Psychopharmacology 69, 11–18 (1980)

Psychopharmacology


# The Use of Extinction to Investigate the Nature of Neuroleptic-Induced Avoidance Deficits

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**Abstract.** Four groups ($N = 8$) of rats received five 15-trial sessions of one-way avoidance training. Each trial was signaled by a ten-second tone stimulus and shock followed on a random 67% of the trials. Prior to each session two groups were injected with 1.0 mg/kg of the neuroleptic pimozide and the other two groups received vehicle injections. The pimozide groups failed to acquire the avoidance response although they escaped readily when shock was presented, and the vehicle groups acquired the avoidance response. Three 15-trial nondrug test sessions followed. For one group that had been trained under pimozide and one vehicle group, shock continued to follow the tone on 67% of the test trials. The remaining two groups were tested in extinction, i.e., shocks were no longer presented. Both groups that were trained under pimozide showed gradual acquisition of the avoidance response in the first nondrug test session. The group that received vehicle during training and shock during testing continued to avoid whereas the other vehicle group showed extinction of the avoidance response across test sessions. The acquisition of responding in the extinction group trained under pimozide indicated that the association of environmental stimuli with shock had been learned during training in spite of the failure to avoid. The gradual acquisition of the response indicated that this group had failed to learn the appropriate motor response during training. These results support previous observations of associative learning in animals treated with neuroleptics but further suggest that dopamine plays a role in mechanisms of response learning.

**Key words:** Avoidance – Neuroleptics – Pimozide – Dopamine – Extinction

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Animals with brain catecholamines (CA) depleted by treatment with reserpine, alpha-methyl-para-tyrosine (AMPT) or by intraventricular injections of the neurotoxic agent 6-hydroxydopamine (6-OHDA) show a deficit in conditioned avoidance responding (CAR; Cooper et al., 1972; Moore and Rech, 1967; Rech et al., 1966; Seiden and Carlsson, 1963; Seiden and Hanson, 1964; Taylor and Laverty, 1972). In addition, the CAR deficits produced by reserpine and AMPT are reversed by the CA precursor 3, 4-dihydroxy-L-phenylalanine [L-Dopa; (Moore and Rech, 1967; Seiden and Carlsson, 1963; Seiden and Hanson, 1964)]. These studies indicate a role for CAs in CAR but do not allow assessment of the relative roles of noradrenaline (NA) and dopamine (DA). However, the observation that relatively greater depletions of DA produced by intraventricular 6-OHDA injections into appropriately pretreated rats resulted in deficits in CAR (Cooper et al., 1973) suggests that DA neurons are important for the acquisition of CAR. This conclusion is further supported by reports that neuroleptic drugs such as haloperidol and pimozide, which in low doses are relatively specific in blocking DA receptors (Pinder et al., 1976), produced deficits in CAR (Fibiger et al., 1975; Niemegeers et al., 1969). Indirect support for a role for DA rather than NA in CAR also was provided by Fibiger and Mason (1978) who reported that bilateral destruction of the dorsal NA bundle failed to disrupt one-way avoidance. In addition, Mason and Fibiger (1979) reported that dorsal bundle lesions actually improve two-way avoidance.

The observation that bilateral microinjections of 6-OHDA into the substantia nigra (SN), the origin of the nigrostriatal DA bundle (NSB), produced CAR deficits (Fibiger et al., 1974; Zis et al., 1974) that could be reversed by L-dopa (Zis et al., 1974) suggested that the NSB was involved in the CAR deficits produced by CA depletion. Corroborative data were provided by other reports that interference with the NSB produced CAR

0033-3158/80/0069/0011/$01.60

deficits; thus, CAR deficits occurred following electrolytic lesions of SN (Mitchum and Thomas, 1972), destruction of the NSB along its course through the lateral hypothalamus by knife cuts (Kent and Grossman, 1973), 6-OHDA injections (Levin and Smith, 1972), or electrolytic lesions (Runnels and Thompson, 1969), and following destruction of the terminal areas of the NSB either with intrastriatal 6-OHDA injections (Cooper et al., 1974; Neill et al., 1974) or electrolytic lesions of the striatum (Kirkby and Kimble, 1968; Thompson, 1959).

