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Differential Effects of Scopolamine and Mecamylamine on Working and Reference Memory in the Rat

P. M. MORAN

Marion Merrell Dow Research Institute, 16, rue d'Ankara -B.P.447 R/9, 67009 Strasbourg, Cedex, France

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MORAN, P. M. *Differential effects of scopolamine and mecamylamine on working and reference memory in the rat.* PHARMACOL BIOCHEM BEHAV **45**(3) 533–538, 1993.—The effects of the muscarinic antagonist scopolamine (0.1–0.6 mg/kg, IP) and the nicotinic antagonist mecamylamine (1–10 mg/kg) were compared in T-maze alternation and discrimination tasks in the rat. Scopolamine dose dependently disrupted performance on the alternation task and potentiated the increase in errors made in controls when the delay between forced and choice runs was increased from 0 to 30 s. Mecamylamine disrupted performance at the 10-mg/kg dose only and dose dependently inhibited the increase in errors made in controls when the delay between forced and choice runs was increased to 30 s. In simple T-maze discrimination, only the 0.6-mg/kg dose of scopolamine disrupted performance of the task, while mecamylamine at both 5 and 10 mg/kg disrupted task performance. These results confirm that working memory tasks are more sensitive to central muscarinic blockade than reference memory tasks. They also demonstrate that in delay conditions working memory performance is enhanced following central nicotinic blockade while reference memory performance is disrupted. This suggests that centrally active muscarinic and nicotinic antagonists have dissociable effects on memory processes in the rat.

Scopolamine Mecamylamine T-maze alternation T-maze discrimination Muscarinic Nicotinic Memory Rat

ALZHEIMER'S disease and related dementias are associated with parallel decline in central cholinergic function and learning and memory performance (1,21,35). These findings, taken in conjunction with those of amnesic effects of cholinergic antagonists in humans (6,16,18,39) and animals (12,46,47), provide strong evidence for a critical role of the cholinergic system in learning and memory. Research on cholinergic contributions to learning and memory has focused on the muscarinic receptor system, suggesting that this system may be a critical substrate for many aspects of cognitive processing (1,46,47). The nicotinic-cholinergic system has received less attention as a possible neurochemical substrate of memory processes, but there is considerable evidence to suggest that nicotinic-cholinergic systems also contribute to some aspects of cognition. While muscarinic-cholinergic receptor systems are largely unaffected in postmortem brains from Alzheimer patients (17), nicotinic receptor loss has been reported particularly in the cortex (17,29,30,37,41,43) and the hippocampus (34), both of these areas playing a key role in learning and memory. Nicotine itself has been shown to have cognitive-enhancing properties in studies of both animal (5,14) and human (45) information processing, while preliminary clinical trials using nicotine in patients with suspected Alzheimer's disease suggest a positive effect on certain aspects of cognitive impairment (40).

One approach to elucidating central cholinergic contributions to cognitive functioning has been to characterise impairments on learning and memory tasks that are found in animals following administration of selective centrally active muscarinic-cholinergic antagonists such as scopolamine or atropine (3,44,47). Although there is still some dispute as to the exact nature of cognitive deficits in animals following cholinergic antagonists (31,33,38), one robust finding is the impairment of performance in tasks that involve working memory, such as delayed alternation in a T-maze or radial arm maze, with little or no effect on tasks that address reference/procedural type memory (2,3,48).

To a lesser extent, investigation of the nicotinic-cholinergic contribution to memory processes has proceeded in a similar way by characterising impairments in learning tasks in rodents induced by mecamylamine, a centrally active nicotinic antagonist. Deficits in active and passive avoidance have been reported (7,13,20) and acquisition deficits have been found in a complex maze (32) and in spatial navigation in a water maze (11,36). Impairments in choice accuracy in a radial arm maze task have been consistently found at a dose of 10 mg/kg (22,25). These findings are congruent with the idea that central muscarinic and nicotinic antagonists induce similar deficits in rodent tests of learning and memory as the muscarinic antagonists scopolamine and atropine also disrupt passive avoidance

