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Scopolamine in Rats Impairs Acquisition but not Retention in a 14-Unit T-Maze

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SPANGLER, E. L., M. E. CHACHICH AND D. K. INGRAM. *Scopolamine in rats impairs acquisition but not retention in a 14-unit T-maze.* PHARMACOL BIOCHEM BEHAV **30**(4) 949–955, 1988.—To follow up a previous report noting that scopolamine impaired acquisition performance of young rats in a shock-motivated 14-unit T-maze, the present study assessed the effects of muscarinic antagonism on retention aspects of the same task. The broader objective was to further the investigation of possible defects in cholinergic neurotransmission that might underlie the age-related impairments previously observed in this task. Young (3-month) male F-344 rats were given preliminary training to criterion in one-way active avoidance in a straight runway. Then on the first day of complex maze training, each rat received 5 acquisition (AQ) trials followed by a second 10-trial retention (RET) session conducted the following day. Subjects were assigned to one of eight groups receiving an intraperitoneal injection of either scopolamine hydrochloride (1.0 mg/kg) or saline as follows: (a) 30 min prior to training on the first day (PRE-AQ); (b) 30 min prior to training on both the first and second day (PRE-AQ-RET); (c) immediately after completing the trial on the first day (POST-AQ); (d) 30 min prior to testing on the second day (PRE-RET). Dependent measures included errors, alternation errors, run time, number of shocks, and total shock received. On the first day of maze training, all performance measures except for alternation errors were significantly higher for the two acquisition groups (PRE-AQ and PRE-AQ-RET) compared to all other groups which did not differ significantly. While on the second day the PRE-AQ group recovered on all measures to levels comparable to other groups, the PRE-AQ-RET group remained impaired throughout training on all performance measures and appeared to maintain an alternation strategy for maze acquisition. Retention aspects of this task appeared unaffected as none of the other groups differed significantly in performance. Thus, further evidence of a scopolamine-induced cognitive impairment in acquisition of this task was noted but was manifested only when given throughout training. These results suggest that the dose of scopolamine used impaired encoding processes while leaving storage and retrieval mechanisms intact.

Maze learning Memory Scopolamine Avoidance conditioning Cholinergic system Aging Rats Muscarinic receptors

DRUGS that block central muscarinic cholinergic receptors have been reported to diminish learning and memory abilities in humans, nonhuman primates, and several rodent species [9,34]. Scopolamine has been utilized frequently to assess the effects of cholinergic blockade on behavioral performance [9]. Scopolamine administered prior to a test session has been reported to disrupt acquisition of a discriminative eyelid conditioning response in rabbits [16], retention of a passive avoidance response in rats and mice [7,25], acquisition and retention of a radial arm maze task in rats [10,17], complex spatial learning in rats [32], impair the acquisition and retention of an object discrimination in marmosets [31] and tactile learning in humans [30]. Recently, Spangler *et al.* [33] reported that scopolamine impaired the acquisition of a 14-unit T-maze task. These deficits appear similar to age-related deficits observed in rats and mice in this task [2, 13–15, 18, 19, 26].

In their review of the literature, Spencer and Lal [34] proposed that centrally-acting muscarinic cholinergic antagonists disrupt mechanisms of encoding and retrieval while sparing memory storage mechanisms. They further suggested that the degree of disruption to retrieval processes is mediated by the strength of the associational link between stimuli. Thus, prior to exposure to a task or the addition of salient stimuli might be expected to attentuate anticholinergic effects.

A similar explanation has been offered by Cheal [8], who suggested that central cholinergic blockade disrupts mechanisms of attention. Soffie *et al.* [32] also implied a deficit in attention in their study in which scopolamine-treated rats

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performed poorly in a complex spatial task that required attention to a particular cue to solve the task.

Progressive memory dysfunction is a cardinal characteristic of senile dementia of the Alzheimer's type [3]. Possible neurobiological linkage to this cognitive dysfunction has been related to losses of central cholinergic cell populations, particularly in the hippocampal formation and the nucleus basalis magnocellularis [4]. Age-related declines in central cholinergic systems (e.g., reduced receptor density and binding) have been reported in animal studies, and some studies have reported correlations between cognitive performance and age-related declines in cholinergic parameters [22,23]. The accumulation of evidence linking central cholinergic degeneration with age-related declines in learning and memory has provided impetus for a cholinergic hypothesis of geriatric memory dysfunction [3,4].

