures to the maze, each of five minutes duration, with food available on each of these trials. On the second test day mice received a single 15 minute test session without any food available. Figures 1 and 2 show the mean values for each dependent variable on the first test day and on the second test day, respectively.

First Test—Food Present

Locomotor activity. Analysis of variance of the number of arm entries revealed that mice treated with pimozide made significantly fewer arm entries than the vehicle treated animals, $F(1,24)=44.91$, $p<0.01$ (see Fig. 1).

Alternation. Analysis of variance of the 4-arm alternation scores revealed only a Drug Treatment effect, $F(1,24)=21.28$, $p<0.01$, indicating that pimozide substantially reduced alternation performance (see Fig. 1). Whereas the vehicle treated animals (Vehicle-Vehicle and Vehicle-Pimozide) exhibited alternation levels which exceeded chance, $\chi^2(1)=17.16$ and 10.31, respectively, p's<0.01, the alternation scores of the Pimozide-Vehicle group did not differ from chance, $\chi^2(1)=1.35$, $p>0.10$, while that of the Pimozide-Pimozide group was actually lower than chance, $\chi^2(1)=8.32$, $p<0.05$. It will be recalled that in the Y-maze pimozide did not disrupt alternation among food-deprived animals relative to vehicle controls. It is likely that the difference between the results of the Y-maze and radial maze experiments is related to the relative significance of the food cup when a limited number of arms are available for exploration as in the Y-maze.

As in the case of 4-arm alternation, the probability of revisiting one of the two least recently visited arms was influenced by the drug treatment, $F(1,24)=46.88$, $p<0.001$. As

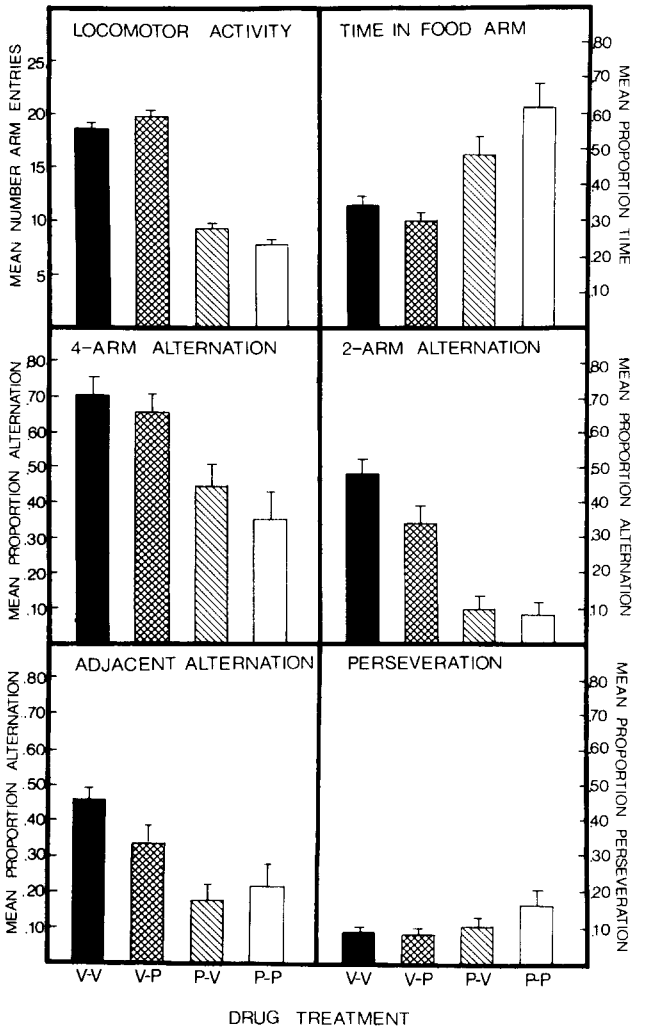

FIG. 1. Effects of pimozide on locomotor activity, proportion of time spent in the food associated arm; four-arm, two-arm and adjacent alternation and perseveration on the first test day. The first and second letters beneath each bar designate Day 1 and Day 2 drug treatments, respectively. (V=vehicle, P=0.8 mg/kg pimozide).

