Psychopharmacology (1988) 96:375–380

Psychopharmacology

Scopolamine produces environment-specific conditioned activity that is not blocked by pimozide in rats

Evalynn J. Mazurski and Richard J. Beninger
Department of Psychology, Queen's University, Kingston, Canada K7L 3N6

Abstract. A classical conditioning paradigm was employed to determine if the stimulant effects of the anticholinergic scopolamine could show conditioning. In experiment 1 rats had 12 60-min pairings of scopolamine (1.0 or 8.0 mg/kg, IP) with a distinctive environment that monitored horizontal and vertical activity. Experimental (paired) groups received the drug 30 min prior to each session, whereas control (unpaired) groups received saline. Following each session the Paired groups were injected with saline, and the Unpaired groups received the same doses of scopolamine. After every fourth pairing a test session assessed conditioning by comparing activity of paired und unpaired groups in response to saline. Scopolamine enhanced horizontal activity, although conditioning was seen only with 8.0 mg/kg. The low dose increased vertical activity, whereas an initial decrease was observed with 8.0 mg/kg. However, conditioned vertical activity was seen with both doses. Experiment 2 assessed the possible role of dopamine in conditioning with 8.0 mg/kg scopolamine. Rats treated as in experiment 1 were additionally given 0.4 mg/kg pimozide 4 h prior to each pairing session. Pimozide did not block scopolamine's stimulant effect. Conditioned horizontal and vertical activity were also observed, suggesting that this effect may be mediated by direct changes within cholinergic systems.

Key words: Rats – Scopolamine – Pimozide – Horizontal activity – Vertical activity – Environment-specific conditioning

Classical conditioning is one of the most widely studied forms of learning. An unconditioned stimulus (UCS), which elicits an unconditioned response, is paired with a conditioned stimulus (CS), which does not initially elicit the same response. Following contingent pairings of the two stimuli, the CS alone begins to elicit the response (Pavlov 1927/1960).

Many stimuli have been used as UCSs. For example, drugs that have the unconditioned effect of increasing activity have been paired with a specific environment, the CS. Conditioning is said to have occurred if presentation of the CS alone (i.e., placement in the test environment following a saline injection) leads to increased activity (Pavlov 1927/1960). Using this procedure it has been shown that environments or specific cues associated with the stimulants (+)-amphetamine, cocaine, apomorphine or methylphenidate elicit conditioned activity or stereotypy (Schreiber et al. 1976; Pickens and Crowder 1967; Hayashi et al. 1980; Post et al. 1981; Schiff 1982; Barr et al. 1983; Beninger and Hahn 1983; Beninger and Herz 1986; Herz and Beninger 1987; Moller et al. 1987). The neurotransmitter dopamine (DA) may play a central role in this conditioning, as these compounds are known to be DA agonists (e.g., Colpaert et al. 1976; Moore 1977; Kuczenski 1983), and it was shown that pretreatment with the DA specific antagonist pimozide on conditioning sessions blocked the establishment of conditioning based on amphetamine (Beninger and Hahn 1983) or cocaine (Beninger and Herz 1986).

There have been some demonstrations of environment-specific conditioned locomotor activity using drugs that may not interact directly with the DA system. Mucha et al. (1981) have shown that the opiate agonist morphine produces conditioned activity. This finding was extended by Vezina and Stewart (1984), who demonstrated the effect with administration of morphine directly into the ventral tegmental area. This latter effect was found to be blocked by pimozide, suggesting that morphine conditioning may be mediated by dopamine.

Thus, the central mediation of environment-specific conditioning of locomotion can be examined by using drugs that produce unconditioned stimulant effects like the DA agonists, but do so by a different mechanism. One such class of drugs is the anticholinergics, including atropine and scopolamine (Goodman and Gilman 1975). These compounds were frequently used to counteract the hypokinesia associated with Parkinson's disease until the discovery of the therapeutic action of the DA agonists (Duvoisin 1967). The anticholinergics also enhance activity in the intact organism (Bauer 1982; Carey 1982; Sanberg et al. 1987).

The anticholinergics have been used in classical conditioning paradigms, although to our knowledge they have not been studied using activity as the unconditioned response. Thus, it was shown that the mydriasis produced by anticholinergics underwent conditoning, as did the change in salivation (Lang et al. 1966). Although the mydriasis exhibited conditioning in a manner expected by the stimulus-substitution theory (Pavlov 1927, 1960), the salivary response appeared to exhibit compensatory conditioning or a conditioned response in the direction opposite to that of the observed drug effect (e.g., see Siegel 1975). Regardless of these differences, however, it appears that the central effects of anticholinergics may support conditioning.