From these data it is not possible to determine if the effect of DA depletion on CAR was related to a failure to learn the association between preshock stimuli and the shock (an associative learning deficit) or an impairment in the animals' ability to learn the avoidance response (a response learning deficit). However, the results of a recent study indicate that associative learning can occur in neuroleptic-treated rats that failed to perform the avoidance response (Beninger et al., in press 1980). In this study, animals injected with pimozide were given several sessions of CAR training and failed to acquire the avoidance response, a result consistent with many previous data. When in an undrugged state, these same animals were trained to lever press for food on a random interval schedule until responding had stabilized and the tone which had signaled shock during CAR training was presented. Significantly greater conditioned suppression (Estes and Skinner, 1941) was observed in the animals that had receiving CAR training than in unshocked controls. This result indicated that animals that usually failed to avoid during CAR training had in fact learned the association of the tone with shock. It seems, therefore, that CAR deficits observed in animals treated with neuroleptics are not related to an impairment in their ability to make association between preshock stimuli and shock.

Animals with impaired synaptic transmission in DA systems probably fail to avoid because of a response deficit. Possibly they are deficient in their ability to initiate responses to conditioned stimuli. Alternatively, such animals may be unable to learn the appropriate motor response despite having learned the significance of the warning stimulus in predicting shock. A number of data have bearing on this issue. The observation of highly efficient avoidance performance in the first drug-free session following several sessions of CAR training with neuroleptic injections (Fibiger et al., 1975) indicates that some aspect of the avoidance response was learned during training and favours the hypothesis that neuroleptics produced a deficit in the animals' ability to initiate responses. However, in a recent study (Beninger et al., in press 1980) we noted that following CAR training with neuroleptic treatment, only 38% of the rats avoided on the first drug-free trial while 94% avoided on the second. Thus, it is possible that the avoidance response was learned rapidly after only one shock to animals that had already learned the association between preshock stimuli and shock. This observation favors the hypothesis that DA is involved in response learning as does the finding of Zis et al. (1974) that animals with lesions of the NSB and that had failed to acquire the CAR showed only gradual improvement in avoidance responding when given L-dopa treatment.

The present experiment was undertaken to investigate the nature of the response deficit in rats treated with neuroleptics. Rats pretreated with pimozide and given several sessions of one-way avoidance training (and failing to avoid) were retested when undrugged in the absence of shock (i.e., extinction). A failure to avoid in extinction or a gradual acquisition of the avoidance response would indicate that the response had not been learned during the training sessions. If any aspect of the response had been learned previously, the undrugged animals now capable of initiating motor responses should display avoidance behavior initially before ceasing to respond during later extinction trials.

If shock had been presented on every trial during training, the absence of shock on the first extinction trial might have served as a signal that shock was no longer going to occur. This possible confusion was avoided by using partial tone-shock pairings during the initial training sessions. Thus, absence of shock on any one trial would not indicate to the rat that the environment now had become safe and hence no longer required an avoidance response.

## Materials and Methods

*Subjects.* Thirty-two experimentally naive male albino rats of the Wistar strain weighing between 238 and 355 g were housed individually in a climatically controlled colony room on a 12 h light-dark cycle. Standard laboratory rat chow and water were continuously available.

*Apparatus.* The one-way avoidance apparatus consisted of a shuttlebox (25 cm × 78 cm × 33 cm deep) divided into two equal-area halves by a partition. One half was painted flat black and the other was metallic gray. The partition could be opened by raising a 13-cm wide guillotine door. A grid floor on the black side could be electrified by a scrambled 2.0 mA d.c. current (BRS/LVE shock generator). A 2900 Hz tone generator (Sonalert) was mounted below the grid floor on the back side of the box. Electromechanical relays and timers were used for environmental control and data collection.