seen in Fig. 1 high levels of alternation, exceeding chance were evident in vehicle treated animals, whereas alternation levels were substantially lower and were significantly less than chance levels among the pimozide groups (χ^2's(1)= 28.11 and 4.28, $p<0.05$ for the vehicle groups and χ^2's(1)=13.23 and 15.51, $p<0.01$ for the pimozide groups). Finally, in the case of adjacent alternation it was found that vehicle treated mice entered an arm immediately adjacent to one which had been visited on a preceding trial at a frequency which exceeded chance levels, χ^2's(1)=100.51, and 49.85, $p<0.01$. Substantially fewer adjacent alternation responses were seen among pimozide treated mice, $F(1,24)=12.78$, $p<0.01$. Pimozide treated animals tended to re-visit the arm entered on the preceding trial (perserveration) somewhat more often than did vehicle treated mice but this tendency was only marginally significant, $F(1,24)=3.71$, $p<0.066$. Moreover, the frequency of perseverative responses did not differ significantly from chance for the two pimozide groups, χ^2's(1)=0.47 and 1.07, p's>0.05. Thus, this treatment can be differentiated from catecholamine stimulants which actually induce a significant perseverative tendency [7]. The results suggest that pimozide does not produce a set pattern of exploration, but rather engenders a profile which is non-specific and random.

Time in food arm. The amount of time spent in the arm containing food significantly exceeded chance for both vehicle and pimozide treated mice, χ^2's(1)=45.23 and 30.33, $p<0.01$ for the Vehicle-Vehicle and Vehicle-Pimozide groups and χ^2's(1)=119.90 and 222.09, $p<0.01$ for the Pimozide-Vehicle and Pimozide-Pimozide groups. Moreover, it was found that once a food pellet was consumed, mice treated with pimozide spent significantly more time in the food arm than did vehicle treated animals, $F(1,24)=16.68$, $p<0.001$. This finding is incongruent with the anhedonic hypothesis. That is, had pimozide reduced the rewarding value of food, a reduction rather than an increase in time spent in that arm should have been evident relative to vehicle controls. The small number of arm entries exhibited by the pimozide treated animals after food consumption precluded a meaningful analysis of the proportion of entries to the food versus non-food arms.

Second Test—Food Absent

Locomotor activity. Analysis of variance of the number of arm entries revealed that pimozide administered on the second test day significantly reduced the number of arm entries, $F(1,24)=37.11$, $p<0.001$ (Fig. 2). Drug treatment applied on test day 1 was not found to influence performance on the second test day, $F(1,24)=1.46$, $p>0.10$.

Alternation. Since alternation behavior declines over the course of a test session, the 15 minute test period was analyzed in blocks of five minutes. In the case of the 4-arm and 2-arm alternation measures (see Fig. 2) significant Drug Treatment × blocks of Time interactions were observed, $F(2,48)=6.92$, $p<0.01$ and $F(2,48)=4.75$, $p<0.05$, respectively. Newman-Keuls multiple comparisons ($\chi^2=0.05$) conducted at each level of blocks revealed that pimozide, relative to vehicle controls, reduced alternation during the first five minutes but was without effect thereafter. Whereas alternation during the first five minutes of the test did not differ from chance among pimozide treated animals, alternation increased thereafter and exceeded chance levels. Alternation for the vehicle exceeded chance levels and was constant over the three blocks.

Adjacent alternation sequences were reduced throughout the entire session by the administration of pimozide $F(1,24)=4.91$, $p<0.05$. The effect of pimozide was not found to interact with blocks of time, $F(2,48)<1$. Thus, it seems that the effects of pimozide were greater, being more evident throughout the test session, on adjacent alternation than on each of the other measures. Indeed, it has been previously observed that this particular measure is more sensitive to the various treatment effects than other measures [7].

With respect to the tendency of animals to re-visit the arm most recently entered differences between the two test days emerged. In contrast to the first test day, the drug treatment was not found to influence the frequency of perseverative responses, $F(1,24)<1$. It is noteworthy that the analyses of variance calculated for all of the measures indicated that drug administration on the first test day did not influence performance on the second test day regardless of whether animals were tested in the pimozide or non-drug state.