Offprint requests to: E. J. Mazurski

Experiment 1 examined the extent to which locomotor effects of scopolamine can become conditioned to a specific environment. Results revealed that conditioning was produced. However, there has been some evidence suggesting that anticholinergics may also interact with DA, specifically by blocking reuptake (Coyle and Snyder 1969). Thus, experiment 2 was conducted to determine if DA played a role in conditioning with scopolamine. Specifically, blockade of the dopaminergic system in conjunction with administration of scopolamine was examined for effects on establishment of conditioned activity.

Method

Subjects

Male Wistar rats, initially weighing 250–275 g, had free access to food (Purina Rat Chow) and water for the duration of the study. They were individually housed in a temperature controlled environment ($21 \pm 1°$ C) kept on a 12-h cycle of light (0600–1800 hours) and dark.

Apparatus

Six automated activity monitoring chambers ($41 \times 50 \times 37$ cm high) were each equipped with two tiers of infrared beams (at 5 and 15 cm above the floor) which detected horizontal and vertical activity, respectively. Each chamber was illuminated by a light (2.5 W) mounted on the ceiling. The chambers were made of plexiglas encased in flat black styrofoam, which blocked visual contact and attenuated sound. A small fan behind each chamber provided background noise and circulated the air. Further details of the apparatus can be found in Beninger et al. (1985).

Procedure

Experiment 1. Twenty-four rats were used to study 1.0 mg/kg and 18 rats were exposed to 8.0 mg/kg. For each dose the rats were randomly assigned to equal size control (unpaired) and experimental (paired) groups, which were tested contemporaneously. Beginning 1 week prior to the study the rats were handled daily. The 1.0 mg/kg study was conducted prior to that of 8.0 mg/kg.

Experimental sessions were conducted on a daily basis in a series of four pairing sessions and one test session, followed by 2 days without experimentation. During the pairing sessions the Paired groups received an intraperitoneal (IP) injection of scopolamine hydrobromide (Sigma) dissolved in distilled water 30 min prior to being placed in the chambers for a 60-min session. The unpaired groups were treated similarly, except they received saline. Three unpaired and three paired rats were tested simultaneously, the first six beginning at 1300 hours. After each group was returned to their home cages, all rats received a second injection; the paired rats received saline, and the unpaired rats received the appropriate dose of scopolamine.

The test session was conducted in a similar manner to the pairing sessions. However, rats in both groups received saline prior to the test. There were no home cage injections, and thus no scopolamine was administered on the test day.

Two more similar sets of four conditioning sessions each followed by one test session were administered. Thus, there was a total of 12 conditioning and three test sessions.

Experiment 2. Twenty-four rats were treated similarly to those receiving 8.0 mg/kg scopolamine in experiment 1. However, all rats were additionally administered an IP injection of 0.4 mg/kg pimozide (Janssen) dissolved in boiling tartaric acid at a 3:1 ratio of acid to pimozide, 4 h prior to each pairing session. Test sessions included administration of saline only at the time corresponding to the scopolamine injection. No pimozide or scopolamine was given on test days.

Results

Experiment 1

Both 1.0 and 8.0 mg/kg enhanced horizontal activity during pairings. However, conditioned increases in horizontal activity were seen only in the 8.0 mg/kg group. Vertical activity was enhanced by 1.0 and initially suppressed by 8.0 mg/kg; however, conditioned increases in activity were seen with both doses. The statistical analyses supporting these observations are reported below.

For each dose, separate analyses were conducted on horizontal and vertical activity, as well as on pairing and testing sessions. As data were cumulated in 10-min periods, in the pairing phase a 6 (time) $\times 12$ (session) $\times 2$ (group) analysis of variance (ANOVA) was conducted, the first two factors being repeated measures. As there was little variability in activity across the three separate blocks of four pairing sessions, the factor comprising block was not included in any statistical analyses. The test data were analysed similarly although the session factor had only three levels. Where significant interactions of a factor with group were found, the simple main effects comparing the groups at each level of the other factor were conducted (Winer 1971).