The correlation of performance deficits with age-related declines in central cholinergic systems, however, does not provide direct evidence that the cholinergic system is solely responsible for memory dysfunction observed in normal aging and dementia. Other central neurotransmitter systems undergo reliable age-related declines (e.g., noradrenergic) and may play a role in learning and memory [40]. Behavioral studies utilizing drugs that block only cholinergic receptors in young animals (e.g., scopolamine, atropine) have been suggested as one means of overcoming this potential confound because such studies should result in greater control over variability [5].

In the present study, scopolamine-induced cholinergic blockade was utilized to further characterize the involvement of central muscarinic cholinergic systems in memory processing required for accurately solving a shock-motivated 14-unit T-maze task. Scopolamine was administered to young rats to determine whether muscarinic antagonism: (a) impaired consolidation of and/or retrieval from memory for this task; and (b) impaired processes of storage and retrieval during retention testing to the same extent that it disrupted encoding processes during acquisition.

METHOD

Subjects

Fifty-five 3-month-old male Fischer-344 rats were obtained from Harlan Sprague-Dawley Breeding Laboratories (Indianapolis, IN). Upon arrival they were 90 days old and weighed approximately 250 g. The animals were housed doubly in suspended, metal cages (Wahmann) in a vivarium maintained at 22°C and on a 12-hr light/12-hr dark photocycle (lights on at 0:600). Food (NIH-07 formula) and water were provided ad lib. The rats were permitted about 3 weeks to acclimate to the vivarium prior to treatment.

Apparatus

Pretraining for one-way active avoidance was conducted in a clear Plexiglas, straight runway (2 m long) that has been described previously [33]. Maze testing was conducted in a clear Plexiglas 14-unit T-maze that has also been described previously [33].

Pretraining

Prior to the start of preliminary one-way active avoidance training in a straight runway (2 m long), all animals were removed from the vivarium and transported in their home cages to the maze room where they were allowed to acclimate for at least 30 min. On the first trial each rat was placed by hand into the start area of a straight runway with a diagonally-oriented steel grid floor. The rat had 10 sec to avoid a 1.0 mA footshock by running to a black goal box at the opposite end of the runway. After the goal box was entered, a guillotine door was lowered, and 30 sec later the entire box was removed to a holding area where it remained until the next trial 90 sec later. On the second and subsequent trials, the rat was pushed from the black box into the start area and, as in the first trial, had to run down the alley to a black box with 10 sec to avoid footshock. All animals received 10 massed practice trials within a 2-min intertrial interval on each of 3 consecutive days (Monday, Tuesday, Wednesday) between 01:00–17:00 hr. Criterion for successful completion of pretraining was 8 out of 10 successful avoidance responses on the third day.

Maze Training

According to a procedure described previously [33], training in the 14-unit T-maze began 24 hr following the final pretraining session. As in pretraining, all animals were brought to the test room at least 30 min prior to training. The training contingency was to traverse each of five maze segments within 10 sec to avoid footshock (1.0 mA). A guillotine door was lowered after successful negotiation of each maze segment.

On Day 1 each rat received acquisition (AQ) training during 5 trials with a 2-min intertrial interval. On Day 2, 24 hr later, a similar 10-trial session was conducted as a retention (RET) test.

Drug Treatment

Experimental subjects were assigned randomly to one of four groups in which they received an intraperitoneal (IP) injection of scopolamine hydrochloride (1.0 mg/kg) while their matched controls received an IP injection of the vehicle, physiological saline. The 1.0 mg/kg dose was selected based upon our previous findings in the dose response study [33]. This dose impaired the cognitive measure of maze performance, errors per trial, in the previous study while a higher dose (3.0 mg/kg) produced a more generalized impairment reflected in significant disruption in all dependent measures of maze performance. The effects of scopolamine upon maze performance were centrally acting since no significant effects were associated with an injection of methylscopolamine, which is principally peripherally acting [33].

The groupings were as follows: (a) an acquisition group that received an injection 30 min prior to training on Day 1 (PRE-AQ); (b) an acquisition/retention group that received an injection 30 min prior to testing on both Days 1 and 2 (PRE-AQ-RET); (c) a memory consolidation group that received an injection 30 sec after the final acquisition trial on Day 1 (POST-AQ); (d) a memory retrieval group that received an injection 30 min prior to retention testing on Day 2 (PRE-RET); and (e) the four respective control groups matched to each experimental treatment group (SAL). The drug was prepared fresh weekly in normal saline so that each dose was administered in a volume of 1 ml/kg.

