

Effects of Scopolamine, Pentobarbital, and Amphetamine on Radial Arm Maze Performance in the Rat¹

DAVID A. ECKERMAN, WINFORD A. GORDON, JOSEPH D. EDWARDS, ROBERT C. MACPHAIL AND MICHAEL I. GAGE

Department of Psychology, University of North Carolina, Chapel Hill, NC 27514
and
Neurotoxicology Division, Health Effects Research Laboratory, U. S. Environmental Protection Agency
Research Triangle Park, NC 27711

Received 30 August 1979

ECKERMAN, D. A., W. A. GORDON, J. D. EDWARDS, R. C. MACPHAIL AND M. I. GAGE. *Effects of scopolamine, pentobarbital, and amphetamine on radial arm maze performance in the rat.* PHARMAC. BIOCHEM. BEHAV. 12(4) 595-602, 1980.—Rats were trained to obtain food pellets from the end of each arm of an eight-arm radial maze. Baseline performance was characterized by very few entries into arms from which the food pellet had already been obtained. In Experiment 1, neither *d*-amphetamine (0.1-3.0 mg/kg) nor pentobarbital (1.0-10.0 mg/kg) affected choice accuracy, although the rate of arm-entry increased after *d*-amphetamine and decreased after pentobarbital. Scopolamine (0.1-1.0 mg/kg), on the other hand, reduced both accuracy and the rate of arm entry. In a second experiment, the effects of scopolamine were replicated using a between-subjects design. Methylscopolamine (0.17, 1.0 mg/kg) was found to have little effect on performance. Multiple response criteria were also compared in the second experiment. Scopolamine was found to affect runs farther out the arm differently than it affected abbreviated arm entrances. A post-trial feeding test was also included to evaluate changes in reinforcer effectiveness, and showed that food continued to be a reinforcer after both scopolamine and methylscopolamine.

Scopolamine	Methylscopolamine	Amphetamine	Pentobarbital	Radial arm maze	Memory
Discrimination learning	Short-term memory	Spatial memory	Spatial discrimination		Rat

THERE have been a number of reports implicating cholinergic mechanisms in the control of response sequences, memorial processes, and the discriminative control of behavior [11]. Further, pentobarbital [7] and amphetamine [20] have been found to influence these processes. Anticholinergic agents have been reported to affect delayed reactions requiring particular response sequences. For example, scopolamine (an antimuscarinic with central and peripheral nervous system actions) decreased the tendency of rodents to alternate entries into arms of a T-maze or Y-maze [1,24] and decreased the frequency of food-reinforced alternation in an operant chamber [9,11]. Methylscopolamine produced little or no effect on such alternation [24].

While these and other data [2, 3, 32] suggest that cholinergic mechanisms are involved in memorial processes, other data argue against such a conclusion. Scopolamine disrupted spatial alternation when delays separated successive opportunities to respond [11]. Since the degree of disruption did not appear to vary with the delay length, however, the

effect was attributed to a reduction in stimulus control rather than to disruption of memorial processes. Similarly, impairment of delayed matching-to-sample by scopolamine was comparable at various delay intervals, again suggesting a disruption of stimulus control rather than of memory [32].

The present experiments offer yet another means of evaluating the effects of drugs on memorial processes. The procedure utilized an elevated maze having eight arms radiating from a central platform like spokes of a wheel [28]. This type of maze has recently received considerable attention as an apparatus for assessing working memory of rodents [26].

EXPERIMENT 1

The first experiment in the present series determined the effects of scopolamine on several measures of rats' performance in the radial arm maze. In order to more fully characterize the performance, determinations were also made of the effects of *d*-amphetamine and pentobarbital.

¹The present work was supported by the Neurotoxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, and by training grant, MH-14269, from the National Institute of Mental Health. Special appreciation is expressed to W. M. Guyer, R. J. Pettinelli, and E. T. Puckett for aid in carrying out Experiment 1 and to the several observers who aided in Experiment 2. Reprints may be obtained by writing the first author, Department of Psychology, Davie Hall 013A, University of North Carolina, Chapel Hill, NC 27514.

METHOD

Subjects

Twenty male, Sprague-Dawley-derived rats were obtained from Charles River, Inc. (Wilmington, MA). They were 90 days old and weighed approximately 300 g upon receipt. Animals were housed individually with free access to water. After acclimation to the colony room, body weights were reduced by food deprivation and subsequently maintained at 80% of free feeding values.

Apparatus

Two eight-arm radial mazes similar to those described by Olton and Samuelson [28] were used. Each of the arms (7 by 75 cm) projected from one side of an octagonal center platform measuring 30 cm in diameter. A Lucite-lined circular food well (4-cm dia., 1.5 cm deep) was positioned at the far end of each arm. The maze was painted black and was elevated 50 cm from the floor.

Each maze was centered in a small room lighted by fluorescent bulbs. One room had a floor area of 2.40 by 2.45 m; the other room had a floor area of 1.92 by 2.71 m. Doors and cabinets made each wall in a room distinguishable. A chair was placed in each room and during trials an observer sat and recorded data.

Procedure

Training trials. Prior to each trial, every arm of the maze was baited with a 45-mg food pellet (Noyes Co., Lancaster, NH). The rat was then placed on the center platform facing a particular arm (same for all trials and for all rats). A trial continued until either all eight food pellets had been consumed, or 10 min had elapsed, whichever occurred first. Placing all four paws on an arm was recorded as an arm entrance. Times of arm entrances and exits and pellet receipts were recorded.

Twenty rats were given a minimum of five and a maximum of seven training trials during the initial baseline-acquisition phase of the experiment. On those trials preceding the development of consistent performance, extra pellets were sometimes placed along the maze arms.