*Procedure.* The 32 rats were randomly assigned to four groups: the Vehicle-CS-US ($N = 8$), Vehicle-EXT ($N = 8$), Pimozide-CS-US ($N = 8$), and Pimozide-EXT ($N = 8$) groups. Training sessions occurred at approximately the same time each day for 5 days; each rat received 15 trials per session in which the intertrial interval was 30 s.

Intraperitoneal injections were given 90–120 min prior to each session. The two pimozide groups received 1.0 mg/kg pimozide dissolved in a ratio of 1:6 in boiling tartaric acid and then cooled to approximately 45° C prior to injection; this dose of pimozide was used because previous studies showed that it effectively blocked avoidance responding (Beninger et al., in press 1980). The two vehicle groups were injected similarly with the tartaric acid vehicle. Each session began by placing the rat into the gray side of the shuttlebox; after 30 s the rat was placed into the black side facing the end opposite the guillotine door. The trial then began with the onset of the tone and the opening of the door. If the rat moved into the gray side during the ten-second 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 ten-second tone period, the offset of the tone was contiguous with the electrifying of the grid floor on a random 67% of the trials. The subsequent movement into the gray side was followed by lowering the door and an *escape* response was recorded. If no shuttle response occurred for ten seconds following the offset of the tone, the rat was pushed gently into the gray side. Entry into the gray side always began the next intertrial interval.

On the third, fourth, and fifth days following the last training session, the three test sessions were given. No drugs were administered during these sessions. The Vehicle-CS-US and Pimozide-CS-US groups continued to receive shocks on a random 67% of the trials (unless, of course, they made an avoidance response). The Vehicle-EXT and Pimozide-EXT groups received extinction sessions, i.e., shocks were no longer given. As was the case during training sessions, if no shuttle response occurred for ten seconds following tone offset, the rat was gently pushed into the gray side and the timing of the next intertrial interval begun. Dependent variables for both training and test sessions were latency and number of avoidance and escape response.

## Results

*Avoidance.* A response was recorded as an avoidance if the rat left the dark side of the shuttlebox during the ten-second tone period prior to shock onset. If an avoidance response failed to occur, shock was presented on 67% of the trials and the shuttle response was recorded as an escape. The mean number of avoidance responses for each group for the fifth training session is shown in Fig. 1. The data from the five training sessions were subjected to a two-way analysis of variance, with repeated measures on the sessions variable. The results revealed that the groups differed ($F = 15.97$; $d.f. = 3, 28$; $P < 0.001$), there was a sessions effect ($F = 6.72$; $d.f. = 4, 112$; $P < 0.001$), and an interaction between these two effects ($F = 5.03$; $d.f. = 12, 112$; $P < 0.001$).

The two vehicle groups improved in avoidance performance over the course of the five training sessions, whereas the pimozide groups failed to acquire the response. These differences in performance reveal the source of the interaction in the overall analysis of variance. This was supported by the results of post hoc tests of simple effects, which revealed that the groups did not differ significantly on session 1 ($F = 2.24$; $d.f. = 3, 28$; $P > 0.05$) but did differ on session 2 ($F = 7.39$; $d.f. = 3, 28$; $P < 0.001$).

The avoidance data from the three drug-free test sessions also are shown in Fig. 1. Analysis of variance of

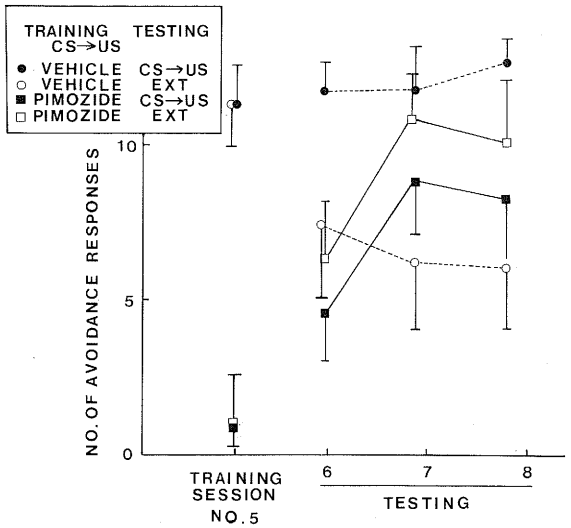


**Fig. 1.** Mean number (± SEM) of avoidance responses for the last 15-trial avoidance training session during which drugs or vehicle were given and during the last three avoidance test sessions during which no drugs were given