Statistical Analyses

Dependent measures included errors (deviations from the correct path), run time, alternation errors (described below), number of shocks, and duration of shock received. Mean scores for blocks of five trials were calculated for each dependent measure. Because one-way analysis of variance

TABLE 1

RESULTS OF ANALYSIS OF VARIANCE (F-VALUES) AND TUKEY (hsd) COMPARISONS FOR EACH DEPENDENT MEASURE OF MAZE PERFORMANCE

	Group Means				
Mean Errors per Trial					
Day 1	A	B	C	D	E
BLOCK 1					
F(4,50)=13.0*	9.7	9.6	10.6	18.2	18.2
Day 2	B	A	C	D	E
BLOCK 2					
F(4,50)=44.5*	3.1	3.4	5.1	6.4	14.5
	B	A	D	C	E
BLOCK 3					
F(4,50)=57.0*	1.8	2.0	2.0	2.3	10.3
Mean Run Time (sec) per Trial					
Day 1	B	C	A	D	E
BLOCK 1					
F(4,50)=5.2*	60.1	60.3	63.3	94.9	98.6
Day 2	A	B	C	D	E
BLOCK 2					
F(4,50)=19.5*	19.3	20.4	24.7	40.2	53.5
	A	B	C	D	E
BLOCK 3					
F(4,50)=25.8*	11.0	11.5	14.5	16.3	41.6
Mean Number of Shocks Received per Trial					
Day 1	B	A	C	D	E
BLOCK 1					
F(4,50)=4.9*	2.6	2.7	2.8	3.7	3.8
Day 2	A	B	C	D	E
BLOCK 2					
F(4,50)=18.9*	0.5	0.5	0.7	1.6	2.6
	A	B	D	C	E
BLOCK 3					
F(4,50)=18.3*	0.1	0.1	0.1	0.1	1.3

TABLE 1

(Continued)

	Group Means				
Mean Duration of Shock (sec) Received per Trial					
Day 1	C	B	A	D	E
BLOCK 1					
F(4,50)=5.1*	18.3	19.4	20.0	43.9	44.9
Day 2	B	A	C	D	E
BLOCK 2					
F(4,50)=9.6*	1.2	1.0	3.3	8.2	12.3
	A	B	D	C	E
BLOCK 3					
F(4,50)=17.3*	0.0	0.1	0.1	0.3	4.7
Mean Ratio of Alternation Errors per Block					
Day 1	B	A	C	D	E
BLOCK 1					
F(4,50)=1.3	0.41	0.42	0.44	0.47	0.52
Day 2	B	A	C	D	E
BLOCK 2					
F(4,50)=14.9*	0.18	0.25	0.30	0.31	0.59
	B	A	C	D	E
BLOCK 3					
F(4,50)=22.1*	0.11	0.13	0.18	0.20	0.58

*$p<0.01$.

A=Saline; B=POST-AQ; C=PRE-RET; D=PRE-AQ; E=PRE-AQ-RET.

Means connected by continuous line are not significantly different ($p<0.05$).

(ANOVA) revealed no differences among the saline controls (ps>0.05), these were combined for further statistical analyses. Applying data from the four experimental groups—PRE-AQ (n=8), PRE-AQ-RET (n=9), POST-AQ (n=10), PRE-RET (n=9)—and combined SAL (n=18) groups, a separate one-way ANOVA was then calculated on each block for all of the dependent measures, and Tukey HSD post hoc analyses were conducted. Statistical significance for the ANOVAs and Tukey tests was accepted at $p<0.05$.

The analysis of alternation errors was undertaken to determine if the rats utilized an alternation strategy to negotiate the maze. A computer program was utilized to score only forward-going sequences of responses (of at least three turns in the maze) that resulted in an error and to count errors that occurred when the opportunity for demonstrating an alternation pattern of responding—left (L): right (R)—was presented, e.g., LRL or RLR. Thus, an alternation error was defined as an error that would have occurred if the rat were utilizing an alternation strategy during forward-going position discriminations in the maze [33].