Two rats which did not develop consistent performance were dropped from the experiment. The remaining rats were assigned to three experimental groups so that each group was composed of three rats trained on each maze (i.e., six subjects per group). One of these groups of rats received subsequent treatments with amphetamine, the second with pentobarbital, and the third with scopolamine.

Training continued according to the following three-day cycle: on day one, a trial was given as before and no injection was administered. On day two, a trial was given 10 or 30 min (see below) following injection of 1 ml/kg body weight of normal saline. On day three, a trial was given 10 or 30 min following injection of a dose of one of the treatment drugs. A drug was not given on day three if a rat did not obtain all eight pellets on day two of this cycle. This three-day cycle continued for each rat until it had received all three dosages of the appropriate drug. The order of dosages was determined by a Latin Square.

Drugs. The rats received IP injections of 0.3, 1.0, and 3.0 mg *d*-amphetamine sulfate/kg body weight (donated by Smith Kline and French, Philadelphia, PA), 1.0, 3.0, and 10.0 mg sodium pentobarbital/kg body weight (obtained from Sigma Chemical Co., St. Louis, MO), or 1.0, 3.0, and 10.0 mg

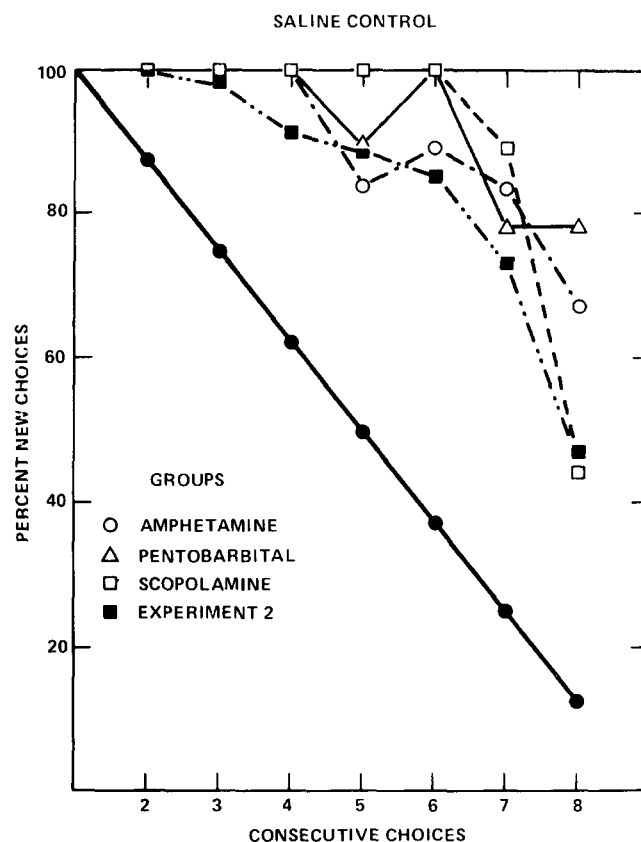


FIG. 1. Accuracy of successive choices within a trial. Mean percent choices of new arms is shown for saline control days for animals of each group from Experiment 1 and for all animals on the saline control day of Experiment 2. The diagonal represents the number of new arms which would be selected if the choice were a random selection (following complete accuracy on prior choices).

scopolamine hydrochloride/kg body weight (obtained from Sigma Chemical Co., St. Louis, MO). Drugs were prepared in normal saline so that each dose was administered in 1 ml/kg. Rats receiving *d*-amphetamine and pentobarbital were injected 10 min prior to testing, and those receiving scopolamine were injected 30 min prior to testing.

RESULTS

Choice Accuracy

If a rat re-entered an arm after food had already been removed, that selection was recorded as an error. By considering the first eight selections, one can calculate average accuracy measures for each animal. Accuracy judged in this manner was quite high. An average of 7.3 (SD=0.85) of the first eight choices were to new arms on the saline control sessions for all rats. Accuracy did not differ across the three groups of rats, $F(2,51) < 1.0$, or between the two mazes, $F(1,134) < 1.0$, so data for the two mazes were combined. As the probability of entering seven or eight new arms by chance (random selection with replacement) is 0.07, the performance is seen to be quite different from that expected by chance.

Choice accuracy changed, however, across the selections made during a particular trial. Figure 1 shows the average proportion of selections which were to new arms on the sec-

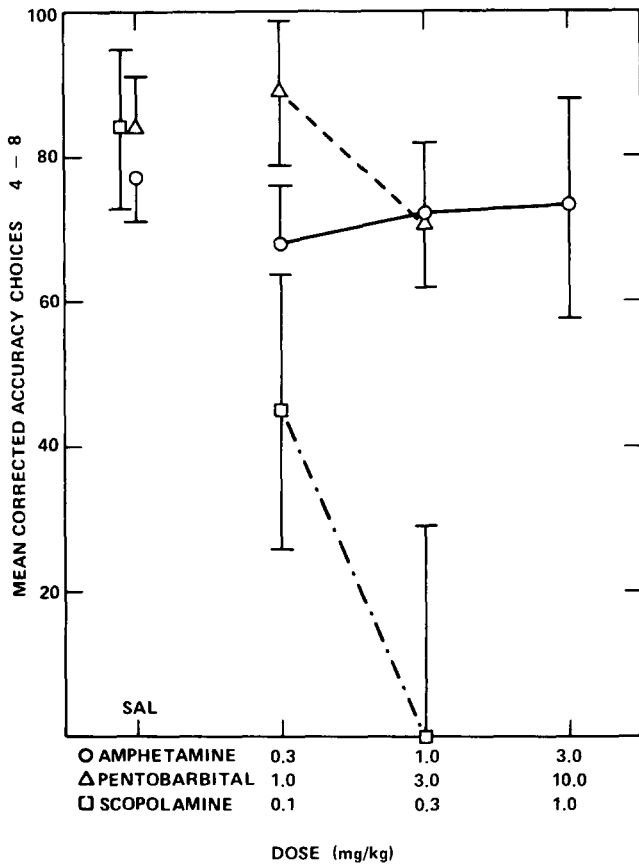


FIG. 2. Mean accuracy for selections 4-8 of saline-control and drug-trials in Experiment 1. Accuracy at each selection was expressed relative to chance-accuracy before averaging (see text). Data are included for each condition in which at least three subjects made at least six selections. The standard error of these means is also shown.