these data revealed that the groups did not differ significantly ($F = 2.56$; $d.f. = 3, 28$; $P > 0.05$). However, there was a sessions effect ($F = 4.16$; $d.f. = 2, 56$; $P < 0.02$) and a significant interaction ($F = 3.60$; $d.f. = 6, 56$; $P < 0.004$). The interaction can be understood with post hoc reference to the simple main effects of sessions for each group; thus, whereas neither the Vehicle-CS-US nor the Vehicle-EXT groups showed a significant change in responding over the three test sessions ($F = 0.29$; $d.f. = 2, 56$; $P > 0.05$ and $F = 2.12$; $d.f. = 2, 56$; $P > 0.05$, respectively), both the Pimozide-CS-US and Pimozide-EXT groups did ($F = 5.96$; $d.f. = 2, 56$; $P < 0.01$ and $F = 6.56$; $d.f. = 2, 56$; $P < 0.01$, respectively).

*Latency.* Latency was defined as the time from tone onset until the animal entered the gray side of the shuttlebox and had a maximum value of 20 s (see Procedure). As described above, the two pimozide-treated groups failed to acquire the avoidance response during the training sessions. These animals also frequently failed to make the shuttle response during the 10-s post-tone interval on shock-free trials and had to be pushed into the gray side of the shuttlebox, resulting in the recording of maximum response latencies of 20 s. To eliminate the bias in the latency data provided by these trials, the latencies for the five trials that were scheduled as nonshock for all four groups were not included in the overall analysis of latencies. Thus, latency data for the five training sessions consisted of ten trials for each session for each rat. The group mean latencies for the fifth session (collapsed over trials) are shown in Fig. 2. A three-way analysis of variance with repeated measures on the sessions and trials variables

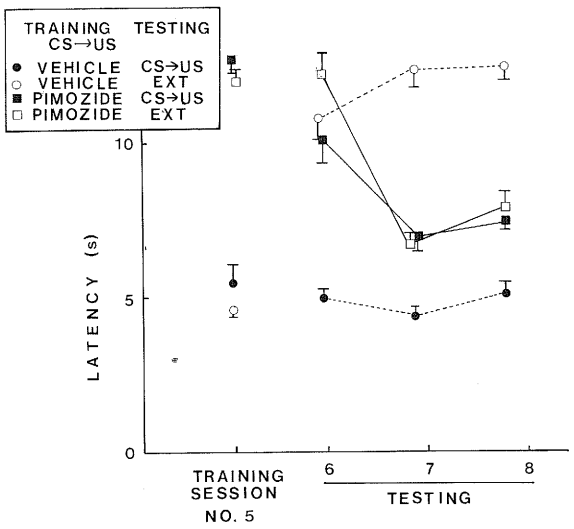


**Fig. 2.** Mean (± SEM) latency (s) of the shuttle response (avoidance or escape) for each group for the ten shock trials for the last avoidance training session during which drugs or vehicle were given and during the last three avoidance test sessions (sessions 6–8) during which no drugs were given

revealed that the groups differed ($F = 16.32$; $d.f. = 3, 28$; $P < 0.001$), there was a sessions effect ($F = 5.88$; $d.f. = 4, 112$; $P < 0.001$), and an interaction of groups and sessions ($F = 5.01$; $d.f. = 12, 112$; $P < 0.001$). The results of this analysis are similar to the avoidance results described above. The data indicate that over sessions the mean latency to shuttle to the safe side was significantly longer for the pimozide-treated rats than for the vehicle groups. Tests of simple effects of groups during session 1 revealed no significant difference ($F = 0.89$: $d.f. = 3, 28$; $P > 0.05$) but group differences were significant by session 2 ($F = 7.79$; $d.f. = 3, 28$; $P < 0.001$), thus supporting this conclusion.