RESULTS

Mean scores for each performance variable at each block of trials are reported in Table 1. All groups appeared to learn as evidenced by a reduction in scores on these measures across blocks of trials. According to the results of separate ANOVAs calculated on each block for each dependent measure (Table 1), only the acquisition groups (PRE-AQ and PRE-AQ-RET) were significantly affected by scopolamine treatment compared to all other groups. No significant effects were observed for any training block in either retention group (POST-AQ and PRE-RET) compared to SAL controls.

The measure of cognitive performance, mean error score per block of 5 trials, was impaired for both the PRE-AQ and PRE-AQ-RET groups during the first block of trials in Day 1. The PRE-AQ-RET group was significantly impaired in this measure compared to all other groups throughout the remaining two blocks of trials on Day 2. The PRE-AQ group, while significantly impaired compared to SAL and POST-AQ groups at block 2, evidenced rapid recovery to achieve levels of error performance equivalent to these groups in the final block of trials. The recovery of the PRE-AQ group can be seen more clearly in Fig. 1. By the seventh trial the PRE-AQ

group achieved levels similar to the SAL, POST-AQ, and PRE-RET groups. The error performance of the two retention groups, POST-AQ and PRE-RET, in blocks 2 and 3 was not significantly affected by scopolamine administration in this task compared to SAL controls.

Returning to Table 1, it can be seen that the PRE-AQ and PRE-AQ-RET groups were also significantly impaired in other performance variables—run time, number of shocks received, and duration of shock received. As in the error measure, the PRE-AQ group recovered to levels indistinguishable from the saline and retention groups on DAY 2 on all dependent measures, whereas the PRE-AQ-RET group was impaired throughout the last two sessions on all of the measures. No significant differences in any performance measure emerged among the SAL, POST-AQ and PRE-RET groups throughout maze testing.

As observed in Table 1, all groups exhibited equivalent utilization of an alternation strategy in the first block of trials. Analyzing the incidence of alternation errors when given the opportunity, these rats made such errors about 40–50% of the time. The PRE-AQ-RET group, but not the PRE-AQ group, significantly differed from the SAL, POST-AQ, and PRE-RET groups at blocks 2 and 3. This finding indicates that rats treated with scopolamine throughout training continued to rely upon an alternation strategy to solve this task since no reduction in alternation errors across blocks of trials was observed. It is important to note that the group treated with scopolamine on the second day (PRE-RET) did not appear to maintain an alternation strategy.

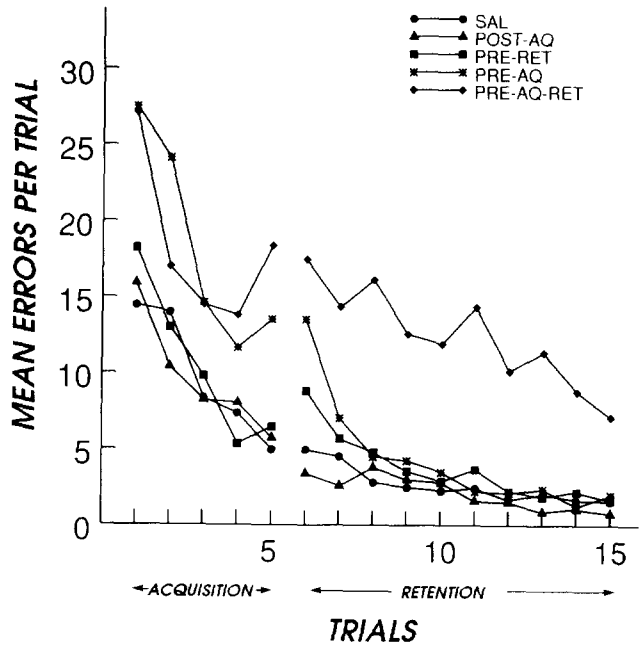

FIG. 1. Mean errors per trial of male F-344 rats in 14-unit T-maze according to scopolamine (1.0 mg/kg) treatment: saline controls (SAL); scopolamine after acquisition (POST-AQ: after trial 5); scopolamine before retention (PRE-RET: before trial 6); scopolamine before acquisition (PRE-AQ: before trial 1); and scopolamine before acquisition and retention (PRE-AQ-RET: before trials 1 and 6).