The activity scores obtained from each level during conditioning and test are shown for the 1.0 mg/kg groups in Fig. 1. Note that the data are averaged over the 12 conditioning or 3 test sessions, and thus illustrate only the time and group variables. As can be seen from the top panel, scopolamine enhanced horizontal activity compared to the control group [$F(1,22) = 27.27$, $P < 0.01$]. Furthermore, there was a significant time by group interaction [$F(5,110) = 10.73$, $P < 0.01$]. Analysis of the simple main effects determined that the scopolamine-treated rats were significantly more active than the control group during the last four time intervals. A significant time effect was also found with horizontal activity [$F(5,110) = 29.92$, $P < 0.01$], demonstrating the decrease in activity across the session. The absence of a significant session effect or interaction involving that factor suggested that activity was not variable as a function of session.

Turning to the horizontal activity from the three test sessions, there was only a significant time effect [$F(5,110) = 29.90$, $P < 0.01$], again demonstrating the decrease in activity across the session. The absence of a significant group or session effect suggested a lack of differentiation between the experimental and control groups during the test sessions, and a lack of variability across those sessions. Table 1 shows the average activity for each group during each of the three tests.

The lower panel of Fig. 1 shows the results with vertical activity using 1.0 mg/kg as the UCS. There was no significant difference between the groups during the pairing ses

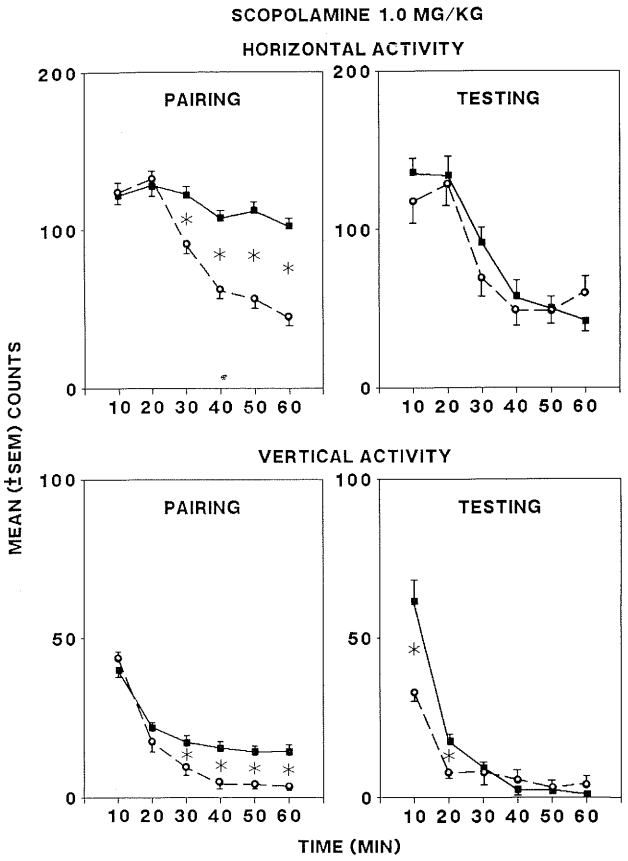

Fig. 1. Mean total activity counts per 10 min for the paired (■–■) and unpaired (o–o) groups during the average of 12 pairing sessions and 3 test sessions for horizontal and vertical activity. UCS was 1.0 mg/kg scopolamine, $n=12$ per group. * Difference between groups significant at $P<0.05$

sions, although a significant time by group effect emerged [$F(5,110)=4.28$, $P<0.01$]. Analysis of the group effect at each time indicated that the significant differences occurred in the last 40 min, where the scopolamine-treated rats were significantly more active than the controls. Significant session [$F(11,242)=3,18$, $P<0.01$], and time by session effects [$F(55,1210)=2.02$, $P<0.01$], were observed, suggesting that the activity on this measure did vary over the course of the study. However, the session effect was observed not to interact with group, suggesting that the variability across sessions was similar in both groups. Examination of the data showed that activity was higher on the first session of each round and tended to decline over the subsequent three sessions.

During the tests a significant time effect was seen [$F(5,110)=65,31$, $P<0.01$], indicating the decrease across the 60 min. A significant time by group effect was also observed [$F(5,110)=8.08$, $P<0.01$] and it was determined that the experimental group was significantly more active than the control group during the first 20 min. Thus, although the unconditioned stimulant effect of scopolamine was seen in the latter part of the conditioning sessions, the conditioned effect appeared in the first 20 min of the test. There was no significant effect of session, or any interactions with the session variable. Table 1 shows the activity scores for each of the three tests.