The three-way analysis of variance also included trials as a variable. The results revealed that there was a change in latencies over trials ($F = 19.17$; $d.f. = 9, 252$; $P < 0.001$). The significant three-way interaction ($F = 1.67$; $d.f. = 108, 1008$; $P < 0.001$) indicates that from session to session the differences among groups from trial to trial were not the same. Tests of simple main effects support this conclusion since the groups did not differ significantly in session 1 but the groups did differ in session 5 (see above). Tests of simple interactive effects also support the conclusion that from session to session there was a trial-by-trial difference in how the groups differed; in session 1 there was a groups-by-trials interaction ($F = 2.84$; $d.f. = 27, 1008$; $P < 0.001$) whereas in session 5 this interaction was insignificant ($F = 1.20$; $d.f. = 27, 1008$; $P > 0.05$).

The latency data from the first five sessions can be summarized as follows. Overall, the two vehicle groups had the shortest latencies while the two pimozide groups took longer to make the shuttle response (see Fig. 2). In the first session the four groups performed in a similar manner for about the first five shock-trials but for the last five shock-trials the latencies of the two vehicle groups decreased markedly whereas the pimozide groups showed little further improvement. These initial across-trial differences disappeared by session 5 when all groups were performing quite consistently but at different levels.

All fifteen trials were included in the latency analysis of the three post-drug test sessions. This was done because no drugs were injected prior to these sessions, thereby eliminating the bias produced by maximum latencies on nonshock trials in animals injected with pimozide. The group mean latencies for these sessions (collapsed over trials) are shown in Fig. 2. A three-way analysis of variance with repeated measures on the sessions and trials variables revealed a group effect ($F = 3.61$; $d.f. = 3, 28$; $P < 0.03$), a sessions effect ($F = 5.97$; $d.f. = 2, 56$; $P < 0.004$), and a groups-by-sessions interaction ($F = 4.48$; $d.f. = 6, 56$; $P < 0.001$). As inspection of Fig. 2 might suggest, the interaction occurred because the Pimozide-CS-US and Pimozide-EXT groups showed changes in shuttle response latencies across sessions ($F = 4.50$; $d.f. = 2, 56$; $P < 0.03$ and $F = 13.22$; $d.f. = 2, 56$; $P < 0.001$, respectively) whereas the Vehicle-CS-US and Vehicle-EXT groups showed no similar significant effect ($F < 1$; $d.f. = 2, 56$; $P > 0.05$ and $F = 1.45$; $d.f. = 2, 56$; $P > 0.05$, respectively). The overall trials effect, which was included in the three-way analysis of variance of the latency data from the three drug-free test sessions, was not significant ($F = 0.41$; $d.f. = 14, 392$; $P > 0.05$) but there was a three-way interaction of trials, groups, and sessions ($F = 1.48$; $d.f. = 84, 784$; $P < 0.005$). During the three test sessions, the Vehicle-CS-US group continued to perform at a constant level. The Vehicle-EXT group showed progressively longer latencies over trials in session 6 and continued at this slower rate in sessions 7 and 8. On the other hand, both the Pimozide-CS-US and Pimozide-EXT groups showed progressive improvement in session 6 and continued to perform at this new level in sessions 7 and 8, although the Pimozide-EXT group possibly was showing the beginning of an extinction curve in session 8. The three-way interaction of trials, groups, and sessions indicates that the relationship between groups from trial to trial differed from session to session. The different trends just described are the source of this interaction.