Time in food arm. The proportion of time mice spent in

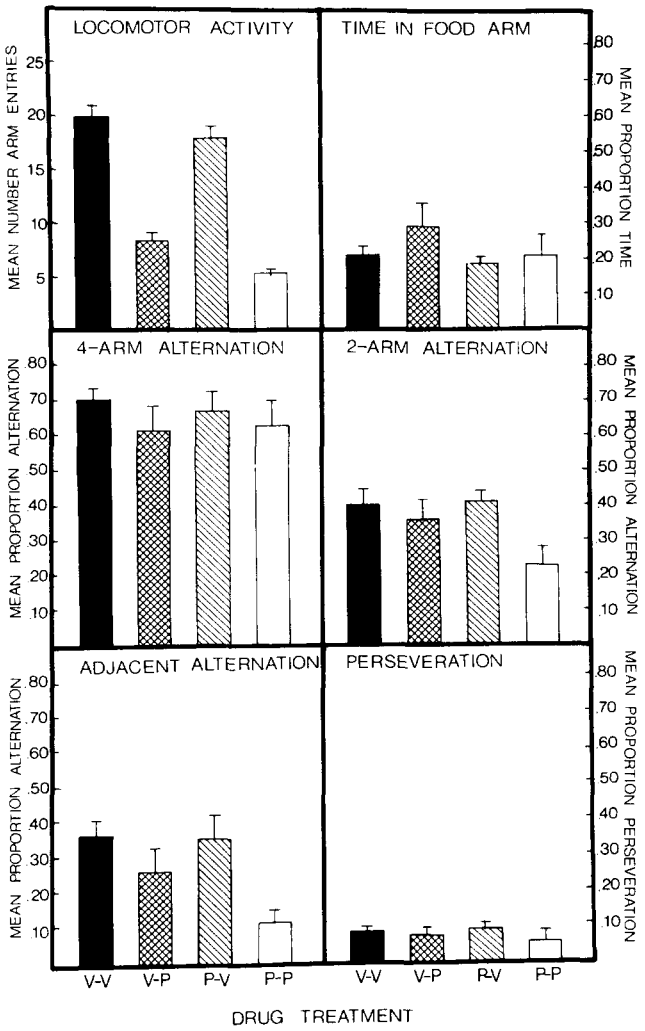

FIG. 2. Locomotor activity; proportion of time spent in the food-associated arm; four-arm, two-arm and adjacent alternation and perserveration as a function of pimozide treatment on the second test day. Note that the mice were food deprived, but no food was present on this test day. The first and second letters beneath each bar designate Day 1 and Day 2 drug treatments, respectively. (V=Vehicle, P=0.8 mg/kg pimozide).

the food-cup arm (see Fig. 2) was not influenced by drug treatment, $F(1,24)=1.16$, $p>0.10$. For both the pimozide and vehicle treated mice the time spent in this arm was greater than that expected by chance, regardless of drug treatment received on test day 1, χ^2's(1)=20.31, 28.92, 18.37 and 21.06, p's<0.01 for Vehicle-Vehicle, Pimozide-Vehicle, Vehicle-Pimozide, and Pimozide-Pimozide, respectively. Although the empty food cup was present in the arm it should be emphasized that the effectiveness of the food cup in maintaining behavior was probably due to its conditioned or secondary reinforcing properties. It will be recalled that in Experiment 4, where the cup was not associated with food, time spent in that arm did not differ significantly from chance. Hence, it is unlikely that the animals remained in the food-cup arm because it was distinctively different or represented a novel stimulus.

Taken together it seems that treatment with 0.8 mg/kg pimozide will change the pattern of alternation exhibited by animals, but will not reduce the propensity to remain in the area that had previously been associated with food reward. Because the arm correlated with food contained an empty food dish on the second day, it cannot presently be determined whether animals responded to that particular cue or to positional cues. However, the possibility might be considered that positional and non-positional cues may be differentially influenced by pimozide.

EXPERIMENT 6

Results from the previous experiments strongly suggest that pimozide does not interfere with the ability of environmental stimuli to acquire secondary reinforcing properties. Alternatively, it is possible that the failure of pimozide to disrupt the establishment of secondary reinforcement effects was because the dose used (0.8 mg/kg) was insufficient to produce a functional effect in mice. However, cross-species comparisons render this explanation unlikely. As previously mentioned, the 0.8 mg/kg dose used in the present series of experiments represents a dose considerably greater than that needed to produce deficits in avoidance and escape performance in a shuttle task in both mice and rats [4, 5, 11]. Additionally, a dose related decrease in exploratory behavior and locomotor activity, ranging from a 28% decrease with 0.2 mg/kg to a 66% suppression of responding with 0.8 mg/kg, was observed in Experiment 1. In the subsequent experiments 0.8 mg/kg of the drug continued to produce substantial response decrements without affecting either alternation behavior or secondary reinforcing effects. Similarly, response decrement effects without any concomitant decreases in accuracy of responding have been observed in both pigeons [27] and rats [30]. Thus it appears that the results of the present series of experiments are commensurate with previous reports and indicate that secondary reinforcement and stimulus control effects are relatively insensitive to the action of pimozide.