(4), complex maze task acquisition (42), and choice accuracy in the radial maze (2). This would suggest an equivalent, or at least similar, contribution of these cholinergic receptor systems to learning and memory processes. Additive effects of combinations of scopolamine and mecamylamine have also been demonstrated in radial arm and water maze tasks (24,25,36), which would further support this contention. However, some studies suggest that scopolamine and mecamylamine produce dissociable effects on learning and memory processes. Glick and Greenstein (19) reported differential effects of scopolamine and mecamylamine in passive avoidance, while Clarke and Fibiger (9) reported that scopolamine but not mecamylamine impaired performance on a delayed alternation task. Lack of effect of mecamylamine in delayed alternation is particularly puzzling in the light of the deficit in radial arm maze performance that has been reported, as both are positively reinforced tasks that address working memory processes. It therefore remains unclear as to whether mecamylamine can be considered to induce the same pattern of memory deficit in rodents as scopolamine. To further investigate whether mecamylamine and scopolamine induce similar effects on learning and memory processes, the effects of these drugs were compared on delayed alternation and discrimination tasks in a T-maze. Scopolamine has previously been shown to disrupt reinforced alternation, but not discrimination (3), which has been interpreted as a selective effect of scopolamine on working memory, but not reference memory, processes. If mecamylamine induces similar memory deficits to scopolamine, then a similar pattern of disruption would be expected.

METHOD

Animals

Naive adult Sprague-Dawley male rats were used weighing 300–400 g. They were housed six per cage in a temperature-(22 ± 2°C) and light-controlled environment (12 L : 12 D schedule).

Fourteen days prior to testing, animals were placed on a 23-h food deprivation schedule. This schedule was maintained throughout the experimental period. All testing was carried out between 9:00 a.m. and 4:00 p.m. during the light cycle.

Apparatus

T-maze. A grey Perspex T-shaped maze was used 20 cm in height with stem arms 45 × 16 × 20 cm and branch arms 65 × 16 × 20 cm. Reinforcement consisted of 3-s access to a dish of concentrated sugared milk placed at the ends of each arm.

Behavioural Testing

Delayed alternation. Animals were given five pairs of training trials per day for 8 days. In the first trial of each pair (information run), one arm of the maze was blocked by lowering a grey Perspex panel and the animal was allowed to run to the end of the free arm to receive 3-s access to the sugared milk reward (the sequence of blocked arms was randomised both between animals and days).

On the second trial of each pair (test run), the animal was placed in the start area of the stem arm with both arms of the maze free. A correct response constituted choosing the arm opposite to that which was blocked in the previous trial. There was a 20-s interval between the end of a test run and the beginning of the next information run.

During the no-delay condition, the animal was replaced in the start arm immediately following the information run, to begin the test run, which in practice took approximately 4 s. During the 30-s delay condition, the animal was placed in a holding cage for 30 s between information and test runs. Latency to find reward on information runs was also recorded as a measure of performance that would be unconfounded by changes in information processing time associated with drug treatment.

Discrimination (Left/Right Runningrresponse)

Ten daily trials were run for 8 days. On each trial, the animal was placed in the start area of the maze and allowed to choose between arms. Choice of a predetermined correct arm led to access to reward. The correct arm was randomised between animals and constant over trials and days. During the 0-delay condition the animal was replaced immediately in the start arm to begin the next trial. During the 30-s delay condition, it was placed in a holding cage for 30 s before the commencement of the next trial. The number of errors made and latency to find reward on information runs were recorded.

Drug Administration and Experimental Design

Animals were assigned to drug and delay conditions such that all animals received all drugs at all doses in a counterbalanced order, half the animals receiving 0- and half receiving 30-s delay conditions. Between treatment days, animals were given a 2-day wash-out period free of testing followed by at least 2 days of training without drug at 0 delay. This retraining period was continued until animals reached stable performance, usually 2–4 days. This procedure was identical for both discrimination and alternation procedures.

All drugs were dissolved in saline (0.9%) and administered IP in a volume of 1 ml/kg body weight 20 min prior to testing.

Statistics

T-maze errors were analysed using nonparametric statistics. Groups were described using means and SEs and compared using the Wilcoxon signed rank test, where Friedman analysis of variance (ANOVA) was significant at $p \leq 0.05$. In the discrimination experiments, a one-tailed test was used as the saline baseline was always zero; therefore, drug effects could only occur in one direction. In the alternation experiments, two-tailed tests were used. All latency data were analysed using ANOVA with posthoc *t*-tests with a Bonferroni correction for α slippage.

RESULTS

T-maze Alternation

In the 0-delay condition, scopolamine induced a significant dose-dependent increase in error number at all three doses tested ($p < 0.05$, Wilcoxon, Fig. 1A). Interpolation of a 30-s delay between forced and choice runs significantly increased error number in saline and 0.1-mg/kg groups (Fig. 1A). At higher doses, within-group effects of delay were not significant, most likely due to the high error score at 0 delay. There was, however, a trend toward a dose-dependent increase (Fig. 1A).