The results of the analysis of the latencies from the three test sessions can be summarized as follows (note that no drugs were given during these sessions): the Vehicle-CS-US group that continued to receive shock following the tone on 67% of the trials continued to avoid consistently. The Vehicle-EXT group that no longer received shocks showed extinction of the avoid-

ance response, generally increasing latencies from trial to trial. The Pimozide-CS-US group that continued to receive shock began to avoid effectively, showing decreasing latencies over the course of the first test session. Of greatest interest is the Pimozide-EXT group that, in spite of receiving no shocks during the test sessions, began to make avoidance responses with progressively shorter latencies from trial to trial in session 6.

Only one additional comparison using the latency data from shock trials was carried out. Over the five training sessions the 16 pimozide-treated rats, although failing to avoid consistently, did make an avoidance response on 86 trials whereas the 16 vehicle-treated rats avoided on 457 trials. The respective mean ($\pm$ SEM) latencies for these responses were 3.98 ($\pm$ 0.25) and 3.52 ($\pm$ 0.11) s. A comparison of these two means was of interest because it might indicate that pimozide-treated rats are deficient in their ability to perform the avoidance response even when they do make it. The data revealed that the avoidance latencies of the two pimozide groups were longer than those of the vehicle groups ($t = 3.42$, $d.f. = 541$, $P < 0.001$). The mean ($\pm$ SEM) escape latencies for the two combined groups with the nonshock trials removed were 13.08 ($\pm$ 0.12) and 11.79 ($\pm$ 0.13) on 714 trials for the pimozide groups and 343 trials for the vehicle groups, respectively. The comparison of these two means similarly revealed that the pimozide-treated rats took longer than the vehicle controls to perform the response ($t = 12.87$, $d.f. = 1055$, $P < 0.001$).

## Discussion

The present results confirm many previous reports that neuroleptics can selectively impair the acquisition of a conditioned avoidance response. More importantly, however, these experiments lend strong support to our recent hypothesis that pimozide does not significantly interfere with the ability of the animal to learn the association between the conditioned stimulus (CS) and shock (Beninger et al., in press 1980). Thus, although pimozide blocked the acquisition of the avoidance response (Figs. 1 and 2), when animals were tested in the absence of pimozide and without shock in sessions 6–8 (Pimozide-EXT group), they began to shuttle in response to the tone alone. Interestingly, during sessions 6–8 the performance of the Pimozide-EXT group did not differ significantly from the Pimozide-CS-US group that continued to receive shock on 67% of the trials during these sessions. The fact that the Pimozide-EXT group failed to extinguish at the same rate as the Vehicle-EXT group might reflect the far greater number of tone-shock pairings received by that group because they failed to avoid on most training trials. It is evident that presentation of the tone by itself was sufficient to produce the 'avoidance' response and that the tone had acquired powerful aversive properties during the CAR training even though the animals did not shuttle in rsponse to this CS when given pimozide. These data, along with our previous demonstration that the CS utilized in the CAR paradigm can produce conditioned suppreession in animals that fail to make avoidance responses under pimozide (Beninger et al., in press 1980), demonstrate that pimozide does not interfere with associative learning. The findings that neuroleptics impair neither classical conditioning (Hunt, 1956) nor short-term memory (Bartus, 1978) are entirely consistent with this conclusion.

Ranje and Ungerstedt (1977) have suggested that spiroperidol impairs the acquisition of an underwater brightness discrimination task by an action that is independent of its effects on motor performance. The acquisition of a spatial discrimination task in the same apparatus was not affected by spiroperidol. However, although this neuroleptic decreases the rate at which the brightness discrimination task is acquired, Ranje and Ungerstedt's (1977) data indicate that it clearly does not block learning. Rather, spiroperidol appears to retard the acquisition of the brightness discrimination response, and as has been discussed previously by Beninger et al. (in press 1980), it remains possible that the attenuated rate of acquisition described by Ranje and Ungerstedt (1977) is due to motor-related performance deficits. Further work appears necessary to determine the precise nature of the deficit described by these workers.