ond through eighth choices for each group during the saline sessions. Very few errors were made on the second, third, or fourth selections. From the fifth to the eighth selection, however, accuracy was consistently and progressively decreased.

Since the number of available new arms changed with succeeding selections, the accuracy of each selection must be judged against its appropriate chance value. Corrections for chance were made (see [28]) for each rat by summing the number of new arms available at the time of a selection over all selections with a comparable ordinal position (all second selections, all third selections, etc.) and dividing by the total number of selections. This value was taken as the estimate of chance accuracy. The actual proportion of selections which were correct and this chance value were then related as shown below to determine the accuracy corrected for chance.

$$\text{Corrected accuracy} = \frac{(\text{observed accuracy} - \text{chance accuracy})}{(100 - \text{chance accuracy})}$$

This corrected value is 1.00 if all selections are correct and 0.0 if a chance number of selections is correct. By multiplying this value by 100, observed accuracies between 100% and chance are scaled between 100 and 0; observed accuracies less than chance are scaled from 0 to $-\infty$.

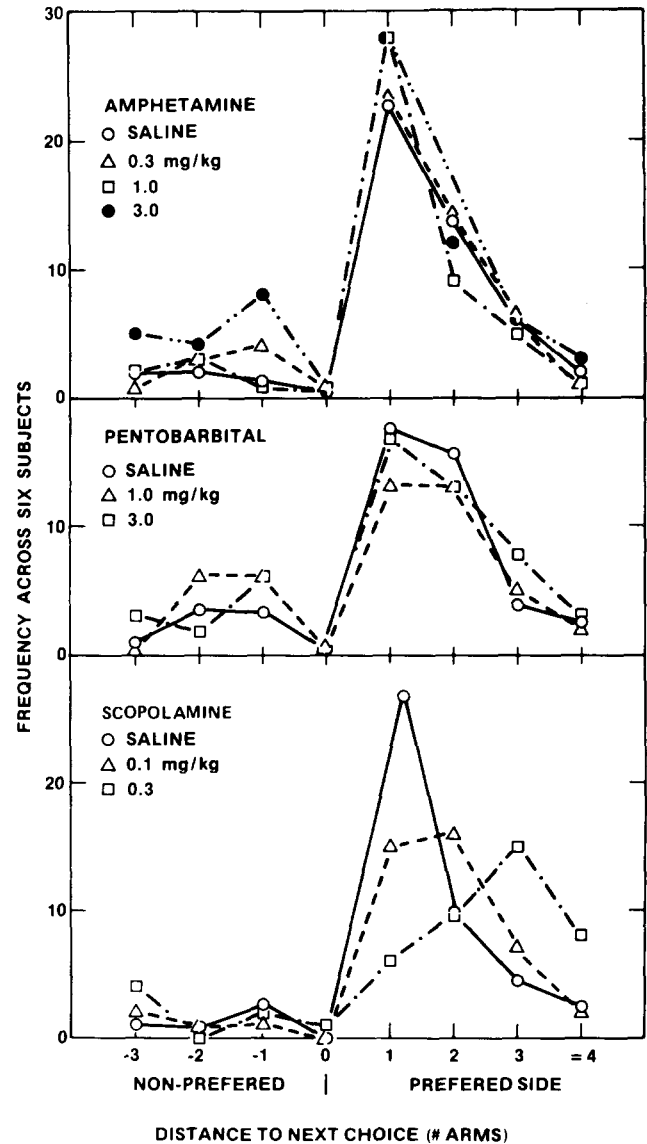


FIG. 3. The frequency of selecting an arm various distances away from the arm just exited (arm 0). For each trial, the direction (clockwise or counterclockwise) with the greater number of selections was designated as preferred for pooling data. Frequencies were simply summed across the subjects of a group at each condition.

Figure 2 shows the effect of drugs on corrected accuracy averaged for choices 4-8 on all trials where at least six selections were available for at least three of the six subjects. With accuracy of each choice calibrated against its corresponding chance value, these successive measures were considered as repeated estimates of accuracy and thus could be averaged. Scopolamine reduced choice accuracy (Friedman two-way analysis of variance with ranks, $\chi^2=7$, $n=3$, $k=4$, $p=0.054$), while neither amphetamine nor pentobarbital were found to affect choice accuracy.