Activity observed with 8.0 mg/kg and its control group

Table 1. Mean (±SEM) activity per 10 min on each test session

		Test session		
		1	2	3
Scopolamine 1.0 mg/kg				
Horizontal	Paired	85.5 (8.6)	84.3 (8.3)	85.2 (9.2)
	Unpaired	78.4 (8.7)	87.8 (8.6)	70.7 (7.7)
Vertical	Paired	18.0 (3.5)	16.2 (3.7)	13.4 (3.3)
	Unpaired	12.3 (2.4)	14.2 (3.1)	5.3 (1.4)
Scopolamine 8.0 mg/kg				
Horizontal	Paired	101.0 (10.2)	95.4 (9.9)	90.7 (10.0)
	Unpaired	82.2 (9.2)	75.2 (8.1)	66.0 (7.7)
Vertical	Paired	28.2 (5.1)	42.1 (7.9)	21.8 (4.1)
	Unpaired	11.9 (2.3)	35.3 (7.8)	9.1 (2.0)
Scopolamine 8.0 mg/kg and pimozide 0.4 mg/kg				
Horizontal	Paired	127.7 (8.3)	123.8 (8.8)	113.9 (8.7)
	Unpaired	103.6 (8.9)	96.0 (8.3)	99.9 (7.6)
Vertical	Paired	31.0 (3.7)	27.1 (3.2)	23.2 (2.9)
	Unpaired	17.5 (3.0)	17.6 (2.9)	20.4 (3.1)

is illustrated in Fig. 2. Again, the experimental group was significantly more active on the horizontal measure than the control [$F(1,16)=7.32$, $P<0.05$]. There was also a significant time by group interaction [$F(5,80)=16.46$, $P<0.01$]. It was determined that the control group was more active in the second time interval, whereas the scopolamine group was consistently more active during the last 30 min of the session. There was also a significant session effect [$F(11,176)=2.60$, $P<0.01$], again suggesting that activity varied across days. Again, higher activity was observed in the first session following the 2-day breaks.

With respect to horizontal activity on test sessions, the paired group was significantly more active than the unpaired group [$F(1,16)=9.63$, $P<0.01$]. The time by group interaction was nonsignificant; however, the groups were nonetheless compared at each time interval. It was determined that the paired group was significantly more active only during the last 20 min. A significant time effect was observed [$F(5,80)=12.80$, $P<0.01$], indicating the trend to lesser activity across the session. The absence of a session effect or session interaction reflected the fairly stable activity scores in each session (see Table 1).

The vertical activity observed with 8.0 mg/kg, as shown in the lower panel, produced a different profile than that seen with 1.0 mg/kg. The time by session by group interaction was found to be significant [$F(55,880)=1.53$, $P<0.01$], suggesting that the time by group effect varied over sessions. There was a significant group effect [$F(1,16)=19.16$, $P<0.01$] during pairing sessions, although the paired group showed *less* vertical activity than the unpaired group. The significant time by group interaction [$F(5,80)=49.28$, $P<0.01$] was analysed and it was found that the paired group exhibited significantly less activity than the control group during the first 30 min of the session. There were also significant session [$F(11,176)=14.93$, $P<0.01$], and session by time effects [$F(55,880)=1.95$, $P<0.01$], indicating a change in activity across the study. The session effect illustrated the trend for activity in general to decrease over the study, and to increase on the first session following each 2-day break.