If the avoidance deficit produced by neuroleptics cannot be attributed to an impairment of associative learning, then to waht can this classic effect of neuroleptics be ascribed? Fibiger et al. (1975) have previously proposed that neuroleptics impair the acquisition of a conditioned avoidance response by selectively blocking initiation of voluntary or operant motor responses. Specifically, the deficit may lie in the disruption of a process whereby the initial components of the motor response are triggered by significant environmental stimuli. In the present context, the rat would learn first the association between tone and shock and then subsequently learn to initiate the avoidance response following tone onset. Presumably, only the latter sequence can be disrupted by neuroleptics.

The present observations also indicate that pimozide has additional properties that can influence the performance of the avoidance response. Evidence for this has been presented previously inasmuch as it is known that the disruptive effects of neuroleptics on conditioned avoidance responding are less pronounced in animals that have received extensive avoidance training prior to the administration of the drug (Fibiger

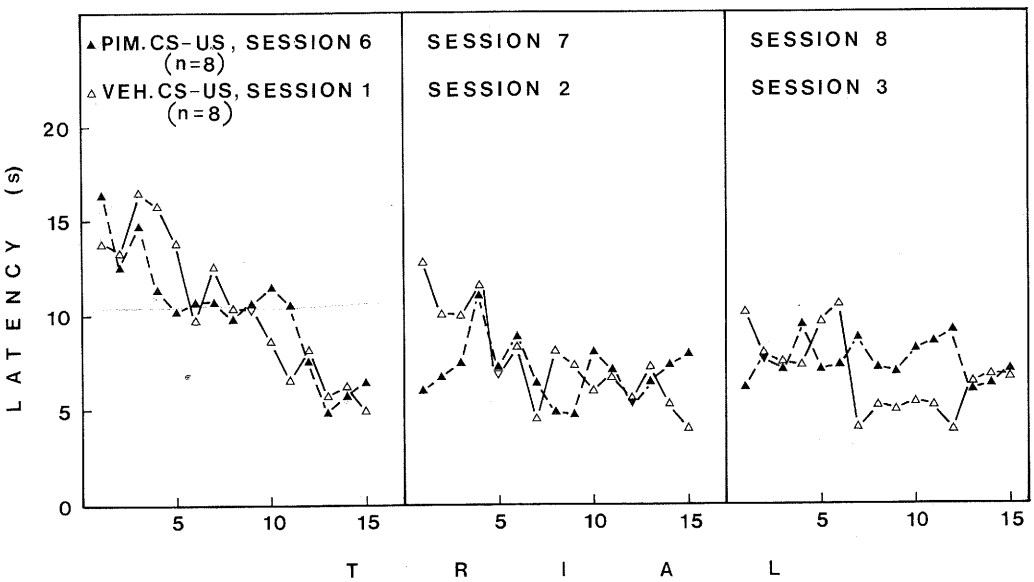


**Fig. 3.** Mean latency (s) of the shuttle response (avoidance or escape) for the Vehicle-CS-US group on sessions 1 to 3 and for the Pimozide-CS-US group when run undrugged on sessions 6 to 8

et al., 1975; Knoll, 1965). In addition, on the basis of impaired acquisition of a complex motor manipulative task following intraventricular injections of 6-OHDA, Mason and Iversen (1974) have suggested that DA neurons are involved in learning to sequence together specific motor acts. With regard to the present experiments, attention is drawn to the finding that animals in both the Pimozide-EXT and Pimozide-CS-US groups gradually acquired the avoidance response during sessions 6–8 (Figs. 1 and 2) as indicated by the significant sessions effects in both the avoidance and latency measures. In particular, both of these groups showed marked improvement in performance from session 6 to 7. This gradual improvement in performance, despite the absence of shock during the sessions in the Pimozide-EXT group, may represent the learning of the appropriate motor response during sessions 6 and 7, and indicates that this aspect of motor learning was impaired during the pimozide treatment.