Scopolamine affected response patterning as well as choice accuracy. Figure 3 shows that there was a strong tendency to choose a neighboring arm on the saline control days for rats in each group. Scopolamine altered this pattern by shifting the modal separation between selections from one

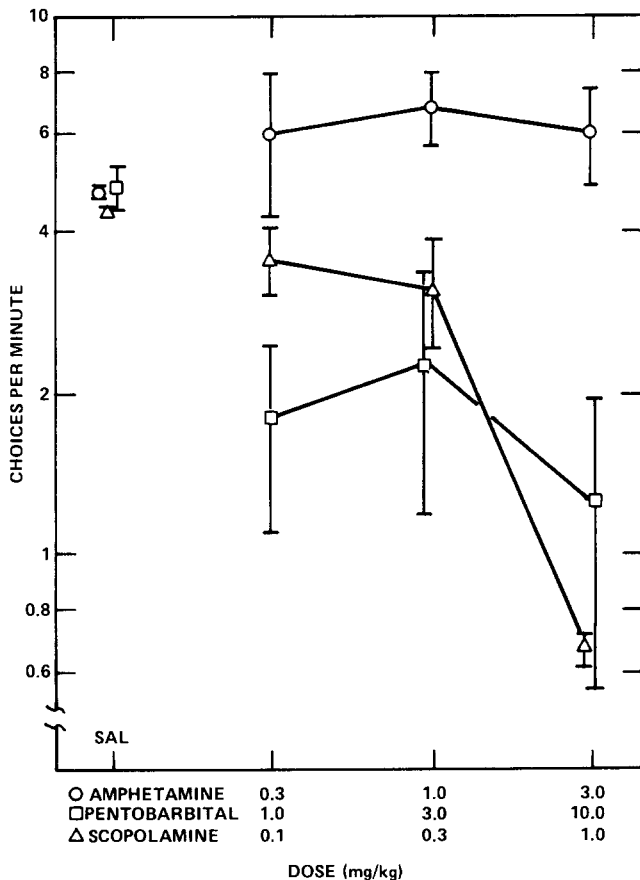


FIG. 4. Mean rate of entering arms (log scale) for each condition of Experiment 1. Rate was taken as the number of arms entered/trial time. The standard error of each mean is also shown.

to two to three arms from the exited-arm, as the dosage increased from 0 to 0.1 to 0.3 mg/kg. Insufficient data were available at 1.0 mg/kg to determine a distribution. Neither pentobarbital nor amphetamine, on the other hand, altered this position preference.

In addition to analyzing the distance between successive selections, the patterning of responses was estimated by the tendency to repeat particular pairs of selections. An unbiased estimate of this repetition tendency was obtained by comparing the location of consecutive errors with the sequence of initial choices of arms (see [29]). Over all groups, the repetition tendency was about 29%. The repetition tendency was above chance, however, for only half the rats. The repetition tendency thus appears to be rather slight.

Whereas only scopolamine affected accuracy, all three drugs altered the rate of selection. Figure 4 shows the number of selections made divided by the time of the trial, averaged within each drug group over all subjects. The values are shown on a log scale to avoid a floor effect. It is clear that amphetamine increased the number of arm entrances per unit time while pentobarbital and scopolamine reduced this rate. Observations, however, revealed that this decreased rate of selection differed considerably for pentobarbital- and scopolamine-treated rats. While pentobarbital-treated rats were inactive after large dosages, scopolamine-treated rats were actively circling the center platform and making abortive arm entrances which did not meet the four-paw criterion.

DISCUSSION

That scopolamine affected choice accuracy on the radial arm maze suggests an effect on spatial working memory. Other accounts, however, must also be evaluated. Prior work has strongly suggested [27, 28, 34] that odor-cues are not potent sources of control and that the performance is, instead, controlled by visual extra-maze cues. Were odor trails responsible for accurate performance, the notion of spatial memory would be unnecessary, and the effect of scopolamine might be attributed to changes in olfactory sensitivity. Similarly, prior work has also emphasized that the performance is not merely due to repetition of a stereotyped sequence of arm entrances (e.g., always go one-arm to the right) or to repetition of some other response strategy (e.g., [21,28]). In the present data, a pattern of selecting adjacent arms was seen; this pattern was probably not, however, a determinant of accuracy. Evidence for the independence of accuracy and patterning is as follows.

If saline-control data for the scopolamine group are considered, only one of six rats showed a pattern of responding which was consistent from day to day. For two of the remaining five, the modal number of arm separations changed from day to day. For the remaining three, there were other daily changes in the pattern of choices. These variations in response pattern occurred despite the very high accuracy already described (in all but one of these 18 sessions, at least seven new arms were selected in the first eight selections). Since accuracy of selection was virtually constant while response patterning varied from day to day and rat to rat, it is unlikely that the scopolamine-induced changes in accuracy merely reflected effects on response patterning.

Amphetamine and pentobarbital did not consistently affect either accuracy or the pattern of selection. They did, however, affect the rate of selection, with amphetamine producing increases and pentobarbital producing decreases in the rate of arm-entry. The dosages, therefore, were behaviorally active despite the fact that accuracy was unchanged. Moreover, that these agents affected rate without affecting accuracy suggests that scopolamine's effect is not simply the result of a reduced rate of selection. The differential effect of amphetamine and scopolamine is especially interesting, since their effects have been shown to be similar in other situations (e.g., [13,16] but see [5,22]).

EXPERIMENT 2

In the second experiment, the effects of scopolamine and methylscopolamine were compared on radial-arm-maze performance. The dose-effect function for scopolamine was more completely evaluated. Different criterion measures of performance were also taken, and a post-trial assessment of pellet eating was included. A between-subject design was used in which each rat was given only one drug treatment. This design allowed an assessment of drug effects that are unconfounded by possible carry-over influences. This experiment was carried out in different rooms with less detail on the walls than in Experiment 1 and thus allowed an assessment of the generality of the effects obtained in Experiment 1.

METHOD

Subjects

Seventy-two male, Sprague Dawley-derived rats were obtained from Charles River, Inc. (Wilmington, MA). The animals were randomly assigned to three groups of 24: each

group was housed for an additional two weeks and then exposed to the procedures described below. All animals were 90 days old and weighed approximately 300 g upon arrival. Animals were housed individually in plastic cages with wood chip bedding and free access to water. The animals were maintained by food deprivation at 80% of their respective free feeding body weights during the week prior to and throughout testing.