DISCUSSION

In a previous study from our laboratory, Spangler *et al.* [33] demonstrated a dose-related disruption of acquisition performance in a 14-unit T-maze by young rats given scopolamine prior to testing. These deficits appeared similar to age-related deficits observed in the acquisition of this task in rats and mice [13–15, 18, 19, 26] and appeared to implicate the cholinergic hypothesis of geriatric memory dysfunction [3,4]. In the current study we sought to further characterize cholinergic involvement in this task by determining whether scopolamine (1.0 mg/kg) disrupted consolidation of and/or retrieval from memory and whether retention was disrupted to the same extent as acquisition. The present results confirmed our previous finding that scopolamine (1.0 mg/kg) increased error performance during task acquisition but only when administered throughout training. Scopolamine had no significant effect on retention in this task since POST-AQ and PRE-RET groups were similar to the SAL group for all dependent measures on Day 2. Furthermore, the low error score performance by the PRE-RET group on Day 2 following scopolamine administration suggests that the impaired performance of the PRE-AQ group on Day 1 and PRE-AQ-RET group on both days was not due to a general nonassociative performance deficit caused by the drug.

The deficits observed in other performance measures in the PRE-AQ and PRE-AQ-RET groups may be partially explained by higher alternation error scores and reflects a tendency by these rats to employ an alternation strategy to solve this task. This hypothesis is reinforced by the stability of the alternation measure across blocks of trials in the PRE-AQ-RET group. Thus, reliance upon an alternation strategy to learn this task following cholinergic blockade appears to represent a salient feature of performance in this task.

The significant disruption in all performance measures in the acquisition groups contrasts with observations from the previous study in which a 3.0 mg/kg dose of scopolamine disrupted these measures. In that study a 1.0 mg/kg dose disrupted the cognitive measure, error performance, while having a relatively minor effect on other performance measures [33]. These disparate results might be attributed to differences in training schedule (10 trials on each of 2 test days in the previous investigation versus 5 trials on the first day and 10 trials on the second in the present study). Additionally, it should be noted that, as in the previous study, the duration and number of shocks were very low by the end of training, an observation suggesting that the PRE-AQ-RET group had learned the shock avoidance contingency.

In their review of the literature, Spencer and Lal [34] proposed that anticholinergic drugs (i.e., scopolamine and atropine) disrupted learning and memory performance by interfering with or distorting encoding and retrieval processes while sparing memory storage. Our findings only partially support this hypothesis. Prior administration of scopolamine disrupted acquisition (i.e., encoding) but not retention (i.e., storage or retrieval). The invariant nature of this task [18], however, makes the corollary hypothesis offered by Spencer and Lal [34] a viable explanation for the present results. Specifically, the young rat may rapidly acquire strong associations concerning the position discriminations in this aversively-motivated task (i.e., LRRLL) during the initial block of five trials. The rapid decline in error scores for all groups on the first day of training, except the PRE-AQ and PRE-AQ-RET groups, and the nearly perfect performance by the final trial of the second day for all groups, except the PRE-AQ-RET group, provides considerable support for such an explanation (see Fig. 1). However, it is also possible that

a higher dose of scopolamine is required to disrupt retrieval in this task [6]. In agreement with Spencer and Lal's major hypothesis, administration of the drug prior to maze training disrupted acquisition performance while administration of the drug immediately following initial maze training did not affect memory storage.

Our findings thus appear to conflict with those of Cherkin and Flood [12], who reported that 1.0 mg/kg scopolamine delivered subcutaneously immediately after training disrupted 1-week retention of a 1-unit T-maze in mice. Whether species or methodological differences account for this discrepancy cannot be ascertained. However, observing rats in a radial arm maze, Beatty and Bierley [6] did not report a scopolamine effect on storage (drug given after trials in a session) but did find a negative effect on retrieval (drug given before last trials). Thus, the current results may be specific to the dose, task, and subject that we used. The importance of our findings, however, concerns further understanding of the age-related impairment in this and similar complex mazes. Scopolamine appears to have greater impact upon encoding processes than upon retention processes in the learning of this task.

State-dependent effects have been reported following administration of anticholinergic drugs by some investigators [9] while others have been unable to rule out such effects [32]. State-dependent effects were not evident in the present study. The PRE-RET group was not impaired following scopolamine administration on the retention trials, and the PRE-AQ group rapidly acquired the task on the second day to indicate that no state-dependent learning effects had occurred (i.e., amnesia for information acquired in a different state, drugged or undrugged).