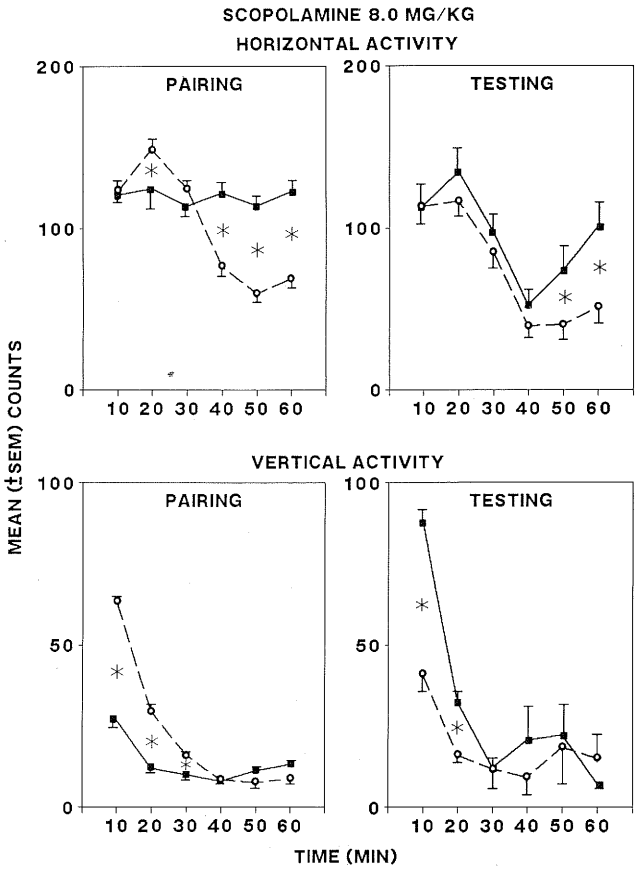

Fig. 2. Mean total activity counts per 10 min for the paired (■–■) and unpaired (o–o) groups during the average of 12 pairing sessions and 3 test sessions for horizontal and vertical activity. UCS was 8.0 mg/kg scopolamine, $n=9$ per group. * Difference between groups significant at $P \leqq 0.05$

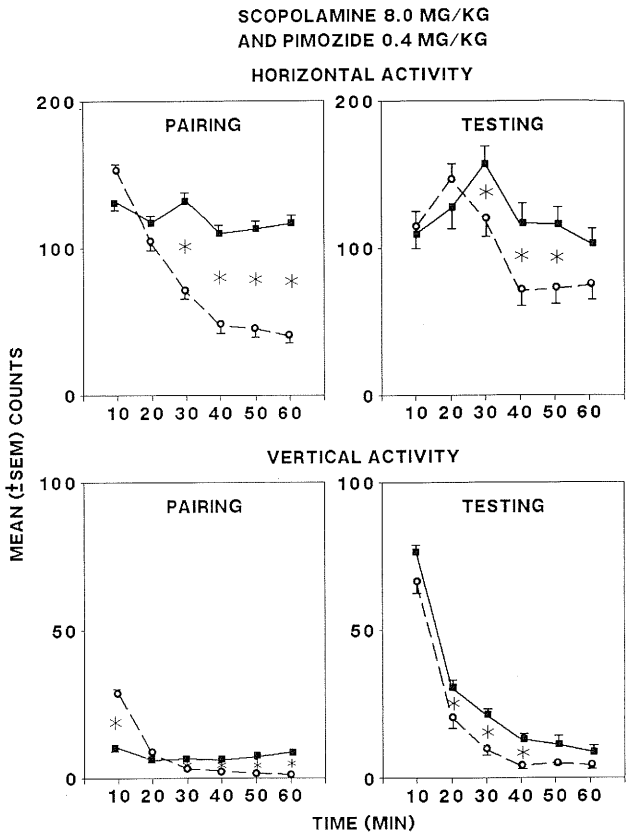

Fig. 3. Mean total activity counts per 10 min for the paired (■–■) and unpaired (o–o) groups during the average of 12 pairing sessions and 3 test sessions for horizontal and vertical activity. UCS was 8.0 mg/kg scopolamine. All rats were pretreated with 0.4 mg/kg pimozide on pairing days. $n=12$ per group. * Difference between groups significant at $P<0.05$

The test sessions also revelaed a significant difference between groups [$F(1,16)=4.55$, $P<0.05$]. However, the experimental group was now significantly more active than the control group. A time by group effect was also found to be significant [$F(5,80)=5.32$, $P<0.01$]. Analyses comparing the groups at each time interval determined that the group previously receiving scopolamine in association with the environment was significantly more active than the control during the first 20 min. A significant time effect was observed [$F(5,80)=23.27$, $P<0.01$] and again demonstrated the general decrease in activity across the session. The significant session [$F(2,32)=7.81$, $P<0.01$] and time by session effects [$F(10, 160)=2.76$, $P<0.01$] indicated that the activity across the three test sessions was variable; in particular, the second test session appeared to have aberrantly high scores (see Table 1). However, these factors did not interact with the group effect, suggesting that the variability did not differentially affect the groups.

Experiment 2

The data were analysed as in experiment 1. Horizontal and vertical activity scores during pairing and testing sessions for the Paired und Unpaired groups are illustrated in Fig. 3. The unconditioned stimulant effect of scopolamine on horizontal activity was evident as there were significant group [$F(1,22)=24.13$, $P<0.01$] and time by group effects [$F(5,110)=20.90$, $P<0.01$]. Simple main effects analyses determined that the paired group was significantly more active in the last 40 min of the session. The significant time effect [$F(5,110)=35.87$, $P<0.01$] demonstrated the general decrease in activity over the session. A significant session by group effect [$F(11,242)=4.30$, $P<0.01$] was also found. Subsequent analyses comparing groups at each session determined that significant group differences did not emerge in initial sessions, but rather tended to occur after the first few sessions, wherein the paired group was more active than the unpaired group. It was also noted that the paired group's activity level remained fairly stable over the study, wereas the unpaired group's activity decreased.