Equipment

The two radial arm mazes used in Experiment 1 were used in this experiment. The mazes were placed in similar rooms that were 2.5 m². The arm designated number 1 was 11 cm from the wall and 1 m from the corner. The door to the room was between arms four and five. The chair was at the end of arm six. Electrical outlets and other features of the two rooms were similar.

Procedure

Prior to each trial the arms of the maze were baited with 45-mg food pellets (Noyes, Co., Lancaster, NH). The rat was then placed on the center platform facing arm one. A trial continued until either all eight food pellets had been consumed or 10 min had elapsed, whichever occurred first. Four criterion levels of arm entrance were recorded along with the time of the greatest penetration into an arm: (1) when a rat's nose crossed the plane extending upwards from the intersection of the center platform and an arm; (2) when two paws were placed on the arm; (3) when all four paws were placed on the arm; and (4) when the head crossed the food cup. These food-cup responses were further separated into those accompanied by eating a pellet and those not so accompanied.

All rats were given six training trials with one trial per day. On those trials preceding development of consistent performance, extra pellets were occasionally placed on the arms of the maze and the rat was sometimes handled while on the maze to facilitate consistent ambulation.

The seventh trial was preceded by an IP injection of normal saline for all rats, 30 min prior to the trial. The eighth trial was not preceded by an injection and was considered a non-injection control trial. Thirty min prior to the ninth trial, each rat was injected with either scopolamine, methylscopolamine or normal saline. The tenth and final trial involved no injection. Any rat which did not obtain all eight pellets on trial eight received no further testing. The remaining rats were randomly assigned to a dosage group with the restriction that each maze have approximately equal numbers of animals in each group.

Following a trial, each animal was placed in a cage in which a ceramic dish containing eight 45-mg food pellets had been placed. The time taken to consume the pellets was recorded, up to 5 min. The number of pellets eaten was also recorded, the ceramic dish was then removed, and the animal was returned to its home cage.

Water was removed at the time of injection for the first twenty rats studied. Subsequently, rats were allowed access to water throughout the treatment time preceding the trial, to aid in keeping the oral cavity and pharynx clear of partially ingested food.

Drugs. Five dosages of scopolamine hydrochloride (Sigma Chemical Co., St. Louis, MO) were studied: 0.10, 0.17, 0.30, 0.56 and 1.0 mg of the base/kg body weight. Methylscopolamine (scopolamine methylnitrate; Sigma

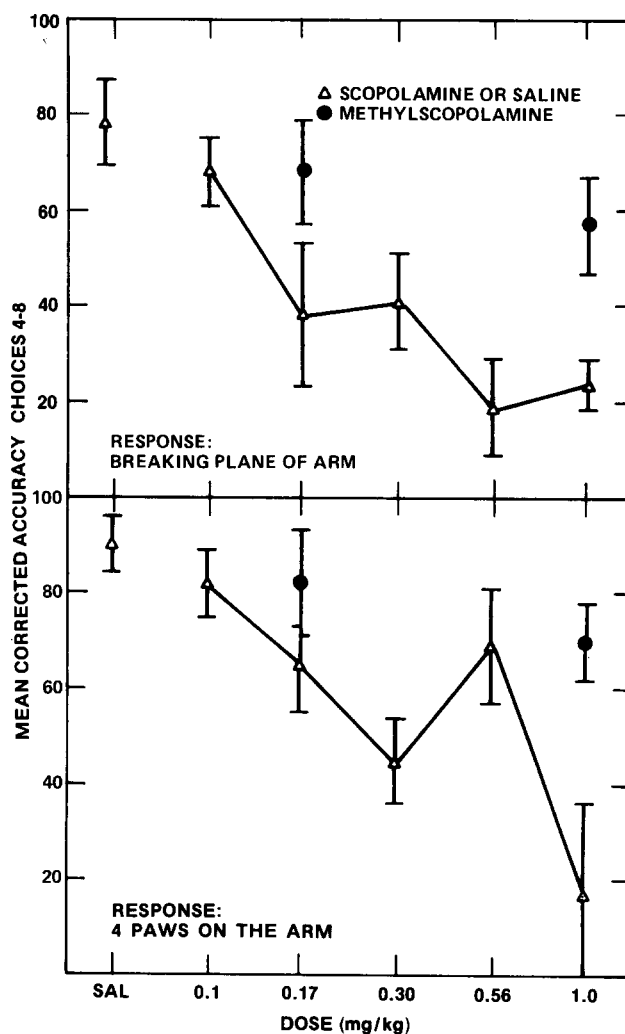


FIG. 5. Mean accuracy for selections 4-8 of the drug or saline trials of Experiment 2 (see Fig. 2).

Chemical Co., St. Louis, MO) was given in dosages of 0.17 and 1.0 mg of the base/kg body weight. Injection volume was 1 ml/kg and rats in the control group received a similar volume of normal saline. All injections were IP.