Cholinergic blockade has been reported to interfere with the memory of arms previously entered for food by rats in a radial arm maze [6, 10, 17, 29, 36, 37]. The ability to make flexible, stimulus-response associations, such as those required to remember baited arms during a trial, has been termed working memory (WM) by Olton *et al.* [27]. WM involves the encoding of incoming stimuli during specific trial performance with aspects of the event pertaining to the specific, personal and temporal context being encoded into a WM store [20]. Initial trials in the learning of a novel task would be expected to draw heavily on the WM store [20]. While this type of short-term memory has been reported to be disrupted by scopolamine-induced blockade [6, 10, 17, 29, 36, 37], more rigid, or fixed, patterns of stimulus response associations as reflected in the ability to remember unbaited arms in the radial arm maze is relatively unaffected by scopolamine [39] and has been termed reference memory (RM). RM involves the coding of more general information, such as rules and procedures gained from events which occur on all trials [27]. Similar deficits in WM but not RM for the radial arm maze have been reported in rats with lesions to the septohippocampal system disrupting cholinergic innervation from the septal nucleus via the frimbria-fornix [27,28]. Results of Spencer *et al.* [35] failed to support the WM model. In their study scopolamine impaired the performance of rats in a delayed nonmatching to sample task (WM) but also impaired a visual discrimination task (RM) suggesting that both components of memory were disrupted.

The results of our previous investigation did not permit us to assess how performance in this task fit into the conceptual model of memory processing offered by Olton *et al.* [27]. However, based upon the performance of the PRE-RET group, the present results strongly suggest that retrieval of RM is not disrupted by 1.0 mg/kg scopolamine in this task. That is, young rats rapidly acquire a fixed series of position discriminations in this task. By the fifth trial, error score performance has dropped in rats that have not received scopolamine treatment by approximately 67% (from 15 errors to 5 errors), and scopolamine-induced blockade prior to the retention test does not significantly impair their ability to retrieve a response rule. The response rule would be to inhibit a tendency to alternate at certain choice-points [18]. Rats in the PRE-RET group did not maintain this strategy.

It would appear that to acquire this task, the rat must rely heavily on WM during initial trials (remembering alleyways previously entered) and for within-trial performance (retaining instances of incorrect turns during that trial) in the 14-unit T-maze [18]. A failure to observe disruption in retention in this task appears to suggest that cholinergic blockade affected only the acquisition of new information (i.e., disrupts working but not reference memory). Still, the 14-unit T-maze is viewed primarily as a spatially-oriented RM task [21] in which the requirements remain constant from trial to trial [21]. The inability to more clearly dissociate WM and RM components of the 14-unit T-maze does not permit us to make a more accurate assessment of how the acquisition data in the present study fit the Olton *et al.* model [27]. It is possible that, as in the Spencer *et al.* study [35], both WM and RM are disrupted by administration of the drug prior to acquisition. This observation also relates to characterizing the age-related learning impairment in complex maze performance. In a two-component T-maze task in which WM and RM were defined distinctly, aged rats were observed to be impaired equivalently in both components compared to young counterparts [24].

Further argument regarding whether mechanisms of memory per se are involved in the disruption of encoding observed in the present investigation need to be addressed. Although error performance in the sixth trial on Day 2 in the PRE-AQ group remained elevated, a rapid decline on the following (see trial 7 in Fig. 1) and subsequent trials suggests that the animal was acquiring information during the initial block of trials (Day 1) in the maze but may have been unable to utilize or retrieve this information from a WM store. Such an interpretation agrees with Eckerman *et al.* [10], who suggested that a scopolamine-induced reduction in accuracy and the number of arm entries in the radial arm maze was due to a loss of discriminative control of the memory for the arms previously entered.

An attentional deficit explanation, such as the ones offered by Cheal [8] and Soffie *et al.* [32], might also explain the present results. However, a generalized attention deficit appears unlikely since the PRE-AQ-RET group, while significantly higher than other groups, were avoiding the shock well by the final block of trials. The alternation error data are supportive of the observation by Soffie *et al.* [32] that following scopolamine administration in complex spatial tasks, rats revert to the simplest response strategy due to an inability to sustain attention. Winocur and Breckenridge [38] also reported that hippocampally-damaged rats utilized an alternation strategy in a complex maze task. Making the task easier to solve by providing cues attenuated these deficits [38]. Our results also agree with the observation by Soffie *et al.* [32] that training prior to scopolamine administration attenuates these deficits, since performance was not significantly disrupted in any of the RET groups in the present study.