Analysis of horizontal activity during the tests produced a significant group [$F(1,22)=5.40$, $P<0.05$] and time by group effect [$F(5,110)=3.05$, $P<0.025$]. It was found that the paired group was significantly more active during the 30-, 40-, and 50-min intervals. A significant time effect was observed [$F(5,110)=8.15$, $P<0.01$] and demonstrated the decline in activity throughout the session. There were no significant effects including the session factor, reflecting a general lack of alteration in activity over sessions (see Table 1).

The lower panel of Fig. 3 shows vertical activity during the pairing and testing phases. During the pairing sessions

all main effects and interactions were significant at $P<0.01$ except the group factor. As the time by group and session by group effects were both significant, the groups were compared at each time and at each session. It was determined that the paired group was significantly less active than the unpaired group during the first 10 min and significantly more active during the last 40 min. Results comparing groups at each session determined that group differences, wherein the paired group was less active overall, occurred in the earlier sessions, but waned with repeated pairing sessions (data not shown). Again, it was determined that activity was stable over the study in the paired group, and tended to decrease in the unpaired group.

Differences between the paired and unpaired groups during the tests in vertical activity were also demonstrated, as evidenced by a significant group effect [$F(1,22)=8.77$, $P<0.01$]. Although the time by group effect was not significant, the groups were compared at each interval, and significant differences were found at the 20-, 30-, and 40-min periods. The time effect [$F(5,110)=240.70$, $P<0.01$] showed the presence of a pronounced decrease in activity across the session. A significant session by group effect was also observed [$F(2,44)=6.72$, $P<0.01$] and merited comparisons of the groups at each session. It was determined that the Paired group was significantly more active than the Unpaired group in the first and second sessions, but not the third (see Table 1).

Discussion

Both 1.0 and 8.0 mg/kg scopolamine stimulated horizontal activity in rats but a conditioned effect was observed only with 8.0 mg/kg. The lower dose enhanced vertical activity in the latter part of the session, whereas the higher dose suppressed vertical activity in the initial portion of the session. However, in both cases, rats previously having scopolamine paired with the environment showed more vertical activity than their respective control group in the first 20 min of the test. Administration of the dopamine blocker pimozide (0.4 mg/kg) prior to pairings of 8.0 mg/kg did not attenuate the establishment of either conditioned horizontal or vertical activity. This is the first demonstration of environment-specific conditioned activity with scopolamine and it also suggest that dopamine may not be involved in its manifestation.

The unconditioned effects on horizontal activity are congruent with previous research demonstrating a stimulant effect of scopolamine (Bauer 1982; Carey 1982; Sanberg et al. 1987). The conditioned effects are in agreement with a large body of previous research utilizing a number of stimulant drugs (Pickens and Crowder 1967; Schreiber et al. 1976; Hayashi et al. 1980; Post et al. 1981; Schiff 1982; Barr et al. 1983; Beninger and Hahn 1983; Beninger and Herz 1986; Herz and Beninger 1987). An interesting aspect of the present results is that conditioned horizontal activity appeared to be related to the drug dosage, although there was no observable difference in the unconditioned effect. Thus, it appears that the magnitude of the unconditioned response is not necessarily a good predictor of the size of the conditioned response, an observation in good agreement with previous studies of (+)-amphetamine (Herz and Beninger 1987).

The absence of a robust stimulant effect on vertical activity with either dose is puzzling. Although 1.0 mg/kg produced a stimulant effect, it was observed only when the control activity levels had stabilized near zero. The 8.0 mg/kg experimental group exhibited a profile similar to that of the 1.0 mg/kg experimental group. Indeed, an analysis comparing the groups revealed no significant difference between them. It appeared that the higher activity level of the control group for 8.0 mg/kg (they were found to be significantly more active than the control group for 1.0 mg/kg), may have resulted in the observation of no significant stimulant effect in the paired group. The fact that a stimulant effect was seen with 8.0 mg/kg when the paired and unpaired groups were treated with pimozide attests to this hypothesis; in this case the unpaired rats showed very low scores.