RESULTS

Accuracy of selection was high for all rats. Taking the four-paw entrance as the criterion for a response, subjects chose 6.8 new arms for the first eight selections on each of the two trials preceding drug administration (S.D. equalled 0.85 and 0.83, respectively). This figure was somewhat lower than that for Experiment 1, but accuracy was still considerably higher than that expected from random selection (probability of a difference this large occurring for an individual trial through random selection with replacement is less than 0.08; probability of this average occurring by chance is very much smaller). If crossing the plane of an arm with the rat's nose was taken to define the response, on these same two trials 6.7 and 6.8 new arms were selected on the first eight opportunities (S.D. equalled 0.92 and 0.58, respectively). As in Experiment 1, there was no difference in

TABLE 1
POST-TRIAL PELLET EATING

	Scopolamine (mg/kg)					M-scop (mg/kg)		
	Saline	0.10	0.17	0.30	0.56	1.00	0.17	1.00
No. tested	7	7	6	8	7	7	3	5
No. ate \geq 1	7	7	6	8	7	6	3	5
No. ate all 8	7	7	5	8	7	5	3	4
Time to eat 8 (sec)	10.5	10	14	27	30	39	10	8

accuracy for rats on the two mazes. Accuracy was again seen to decline across successive choices within a trial (see Fig. 1). Estimates of selection accuracy were determined after correcting for the appropriate chance level (see Experiment 1) and averaged for choices 4–8 to characterize the effect of each treatment. Scopolamine was again found to decrease accuracy (Fig. 5). When the four-paw criterion was taken to define the response, accuracy tended to decrease with increasing dosage, $F(5,24)=3.72$, $p<0.025$, the greatest decrease being obtained at 1.0 mg/kg. When the crossing-the-plane criterion was used, dosages of 0.17, 0.30, and 0.56 mg/kg also decreased accuracy (analysis of variance showed $F(5,24)=9.34$, $p<0.001$). Methylscopolamine, also tended to decrease accuracy with increasing dosage, but regardless of the response criterion, the decreases were much smaller than those produced by an equivalent dosage of scopolamine (Fig. 5).

The subjects showed a slight tendency to select an arm that was close to the one just exited. This tendency was not as great, however, as it had been in Experiment 1. The average number of arms separating one selection from the next was just over 2, while this figure had been 1.7 for saline control days of Experiment 1. Further, in this experiment, scopolamine did not change the patterning. Methylscopolamine also left patterning unchanged. As in Experiment 1, response patterning was not related to accuracy. Of the 57 subjects, only 10 showed similar patterns of responding on both saline and non-injection trials. These subjects were no more accurate than the others and showed comparable effects of scopolamine.

Figure 6 (four-paw criterion) shows that rate of arm selection decreased in a dose-related fashion following scopolamine. Methylscopolamine, on the other hand, produced only slight decreases over a comparable range of dosages. The rate of selection, however, was not decreased as much following scopolamine when the response was defined as the nose crossing the plane of the arm, demonstrating that the rats were still active, but did not venture onto the arms as frequently. With this response criterion, methylscopolamine did not affect rate of arm selection.

A post-trial measure of food consumption was taken as described in Method. In general, animals in all drug conditions consumed post-session pellets. Of the 50 subjects tested, 49 ate at least one pellet within 5 min and 46 ate all eight. The time to consume the eight pellets did, however, increase (Table 1) with increasing dosages of scopolamine, but was unaffected by methylscopolamine.

DISCUSSION

Scopolamine again decreased both accuracy of selections

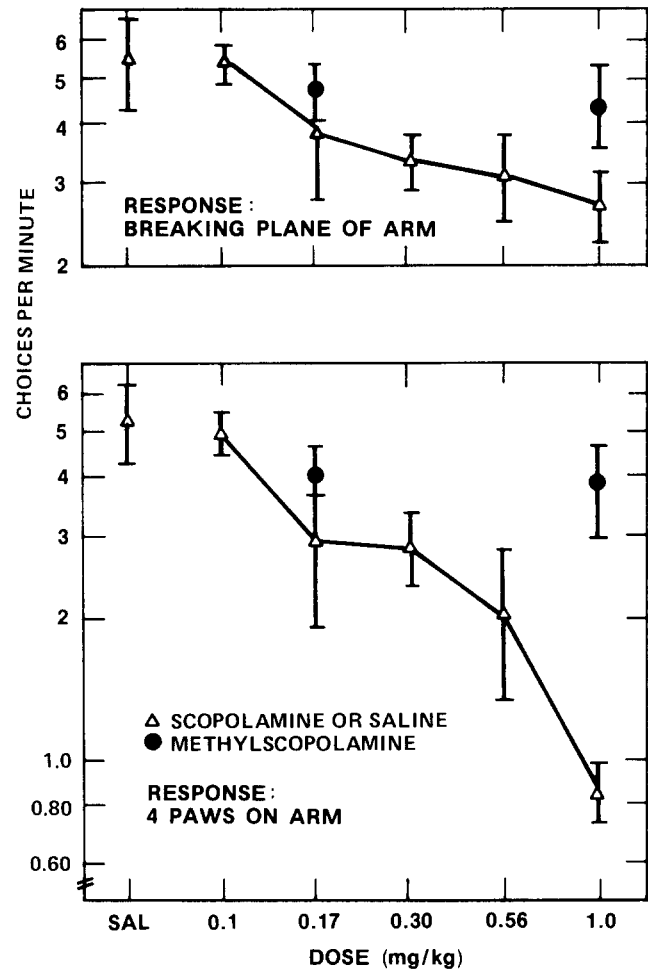


FIG. 6. Mean rate of entering arms (log scale) for the drug or saline trials of Experiment 2 (see Fig. 4).

and the rate of entering arms, adding generality to the results of Experiment 1. Since Experiment 1 involved multiple injections of each subject and Experiment 2 involved a single injection per subject, the similarity of the results confirms that these effects transcend differences in experimental design. The importance of central as opposed to peripheral antimuscarinic actions was shown in that scopolamine affected the performance considerably more than did methylscopolamine. This differential effect is comparable to

that found in other discrimination situations (see General Discussion) and shows that peripheral antimuscarinic effects alone (e.g., decreased salivation) did not produce the scopolamine effects. Although difficulty in eating was observed and involved some choking on, and dropping of, pellets, consumption of pellets given after the drug trial shows that they continued to be reinforcers. We therefore concluded, as did Robustelli, *et al.* [32], that motivational change did not interact with the drug in disrupting performance.