Nevertheless, the fact remains that data are not available which directly demonstrate that 0.8 mg/kg was sufficient to attenuate responding for food reinforcement in the mouse, as doses of 0.5–1.0 mg/kg do in rats and pigeons. Thus the possibility remains, albeit remote, that the 0.8 mg/kg dose did not produce an "anhedonic-like effect" in the mouse and therefore could not be expected to influence secondary reinforcement effects. Consequently, an additional experiment was undertaken to demonstrate that, as in rats, pimozide treatment among mice results in diminished responding for food reinforcement just as decreased responding is seen in extinction.

METHOD

Subjects and Apparatus

Eighteen naive CD-1 mice served as subjects as described in Experiment 1. The testing apparatus was a white Plexiglas alleyway measuring 77.0×12.5×29.5 cm. The start box measured 14 cm in length and at the opposite end of the alley a small plastic food cup was placed in an area 16 cm in length.

Procedure

Mice were individually housed and given ad lib access to food and water for the first three days of the experiment.

Animals were then maintained on a 12 hr food deprivation schedule for the rest of the experiment. After four days of deprivation animals' weights had stabilized at approximately 85% of baseline and training began. Eight trials per day were given for 3 days. On each trial a mouse was placed in the start box and after 2 sec the start box gate was opened. Reward consisted of a single 45 mg Noyes pellet placed in the food cup. Following each trial animals were returned to the home cage for the 25 sec intertrial interval. Latency to traverse the alley was recorded on each trial.

Twenty-one hrs after the last training session (day 11) mice were divided into 2 groups and injected IP with pimozide (0.8 mg/kg) or its vehicle. Three hrs after injection mice were tested in the alley. For pimozide treated mice a food pellet was placed in the food dish before each trial, whereas vehicle treated animals were presented with an empty food dish. All animals received 8 trials and were then returned to the home cage. Seventy-two hrs later the identical testing procedure was repeated.

RESULTS AND DISCUSSION

An analysis of variance performed over the latency data for the last day of training showed that both groups of animals performed at comparable levels prior to the introduction of drug treatment, $F(1,16)<1$ (Means: Pimozide $=5.72\pm0.64$; Vehicle $=5.45\pm 1.18$). Comparison of the group means during test (Pimozide $=15.85\pm1.36$; Vehicle $=11.25\pm1.38$) indicates that pimozide tended to suppress behavior to a somewhat greater degree than did extinction. An analysis of variance with repeated measures performed over the two test days confirmed this observation: Drug: $F(1,16)=4.33$, $p=0.054$; Days: $F(1,16)<1$; Drugs $\times$ Days: $F(1,16)<1$.

In general, these results are in agreement with those reported elsewhere [16, 32, 33, 34] and illustrate that the "anhedonic-like effect" occurs in mice as it does in rats. As such, these data clearly indicate that the failure of pimozide to interfere with the acquisition of secondary reinforcers in mice is not because the 0.8 mg/kg dose was insufficient to produce the effect. If anything, the results of Experiement 6 indicate that the dose used in the present series of experiments was somewhat more effective than the extinction procedure in increasing response latencies.

GENERAL DISCUSSION

In contrast to the high levels of spontaneous alternation performance seen in vehicle treated animals, mice injected with pimozide exhibited a dose dependent reduction of alternation behavior. At doses of 0.4 and 0.8 mg/kg, mice displayed chance levels of alternation. Although the decrease in alternation behavior was coincident with a reduction in number of arm entries, it is unlikely that the two effects are causally related since it has been shown previously that motor activity and levels of alternation are independent [18]. That is to say, treatments that reduce motor activity do not necessarily influence alternation performance, and reductions of alternation performance are not necessarily accompanied by variations in motor activity. It may be added here as well, that drugs which result in direct or indirect stimulation of catecholamine receptors will also disrupt alternation performance; however, these effects are readily distinguishable from those produced by pimozide in the present study. Specifically, treatment with d-amphetamine will induce stimulus perseveration, such that animals display successive visits to two arms of the maze [21]. In contrast, the behavior of pimozide treated mice is best characterized as random entries into the arms of the maze.

When food deprived animals were tested in the Y-maze with one arm of the maze baited, pimozide was not found to disrupt alternation behavior. However, when an 8-arm radial maze was employed, a reduction of alternation was observed under similar conditions. It is known that when arms of a maze are readily distinguishable from one another, alternation levels may be somewhat increased and the effectiveness of treatments which ordinarily reduce the alternation tendency is minimized [20]. The fact that the reduction of alternation induced by pimozide in the Y-maze was eliminated with the presence of food is consistent with these previous observations. The finding that pimozide disrupted alternation in the radial maze, particularly adjacent alternation, even when one arm of the maze was baited supports the contention that the radial maze is more sensitive to the effects of pharmacological manipulations than is the Y-maze [7].