Bauer (1982) and Sanberg et al. (1987) reported that doses of scopolamine in ranges comparable to those used here (0–16.0 and 0–4.0 mg/kg, respectively), increased rearing behavior in rats. It is interesting that in Bauer's (1982) research, the scopolamine-treated rats appeared to show enhanced rearing primarily after the saline-treated rats' activity levels had practically ceased. As Sanberg et al. (1987) studied the rats for a 2-h period, presumably activity in nondrugged animals was also very low. It is possible that a more pronounced stimulant effect may have been observed presently had the rats been tested for longer time intervals.

Carlton (1969) suggested that the stimulant effect of anticholinergics may be due to their apparent interference with normal habituation processes. Following this line of reasoning, drug-free tests after scopolamine-environment pairings would be expected to result in higher activity in the subjects receiving these drug pairings than in subjects who had been habituated in the same environment without the drug. Such an hypothesis would predict similar results to those based on a conditioning model. Discrimination between the two hypotheses cannot be made based on the data presented here. However, it should be noted that the subjects underwent 12 h of training in the chambers and 3 h of drug-free tests. If differential rates of habituation were solely responsible for the results, one would possibly expect weaker effects with repeated tests: this did not appear to be the case.

The role of dopamine in conditioned locomotor activity has been investigated previously (Beninger and Hahn 1983; Beninger and Herz 1986). The finding that 0.4 mg/kg pimozide blocked the establishment of cocaine-or amphetamine-induced conditioning suggested that it was indeed the dopaminergic effect of these drugs that was responsible for learning. In the present study, the *same* dose of pimozide which effectively blocked conditioning with those drugs did not block the establishment of scopolamine-produced environment-specific conditioning. This finding might suggest that a different mechanism underlies environment-specific conditioning with anticholinergics and the previously studied stimulants. However, the present results are preliminary and future studies should investigate if higher doses of pimozide are capable of attenuating scopolamine-based conditioning. The finding that the third test session on vertical activity in the groups pretreated with pimozide did not exhibit a significant difference between the two groups treated with pimozide is reminiscent of the extinction-like effects of dopamine antagonists (e.g., see Wise 1982). Future studies examining several consecutive test sessions would more fully be able to assess this hypothesis.

The present study suggests that conditioned alterations in locomotor activity can be produced utilizing the anticholinergic scopolamine. An interesting difference between the results with scopolamine and other stimulant drugs used in similar paradigms is that it appears scopolamine enhances horizontal activity to a much greater degree than it does vertical activity. Earlier research from our laboratory suggested that vertical activity was influenced more than horizontal with dopamine agonists (Beninger and Herz 1986; Herz and Beninger 1987). Perhaps these differences in the unconditioned response to the drugs are reflective of differing mechanisms of action.

The observed differentiation between the paired and unpaired groups over the course of training and testing suggests that the contingent pairing of the drug and environment was responsible for the present results. However, there are several points which merit consideration. Little evidence was apparent with respect to aquisition of the conditioned response over training, suggesting that a maximal conditioned response was achieved following four pairing sessions. Although surprising, similar results have been found by previous investigators (Pickens and Crowder 1967). Extended test sessions may produce acquisition-like effects, as it is possible that acquisition was occurring in the duration of the conditioned response rather than the magnitude. However, these speculations await testing.

A control group that did not receive, the unconditioned stimulus throughout the study was not included in the present study. Although desirable, the data suggest that the unpaired groups may have been sufficient controls. There was differentiation between the paired and unpaired groups: scopolamine was shown to be a stimulant. Thus, if there were carryover effects (for which a drug-naive group would control) a systematic alteration of activity in the unpaired group would be expected. However, the only effect that appeared consistently was a reduction in activity across the study, with increases following the 2-day breaks after each test. This pattern of activity is very similar to that observed by Herz and Beninger (1987) in a drug-naive control group in a similar study. Thus, the absence of a consistent dose-related change in activity in the controls suggests that there were no apparent effects of home cage injections on activity in the test chambers.

Acknowledgements. The authors wish to thank R. Eikelboom and D.C. Hoffman for their valuable comments on the manuscript. Pimozide was the generous gift of Janssen Pharmaceuticals. This research was supported by grants from the Natural Sciences and Engineering Research Council and the Ontario Ministry of Health to R.J.B.