Mecamylamine at the 10-mg/kg dose induced a significant deficit in performance at 0 delay ($p < 0.05$, Wilcoxon, Fig. 1B). No effect of 1- or 5-mg/kg doses was found. Interpolation of a 30-s delay significantly increased the number of er-

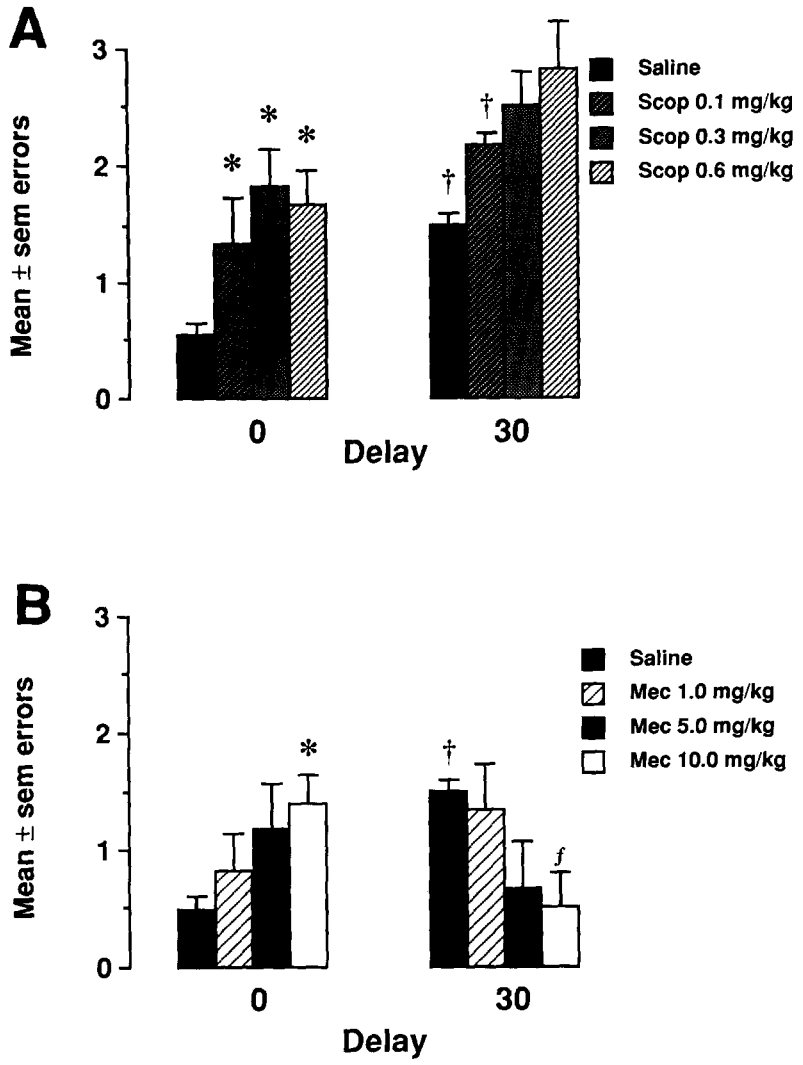

FIG. 1. Effect of scopolamine (A) or mecamylamine (B) on mean (± SEM) number of errors made in the T-maze alternation task under either 0- or 30-s delay conditions. $n = 6$ per group. $*p < 0.05$ significant difference from saline at 0-s delay. $^{f}p < 0.05$ significant difference from saline at 30-s delay. $\dagger p < 0.05$ significant difference from same treatment at 0-s delay.

rors following saline and mecamylamine at the 1-mg/kg dose (Fig. 1B). At the 5- and 10-mg/kg doses of mecamylamine, however, a significantly *reduced* number of errors was found relative to saline treatment (Fig. 1B, $p < 0.05$, Wilcoxon, compared to saline at 30-s delay).

A trend to increased latency was found following scopolamine in the alternation task (Table 1); this, however, did not reach significance at any dose. Mecamylamine also increased latency; this increase was significant at the 10-mg/kg dose, $t(10) = 4.628, p < 0.01$.