Experiment 2 allowed confirmation of the casual observation made in Experiment 1 that rats continued to move about and make abbreviated arm entrances (crossing plane of the arm and then drawing back) even after the largest dose of scopolamine. The rate of breaking the plane of an arm with the nose did decrease with increasing dosage of scopolamine, but not nearly as much as did venturing out onto the arms (with all four paws). Accuracy of entrance was reduced at lower dosages of scopolamine when breaking the plane of the arm was taken to define the response than when the four-paw criterion was used.

GENERAL DISCUSSION

Scopolamine decreased the accuracy of arm selections on a radial-arm maze while *d*-amphetamine and pentobarbital were without effect. It is unlikely that this lack of effect was due to inappropriate selection of dosages because both drugs have been shown to affect several other types of performance over comparable ranges. Furthermore, *d*-amphetamine and pentobarbital did affect the rate of arm selection in Experiment 1. In Experiment 2, moreover, the predominantly peripherally-acting drug methylscopolamine only minimally altered performance measures that were substantially changed by a comparable dosage of scopolamine. Taken together, these results provide comparatively strong evidence for the selective involvement of central cholinergic mechanisms in performance on the radial-arm-maze. Studies demonstrating an effect of hippocampal lesions on radial arm maze performance also imply cholinergic mechanisms [12, 25, 30].

Consideration should be given to the extent to which performance on the radial-arm maze, and the behavioral effects of scopolamine, depend on a rat's memory of prior locations from which food was taken, on the repeated emission of a response sequence, or on control by discriminative stimuli. Sequences of responses have been obtained using several procedures, and for most of these, scopolamine has been shown to disrupt the likelihood of the sequence. Scopolamine decreased the frequency of single alteration performance to chance level in a Y-maze and a T-maze [1,24]. Scopolamine also decreased alternation between two levers in an operant paradigm and in a trials design with variable intertrial intervals [9, 11, 17]. With few exceptions [9,15], the disruption in response sequences does not appear to be the result of response perseveration, cf. [12]. In fact, in a situation in which perseveration was required, scopolamine decreased the frequency of response runs [33]. The disruption then, represents the loss of control by the location of the previous response rather than a reversal of

this control. Most experiments are in agreement, however, in showing that methylscopolamine has little effect on performance. In the present experiments, response patterning was evident in some rats, but these rats were no more accurate than those that showed no evidence of patterning. Many of the rats that patterned responses, moreover, showed shifts in the pattern without concomitant decreases in accuracy. Consequently, it seems unlikely that accuracy was due to repetition of response sequences or that scopolamine's effects on accuracy were due to a disruption of response sequences. What the performance on the radial-arm maze demonstrates, in fact, is control of arm-selection by all locations previously selected within the trial rather than merely control by the last response. This delayed stimulus control is what was disrupted by scopolamine. In the radial-arm maze procedure, as opposed to response alternation, the disruption may be more clearly laid to loss of stimulus control rather than to a mere alteration in a response algorithm.

The issue of whether scopolamine affects an organism's memory of responses and their consequences appears open to debate. While some studies imply that the ability of stimulus control to bridge delays (i.e., memory) is disrupted by scopolamine, e.g., [2,23], other studies stress that scopolamine's effect is on stimulus control and not memory [3, 5, 8, 11, 32]. For example, scopolamine was found to disrupt spatial alternation when variable delays separated the opportunity to respond, but the degree of disruption was independent of the delay length [11]. Scopolamine also disrupted accuracy of delayed matching-to-sample performance in monkeys although the effect of delay length on accuracy obtained under nondrug conditions was preserved after scopolamine [3,32]. By the same token, in several studies in which delays did not separate presentation of stimuli from the opportunity to respond, stimulus control was disrupted by scopolamine [4, 5, 10, 18, 19, 33]. Bartus and Johnson [2], however, have observed an increased disruption of stimulus control at long delays, indicating that an effect on memory cannot be ruled out.

Accurate performance on the radial-arm maze appears to involve the rat's selecting from a list of arms without replacement. This performance demonstrates delayed discriminative control (i.e., memory). The disruption of this performance, however, might result from either disruption of this memory process or from a lowered discrimination between items on the list (i.e., confusion of arm locations). Determining which is involved requires inserting delays into the procedure to see interactions of accuracy with delay, e.g., [31]. In the present study, experimenter-imposed delays were not inserted and therefore a conclusive answer is not available. A tentative answer, however, is suggested by comparing accuracy at successive selections within the trial. If scopolamine's effect was on memory, the decrease in accuracy across successive selections within a trial (see Fig. 1) should have been accelerated. Scopolamine, however, dropped corrected accuracy about the same amount at each selection in a trial. The present data thus suggest that scopolamine may reduce discriminative control without changing the loss of this stimulus control over time (i.e., memory).