References

Barr GA, Sharpless NS, Cooper S, Schiff SR, Paredes W, Bridger WH (1983) Classical conditioning, decay and extinction of cocaine-induced hyperactivity and stereotypy. Life Sci 33:1341–1351

Bauer RH (1982) Age-dependent effects of scopolamine on avoidance, locomotor activity, and rearing. Behav Brain Res 5:261–279

Beninger RJ, Hahn BL (1983) Pimozide blocks the establishment but not expression of amphetamine produced environment specific conditioning. Science 220:1304–1306

Beninger RJ, Herz RS (1986) Pimozide blocks establishment but not expression of cocaine-produced environment specific conditioning. Life Sci 38:1425–1431

Beninger RJ, Cooper TA, Mazurski EJ (1985) Automating the measurement of locomotor activity. Neurobehav Toxicol Teratol :79–85

Carey RJ (1982) Septal lesions augment locomotor hyperactivity induced by amphetamine and not scopolamine. Psychopharmacology 76:96–97

Carlton PL (1969) Brain-acetylcholine and inhibition. In: Tapp JT (ed) Reinforcement and behavior. Academic Press, New York pp 286–327

Colpaert FC, Van Bever WFM, Leysen JEMP (1976) Apomorphine: Chemistry, pharmacology, biochemistry. Int Rev Neurobiol 19:225–268

Coyle JT, Snyder SH (1969) Antiparkinsonian drugs: inhibition of dopamine uptake in the corpus striatum as a possible mechanism of action. Science 156:899–901

Duvoisin RC (1967) Cholinergic-anticholinergic antagonism in parkinsonism. Arch Neurol 17:124–136

Goodman LS, Gilman A (eds) (1975) The pharmacological basis of therapeutics, 5th edn. MacMillan, New York

Hayashi T, Ohashi K, Tadokoro S (1980) Conditioned drug effects to *d*-amphetamine- and morphine-induced motor acceleration in mice: experimental approach for placebo effect. Jap J Pharmacol 30:93–100

Herz RS, Beninger RJ (1987) Comparison of the ability of (+)-amphetamine and caffeine to produce environment-specific conditioning. Psychopharmacology 92:365–370

Kuczenski R (1983) Biochemical actions of amphetamine and other stimulants. In: Creese I (ed) Stimulants: neurochemical, behavioral, and clinical perspectives. Raven Press, New York, pp 31–62

Lang WJ, Brown ML, Gershon S, Korol B (1966) Classical and physiologic adaptive conditioned responses to anticholinergic drugs. Int J Neuropharmacol 5:311–315

Moller H-G, Nowak K, Kuschinsky K (1987) Conditioning of pre- and post-synaptic behavioural responses to the dopamine receptor agonist apomorphine in rats. Psychopharmacology 91:50–55

Moore KE (1977) The actions of amphetamine on neurotransmitters: a brief review. Biol Psychiatry 12:451–461

Mucha RF, Volkoviks C, Kalant H (1981) Conditioned increases in locomotor activity produced with morphine as the unconditioned stimulus, and the relation of conditioning to acute morphine effect and tolerance. J Comp Physiol Psychol 95:351–362

Pavlov IP (1960) Conditioned reflexes (Translated by G.V. Anrep.) Dover, New York (Original work published 1927)

Pickens RW, Crowder WF (1967) Effects of CS-US interval on conditioning of drug response, with assessment of speed of conditioning. Psychopharmacologia 11:88–94

Post RM, Lockfeld A, Squillace KM, Contel NR (1981) Drug environment interaction: context dependency of cocaine induced behavioral sensitization. Life Sci 28:755–760

Sanberg PR, Henault MA, Hagenmeyer-Houser SH, Russel KH (1987) The topography of amphetamine and scopolamine-induced hyperactivity: toward an activity print. Behav Neurosci 101:131–133

Schiff SR (1982) Conditioned dopaminergic activity. Biol Psychiatry 17:135–154

Schreiber HL, Wood WG, Carlson RH (1976) The role of locomotion in conditioning methylphenidate-induced locomotor activity. Pharmacol Biochem Behav 4:393–395

Siegal S (1975) Evidence from rats that morphine tolerance is a learned response. J Comp Physiol Psychol 89:498–506

Vezina P, Stewart J (1984) Conditioning and place-specific sensitization of increases in activity produced by morphine in the VTA. Pharmacol Biochem Behav 20:925–934

Winer BJ (1971) Statistical principles in experimental design, 2nd edn. McGraw-Hill, New York

Wise RA (1982) Neuroleptics and operant behavior: the anhedonia hypothesis. Behav Brain Sci 5:39–88

Received May 11, 1987 / Final version May 3, 1988