T-Maze Discrimination

No effect of scopolamine was found at 0.1- or 0.3-mg/kg doses (these data are not shown graphically because mean values were equal to zero). At the 0.6-mg/kg dose, there was a significant increase in error number at both delays ($p < 0.05$, Wilcoxon, Fig. 2).

Mecamylamine at 1 mg/kg was without effect at either of the delay conditions. At 5- and 10-mg/kg doses, however, mecamylamine induced a significant increase in error number at both 0- and 30-s delay conditions (see Fig. 2).

Scopolamine increased mean latency(s) to complete trials (Table 1), reaching significance compared to saline at the 0.6-mg/kg dose, $t(10) = 4.0, p < 0.01$. Mecamylamine also dose dependently increased mean latency to complete trials (Table 1). These effects were significant at the 5-mg/kg, $t(10) = 3.76$, $p < 0.01$, and 10-mg/kg, $t(10) = 5.707$, $p < 0.001$, doses (Table 1).

DISCUSSION

These experiments demonstrate that scopolamine and mecamylamine do not have similar effects in either T-maze alternation or discrimination tasks. In the T-maze alternation task, scopolamine impaired performance in both delay conditions

TABLE 1
LATENCY TO LOCATE REWARD

	Scopolamine (mg/kg)			
	0.0	0.1	0.3	0.6
Alternation	2.55 ± 0.90	2.92 ± 0.22	3.27 ± 0.22	5.03 ± 1.99
Discrimination	4.36 ± 0.90	6.42 ± 2.20	7.66 ± 2.70	15.37 ± 3.48*
	Mecamylamine (mg/kg)			
	0.0	0.1	5.0	10.0
Alternation	2.55 ± 0.90	2.75 ± 0.26	4.17 ± 0.76	3.76 ± 0.29*
Discrimination	4.36 ± 0.90	5.75 ± 1.48	13.6 ± 2.96*	26.36 ± 3.69†

*$p < 0.01$, †$p < 0.001$ significant difference from saline on same task using a paired t-test with Bonferroni correction.

at all doses tested. Mecamylamine disrupted performance only in the 0-delay condition and, surprisingly, improved performance when delay was increased to 30 s. In the discrimination task, mecamylamine dose dependently disrupted performance while scopolamine treatment resulted in a deficit only at the highest dose tested.

The pattern of memory deficit found following scopolamine agrees with previous findings that tasks involving working memory such as alternation are disrupted (3) and confirms suggestions that muscarinic-cholinergic systems are involved in working memory performance. The present results also confirm that reference memory tasks such as T-maze discrimination are less susceptible to the deleterious effects of scopolamine but can nevertheless be disrupted if a high enough dose is given (3,31). It is difficult to attribute the disruptive effect of this high dose of scopolamine to a pure memory deficit as, at this dose, nonmnemonic effects of scopolamine on locomotor and exploratory activity become more evident and could confound interpretation. The present paradigm does not comprehensively control for this, but increased latency scores were found following the highest dose of scopolamine, which may indicate general behavioural disruption. This effect of scopolamine presents less of an interpretative problem in the case of the alternation experiment, as increased numbers of errors were seen at doses that did not affect latencies.

The pattern of disruption found following mecamylamine in the present experiments has not been reported previously. If considered separately, results from the 0-delay condition confirm the findings of Clarke and Fibiger (9) that doses up to 5 mg/kg mecamylamine do not disrupt performance of this task. Their findings are extended by the present study suggesting that a dose of 10 mg/kg may be required to induce alternation deficits when animals are tested at the same delay interval used during training. However, the present study also demonstrates that when the delay interval between forced and choice runs is increased this deficit is abolished and improved