Of particular significance in the present study were the findings that (1) food deprived mice treated with pimozide approached and ate food placed in the maze and (2) these mice tended to remain in the arm associated with food for longer periods than in the other arms. Indeed, the duration of time pimozide treated animals spent in the arm associated with food did not differ from that seen in vehicle treated mice, with the time spent in this arm exceeding chance for both groups. It is interesting to note that once food was consumed mice treated with pimozide remained in the food arm for lengthy periods, with some animals not leaving the arm at all. Several of these animals, in fact, hovered over the food dish or actually sat in the dish. These observations are similar to those reported by Tombaugh *et al.* [29] in a study investigating the effects of pimozide on sign-tracking behavior. Thus, it almost appears as if the reinforcing value of stimuli paired with food had actually been increased by the pimozide treatment rather than being decreased as assumed by the anhedonia hypothesis [35]. If pimozide had reduced the reward value of food, then it would have been expected that animals would certainly have spent less time in the vicinity of the food than that seen among vehicle treated mice. In operant studies evaluating the effect of pimozide on lever pressing for food reward a marked decline in response rate is typically observed. Albeit speculative, it is possible that animals in these studies, like those of the present investigation, remained in the vicinity of the food cup after receiving reward rather than returning to the lever and pressing again. Such an event might occur owing either to a motor deficit or because of a relative increase in the tendency to approach and remain near cues most closely associated with food reward (i.e. the food cup itself rather than the lever). In fact, support for such a position was provided by Clody and Carlton [9] who reported that the efficacy of stimuli spatially associated with food delivery was increased by the neuroleptic agent chlorpromazine.

The fact that mice treated with pimozide remained in the vicinity of the food cup appeared to be due to secondary reinforcing values associated with the cup, since animals did not exhibit a preference for the arm containing the cup in situations where the cup had not been previously paired with food. Furthermore, the apparent preference for the arm associated with food was not attributable to a motor deficit engendered by pimozide treatment. When food deprived animals were re-tested in the non-drug state 96 hours after

the initial test session, a preference for the arm previously associated with food was still observed. Again, these data support the contention that the arm containing the cup acquired secondary reinforcing properties which were not diminished by previous pimozide administrations. This finding is commensurate with two recently completed studies which show that pimozide does not impair the capacity of environmental stimuli to acquire secondary reinforcing properties [29]. In the first study, light and food were initially paired under conditions of 1.0 mg/kg of pimozide or vehicle. When tested drug-free, both groups were equally proficient at behaviorally tracking the light cue when it was presented at different spatial locations within the test cage. The second experiment employed a place preference procedure where, during conditioning, vehicle and 1.0 mg/kg pimozide treated animals were confined in distinctive compartments associated with either food or no food. On a later drug-free test, animals were given unrestricted access to both chambers. Comparable increases in preference toward the food-associated chamber occurred for both groups demonstrating that pimozide at the dose tested did not disrupt the ability of the cues to acquire secondary reinforcing strength.

In contrast to the studies conducted in our laboratories earlier studies have indicated that pimozide reduces the rewarding value of cues associated with food reward [6,12]. The inconsistencies between the present findings and those previously reported cannot readily be determined given the great number of procedural differences between the studies. Nevertheless, it is noteworthy that in the present investigation a natural approach response was employed in a situation where strong position preferences were absent, whereas in previous experiments a less natural response (bar-press) was used, and in one instance strong positional biases were reported.

Summarizing, the present investigation revealed that pimozide alters the pattern of exploration as measured by alternation performance in both the Y- and 8-arm radial mazes. Whether this change is due to variations in habituation, attention, or the the intrinsic motivation to explore remains to be determined. The tendency to approach and remain in an arm associated with food was not altered by treatment with pimozide regardless of whether animals were tested in the drug state or subsequently re-tested in the absence of drug treatment. Together these results provisionally suggest that pimozide, at least at the dose tested, does not alter the secondary reinforcement derived from cues closely associated with food. To the contrary, there is some indication that animals treated with pimozide may attend more to significant environmental cues (defined here as those stimuli most closely aligned with the primary reinforcer) raising the possibility that performance deficits in operant tasks may be secondary to this focused response bias.

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