A spatial working memory explanation must also be acknowledged. In the radial arm maze, cholinergic blockade did not disrupt the performance of rats that adopted a non-

spatial response strategy, i.e., entering adjacent arms or every other arm [36]. However, scopolamine-treated rats were reported to be impaired when they were confined to the center of the radial maze prior to each trial and thus forced to utilize environmental cues to solve the task [37]. Ellen *et al.* [11] have also reported scopolamine-induced disruption on initial trials in the Maier three table task in which rats must integrate information regarding the spatial relationships of the tables. However, in this task the rats were reported to rapidly acquire a response strategy, i.e., RM, which could be utilized to successfully locate the table with food each time (win-stay, lose-shift).

In comparing the present task with the radial arm maze and the Maier three table task, several critical factors emerge. First, in the radial arm maze task, adopting a non-spatial strategy is adaptive throughout training. Following the initial trial in the Maier three table task, an adaptive strategy may be employed successfully on all subsequent trials. However, while an alternation strategy appears to be most adaptive on initial trials in the 14-unit T-maze, it must be abandoned in later trials to successfully master the maze Second, in the Maier three table task, the rat is faced with two choices on a test trial. In the 14-unit T-maze the rat must be able to make 14 correct position discriminations to successfully negotiate the maze. Thus, task complexity may play an important role in this task which requires cognitive flexibility in that the rat must abandon an initially adaptive strategy in order to negotiate the maze without error. Goodrick [14] proposed that task complexity was responsible for the deficits in short-term memory he observed in aged rats in this task. However, perseveration at selected choice-points was also a cardinal feature of the aged rat's performance [13–15].

In general, our findings appear to support the cholinergic hypothesis of geriatric memory dysfunction [3]. However, the present findings suggest that age-related declines in central cholinergic mechanisms may not be linked to memory storage and retrieval processes, such as consolidation or retrieval per se, but to other encoding mechanisms, possibly involving stimulus processing and formation of response strategies. Future studies utilizing aged rats in similar paradigms will be required to support and expand the present findings.

In separate reviews of the literature, Collerton [9] and Spencer and Lal [34] have underscored the need for additional studies utilizing cholinergic agonists to reverse the effects of scopolamine. These studies have been suggested to further assess the utility of this protocol as an animal model of human geriatric dysfunction and to further assess the cholinergic hypothesis [34]. Flood and Cherkin [12] recently undertook such an investigation utilizing not only cholinergic agonists but also drugs that act upon other central neural systems (e.g., catecholaminergic) to assess the ability of these drugs in mice to reverse the amnestic effects of scopolamine in a T-maze performance task. Drugs known to act on other neural systems as well as several cholinergic agonists were observed to improve T-maze performance in scopolamine-treated mice. Thus, cholinergic specificity of the scopolamine-induced amnestic syndrome was questioned. The use of drugs that act upon other neural systems should be evaluated to determine their feasibility in attenuating the cognitive deficits attributable to cholinergic blockade. In addition, Flood and Cherkin emphasized the biphasic behavior of anticholinergics by observing that scopolamine could facilitate retention at low doses and impair learning and retention at higher doses. The role of presynaptic autoreceptors was thus considered and complicated the issue of whether anticholinergics could be used as effective pharmacological models of dementias.

To reiterate the present conclusions, scopolamine (1 mg/kg) was not observed to impair the consolidation of, nor to impair the retrieval of, a memory for a complex shock-motivated T-maze task. Acquisition was impaired when the drug was administered throughout training. The absence of a retention impairment in this complex maze task in the presence of acquisition deficits suggest the involvement of cholinergic systems in mechanisms other than memory storage and retrieval in this task. It is unlikely that the group given scopolamine throughout training was merely unable to perform or respond to environmental stimuli since the PRE-RET group given the drug prior to the second session did not exhibit significant impairment in any of the dependent measures. A more likely explanation for the present results is that cholinergic blockade disrupted mechanisms of attention or interfered with the ability to discriminate between stimuli and thus disrupted encoding of associational links required to learn this spatial environment.

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