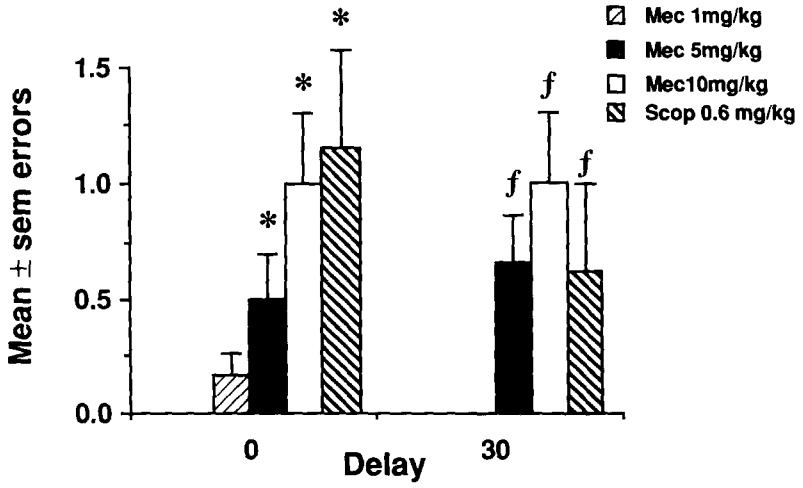

FIG. 2. Effect of mecamylamine and scopolamine (0.6-mg/kg dose only) on mean (±SEM) number of errors made in the T-maze discrimination task under either 0- or 30-s delay conditions. Mean values for saline and for 0.1- and 0.3-mg/kg treatments of scopolamine were equal to zero and therefore not shown. $n = 6$ per group. *$p < 0.05$ significant difference from saline at 0-s delay. $^{f}p < 0.05$ significant difference from saline at 30-s delay.

performance is seen. If mecamylamine disrupts working memory, as could be inferred from the 0-delay condition and from previous reports using the radial arm maze (22), then the effect of delay would have been expected to be potentiated as was found following scopolamine, rather than abolished.

This differential effect of mecamylamine in the two delay conditions of the alternation task is not easily explained. General enhancement of performance via changes in activity or arousal is unlikely because although mecamylamine increased latencies the deficit in performance in the 0-delay condition was found at the same dose (10 mg/kg) that improved performance in the 30-s delay condition. Thus, changes in activity of animals following mecamylamine at this dose would be unlikely to exert opposite effects in the two delay conditions. One possible interpretation of the decrease in errors following delay interpolation in the alternation experiment is that mecamylamine is in some way protecting against interference during the delay interval. This effect may not have been detected without placing greater demands on attentional processes such as by lengthening the delay interval between that used during training and that used during testing. How mecamylamine could exert such an effect is not clear, but it could be mediated by interactions with the central dopamine system. Interactions between dopaminergic and nicotinic systems are now well established (8), and there is strong evidence to suggest that attentional processes are subserved at least in part by the dopaminergic system (26). Dopamine antagonists such as haloperidol have been shown to improve selective attention in animals (15,28). Haloperidol has also been shown to potentiate mecamylamine-induced deficits in radial arm maze performance (27). It could therefore be possible that mecamylamine exerts similar behavioural effects to haloperidol, in this case improved attentional processes. This hypothesis would have to be tested directly as interpretation of improved alternation performance following delay interpolation in terms of an attentional process is speculative.

The finding of a deficit in a reference memory task following mecamylamine is in accordance with previous reports using a water maze paradigm (11,36). The present study extends these findings by suggesting that both egocentric reference memory as well as allocentric reference memory as measured in the water maze paradigm is disrupted by mecamylamine. A hypothesis linking mecamylamine's behavioural effects to central dopaminergic systems might also help to explain the deficit in T-maze discrimination performance found following mecamylamine in the present study. It has previously been shown that in rats egocentric reference memory is disrupted by lesioning of the caudate nucleus (10). As simple left–right discrimination in the T-maze is essentially an egocentric reference memory paradigm, a formal similarity between behavioural effects of interference with central dopamine systems and mecamylamine could again be considered.

The suggestion that mecamylamine's behavioural effects may in part be due to interactions with nonnicotinic cholinergic neurotransmitter systems is supported by the observation that the doses of mecamylamine required to disrupt or facilitate performance in memory-based tasks exceed those that are required to block central nicotinic receptors (9,11). These authors point out that mecamylamine at high doses also antagonises NMDA receptors. While such an interaction might help explain the deficits reported in the present study, it is not, however, consistent with the facilitation of performance seen following delay interpolation in the alternation task.

In conclusion, these results demonstrate a dissociation between the effects of mecamylamine and scopolamine in tasks addressing working and reference memory processes. This suggests that central nicotinic and muscarinic cholinergic systems do not play a similar role in memory processes as suggested by previous studies showing similar amnesic effects of scopolamine and mecamylamine. The high doses of mecamylamine required to produce either the deleterious or facilitatory effects found in the present study suggests that caution must be exercised in interpreting the effects of mecamylamine purely in terms of the nicotinic cholinergic system. The formal similarity between the pattern of deficits and improvements found following mecamylamine and that previously reported following lesions or antagonism of central dopaminergic systems suggests that further work should include more thorough examination of central nicotinic–dopaminergic interactions in cognitive processes.

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