To examine further the extent to which motor learning may have been disrupted by pimozide, the latencies to avoid or escape in the Vehicle-CS-US (sesssions 1–3) and the Pimozide-CS-US group (sessions 6–8) were compared (Fig. 3). The latencies for the Vehicle-CS-US group on sessions 1–3 represent the latencies to respond in naive undrugged animals during the first three sessions of the acquisition of the avoidance response. The latencies of the Pimozide-CS-US group on sessions 6–8 represent the latencies of animals that for the first time were tested in the CAR paradigm in an undrugged state but that had extensive previous experience in the avoidance test under the influence of pimozide. It was reasoned that if significant motor learning occurred during the pimozide-pretreated sessions, then the latencies to respond should be significantly shorter than naive controls when these animals were tested for the first time in the absence of the drug. However, in Fig. 3 it is evident that these animals responded in a manner that was identical to the naive rats (i.e., the groups did not differ, $F < 1.0$; $d.f. = 1, 14$; $P > 0.05$). Further, the latencies of both groups decreased at similar rates during the additional training on the subsequent 2 days. This was supported by the observation of a significant sessions ($F = 10.54$; $d.f. = 2, 28$; $P < 0.001$) and trials effect ($F = 7.01$; $d.f. = 14, 196$; $P < 0.001$) but no significant sessions-x-group ($F = 0.40$; $d.f. = 2, 28$; $P > 0.05$) or trials-x-group interaction ($F = 1.66$; $d.f. = 14, 196$; $P > 0.05$). These results lend strong support to the hypothesis that pimozide can block or retard the learning of new motor responses, and may help to explain why well-trained animals are more resistant to the disruptive effects of neuroleptics on avoidance responding.

The conclusion that DA neurons are involved in some aspect of motor learning is consistent with the finding of Zis et al. (1974) that rats with NSB lesions that failed to make avoidance responses showed only a gradual acquisition of the shuttle response when given L-Dopa treatment. Previous findings that animals given CAR training while injected with pimozide or haloperidol show rapid acquisition of the avoidance response during the first nondrug session (Beninger et al., in press 1980; Fibiger et al., 1975) appear to be inconsistent with the data of Zis et al. (1974) and with the observation of gradual acquisition of the CAR on the

drug-free trials reported here. This apparent inconsistency is probably due to methodological differences. One important difference between the present study and those of Beninger et al. (in press 1980) and Fibiger et al. (1975) is that in these earlier experiments the presentation of shocks followed the tones on 100% of the trials, whereas partial tone-shock pairings were utilized in the present experiments. This partial pairing procedure resulted in slower acquisition of the avoidance response and this may account for the difference in performance on the first drug-free session. The observation that many pimozide-treated animals fail to avoid on the first drug-free trial (62%) in the study of Beninger et al. (in press 1980), even with 100% tone-chock pairings during the training trials, suggests that motor learning occurs rapidly during the first drug-free session. It is speculated, therefore, that because a partial pairing schedule was used in the present experiments, the course of the motor learning during the first drug-free session was more evident than in previous experiments in which 100% CS-US pairings were utilized (Fibiger et al., 1975; Beninger et al., in press 1980).

The observation that overtraining of a CAR prior to 6-OHDA lesions of SN or haloperidol treatment results in experimental subjects that still can initiate the appropriate avoidance response (Fibiger et al., 1975; Zis et al., 1974) would seem to indicate that although DA neurons play a role in learning specific motor responses, their importance is diminished once the behavior is under strong stimulus control or becomes well-learned and highly reflexive in nature. However, it should be noted that pretrained animals with extensive damage to DA pathways eventually stop making the avoidance response when given extended testing (Beer and Lenard, 1975). This suggests that DA neurons may also be involved in the maintenance of avoidance responding. Experiments are currently in progress to define more precisely the effects of neuroleptics on the maintenance of previously learned operant behaviors.

*Acknowledgements.* This research was supported by grants from the Medical Research Council of Canada. R. J. Beninger and S. T. Mason are Medical Research Council of Canada post-doctoral fellows. A. G. Phillips is a Killam Senior Research Scholar.

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Received July 18, 1979; Final Version January 11, 1980