REFERENCES

1. Anisman, H. and L. Kokkinidis. Effects of scopolamine, *d*-amphetamine and other drugs affecting catecholamines on spontaneous alternation and locomotor activity in mice. *Psychopharmacology* **45**: 55-63, 1975.
2. Bartus, R. T. and H. R. Johnson. Short-term memory in the rhesus monkey: Disruption from the anti-cholinergic scopolamine. *Pharmac. Biochem. Behav.* **5**: 39-46, 1976.
3. Bohdanecky, A. and M. E. Jarvik. Impairment on one-trial passive avoidance learning in mice by scopolamine, scopolamine methylbromide, and physostigmine. *Neuropharmacology* **6**: 271-282, 1967.
4. Dews, P. B. Studies on behavior. II. The effects of pentobarbital, methamphetamine, and scopolamine on performances in pigeons involving discriminations. *J. Pharmac. exp. Ther.* **115**: 380-389, 1955.
5. Dews, P. B. Schedules of reinforcement. In: *Animal Behavior and Drug Action*, edited by H. Steinberg. Boston: Little, Brown and Co. 1964, pp. 191-201.
6. Dilts, S. L. and C. A. Berry. Effects of cholinergic drugs on passive avoidance in the mouse. *J. Pharmac. exp. Ther.* **158**: 279-285, 1967.
7. Eckerman, D. A., R. N. Lanson, and R. Berryman. Effects of sodium pentobarbital on symbolic matching and symbolic oddity performance. *Bull. Psychon. Soc.* **11**: 171-174, 1978.
8. Glick, S. D. and B. Zimmerberg. Amnesic effects of scopolamine. *Behav. Biol.* **7**: 245-254, 1972.
9. Hearst, E. Effects of scopolamine on discriminated responding in the rat. *J. Pharmac. exp. Ther.* **126**: 349-358, 1959.
10. Hearst, E. Drug effects on stimulus generalization gradients in the monkey. *Psychopharmacology* **6**: 57-70, 1964.
11. Heise, G. A., R. Conner and R. A. Martin. Effects of scopolamine on variable interval spatial alteration and memory in the rat. *Psychopharmacology* **49**: 131-137, 1976.
12. Heise, G. A., B. Hrabrich, N. L. Lilie and R. A. Martin. Scopolamine effects on delayed alteration in the rat. *Pharmac. Biochem. Behav.* **3**: 993-1002, 1975.
13. Heise, G. A. and N. A. Lilie. Effects of scopolamine, atropine, and *d*-amphetamine on internal and external control of responding on non-reinforced trials. *Psychopharmacology* **18**: 38-49, 1970.
14. Jarrard, L. E. Selective hippocampal lesions: Differential effects on performance by rats of a spatial task with preoperative versus postoperative training. *J. comp. physiol. Psychol.* **92**: 1119-1127, 1978.
15. Khavari, K. A. Effects of central versus intraperitoneal *d*-amphetamine administration on learned behavior. *J. comp. physiol. Psychol.* **68**: 226-234, 1969.
16. Khavari, K. A. Adrenergic-cholinergic involvement in modulation of learned behavior. *J. comp. physiol. Psychol.* **74**: 284-291, 1971.
17. Ksir, C. J., Jr. Scopolamine effects on two-trial delayed-response performance in the rat. *Psychopharmacology* **34**: 127-134, 1974.
18. Laties, V. G. The modification of drug effects on behavior by external discriminative stimuli. *J. Pharmac. exp. Ther.* **183**: 1-13, 1972.
19. Laties, V. G. and B. Weiss. Influence of drugs on behavior controlled by internal and external stimuli. *J. Pharmac. exp. Ther.* **152**: 388-396, 1966.
20. Lyon, M. and T. W. Robbins. The action of central nervous system stimulant drugs: A general theory concerning amphetamine effects. In: *Current Developments in Psychopharmacology, Vol. 2*, edited by W. Essman and L. Valzelli. New York: Spectrum, 1975, pp. 89-163.
21. Maki, W. S., S. Brokofsky and S. Berg. Spatial memory in rats: resistance to retroactive interference. *Anim. Learn. Behav.* **7**: 25-30, 1979.
22. MacPhail, R. C. and L. R. Gollub. Separating the effects of response rate and reinforcement frequency in the rate-dependent effects of amphetamine and scopolamine on the schedule-controlled performance of rats and pigeons. *J. Pharmac. exp. Ther.* **194**: 332-342, 1975.
23. Meyers, B. Some effects of scopolamine on a passive avoidance response in rats. *Psychopharmacology* **8**: 111-119, 1965.
24. Meyers, B. and E. F. Domino. The effect of cholinergic blocking drugs on spontaneous alteration in rats. *Arch. Int. Pharmacodyn.* **150**: 525-529, 1964.
25. Olton, D. S. Spatial memory. *Scient. Am.* **236**: 82-98, 1977.
26. Olton, D. S. Characteristics of spatial memory. In: *Cognitive Aspects of Animal Behavior*, edited by S. H. Hulse, W. K. Honig and H. Fowler. Hillside, NJ: Erlbaum, 1978.
27. Olton, D. S. and C. Collison. Intramaze cues and "odor trails" fail to direct choice behavior on an elevated maze. *Anim. Learn. Behav.* **7**: 221-223, 1979.
28. Olton, D. S. and R. J. Samuelson. Remembrance of places passed: spatial memory in rats. *J. Exp. Psychol. Anim. Behav. Processes* **2**: 97-116, 1976.
29. Olton, D. S., J. A. Walker and F. H. Gage. Hippocampal connections and spatial discrimination. *Brain Res.* **139**: 295-308, 1978.
30. Olton, D. S. and M. A. Werz. Hippocampal function and behavior: spatial discrimination and response inhibition. *Physiol. Behav.* **20**: 597-605, 1978.
31. Roberts, W. A. and W. E. Smythe. Memory for lists of spatial events in the rat. *Learn. Motiv.* (in press), 1979.
32. Robustelli, F., S. D. Glick, T. L. Goldfarb, A. Geller and M. E. Jarvik. A further analysis of scopolamine impairment of delayed matching with monkeys. *Commun. Behav. Biol.* **3**: 101-109, 1969.
33. Wagman, W. D. and G. C. Maxey. The effects of scopolamine hydrobromide and methylscopolamine hydrobromide upon the discrimination of interoceptive and exteroceptive stimuli. *Psychopharmacology* **15**: 280-288, 1969.
34. Zoldeck, L. and W. A. Roberts. The sensory basis of spatial memory in the rat. *Anim. Learn. Behav.* **6**: 77-81, 1978.