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Effects of Concurrent Manipulations of Nicotinic and Muscarinic Receptors on Spatial and Passive Avoidance Learning

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RIEKKINEN, P., JR., J. SIRVIÖ, M. AALTONEN AND P. RIEKKINEN. *Effects of concurrent manipulations of nicotinic and muscarinic receptors on spatial and passive avoidance learning.* PHARMACOL BIOCHEM BEHAV **37**(3) 405–410, 1990.—The present study investigates the effects of concurrent manipulations of nicotinic and muscarinic cholinergic receptors on spatial and passive avoidance learning/retention in rats. Daily pretraining test injections of combinations of the subthreshold doses of muscarinic (scopolamine 0.3 mg/kg) and nicotinic (mecamylamine 2.5 mg/kg or 10 mg/kg) antagonists impaired acquisition of the water-maze task (WM). Drug-induced deficits were also observed during the retention trial: the groups injected with scopolamine 0.3 mg/kg, mecamylamine 10 mg/kg and scopolamine 0.3 mg/kg in combination with mecamylamine 2.5 mg/kg showed reduced spatial bias compared with controls. Single preretention test injections of the combination of subthreshold doses of mecamylamine (10 mg/kg) and scopolamine (0.8 mg/kg) impaired memory retrieval in WM. Combined pretraining injections of subthreshold doses of scopolamine (1.0 mg/kg) and mecamylamine (10 mg/kg) induced a severe passive avoidance impairment comparable to 2.0 mg/kg of scopolamine. However, preretention test injections did not impair passive avoidance retention. Either single or combined injections of hexamethonium (5.0 mg/kg, SC) and methylscopolamine (1.0 mg/kg) did not impair either passive avoidance or water-maze performance. The present results suggests that 1) nicotinic and muscarinic systems jointly modulate performance in spatial and avoidance learning tasks and 2) cholinergic antagonists affect acquisition functions more effectively than retention ability. These findings may be relevant to the clinical disorders, like Alzheimer's disease, which are associated with a loss of both cholinergic neurons and nicotinic receptors.

Scopolamine Mecamylamine Spatial learning Passive avoidance Acquisition Retention Interaction Alzheimer's disease

THERE is much evidence which suggests that central cholinergic systems are involved in the processes underlying learning and memory. Several studies have shown that learning behavior is impaired following lesions of cholinergic neurons projecting to the hippocampus or cortex (3, 4, 9, 12–14). Furthermore, one of the most widely replicated findings in psychopharmacology is that the administration of scopolamine, a muscarinic antagonist, impairs performance in several learning tasks (1, 2, 5, 6, 9, 10, 18, 19). There is also evidence which indicates that nicotinic receptors play an important role in processes underlying learning and memory. For example, mecamylamine, a nicotinic antagonist, impairs passive avoidance (2) and radial-arm maze performance (7,8).

Interestingly, combined blockade of muscarinic and nicotinic receptors has been shown to interact in greater than additive fashion in producing an anterograde amnesia in a spatial learning task (radial-arm maze) (7,8). However, the effects of combined injections of muscarinic and nicotinic antagonists on acquisition and retention of spatial reference memory or passive avoidance retention paradigms have not been extensively studied.

These issues are important, in the light of the fact that in patients with Alzheimer's disease (AD), the generalized loss of basal forebrain cholinergic projection neurons (20) may render both muscarinic and nicotinic receptors understimulated. Moreover, nicotinic receptor binding is decreased in patients with AD (21), further supporting the involvement of a nicotinic system deficit in the cognitive decline.

The aim of the present study was to elucidate the interaction between nicotinic and muscarinic receptors in the acquisition and retention of spatial reference memory (water-maze, fixed platform location) and aversively motivated avoidance (one-trial passive avoidance retention) behavioral paradigms.

METHOD

Animals

One hundred and eighty male Wistar rats were used in this study (275–310 g). The rats were housed in cages in groups of

TABLE 1

GROUPS USED IN THE PRESENT EXPERIMENTS

Experiment I: Effect of cholinergic antagonists on the acquisition of water-maze task. Drug injections were made 30 min before daily behavioral testing.

	Dose	No.	Abbreviation
Saline	—	9	C
Mecamylamine	2.5 mg/kg	7	ML
Mecamylamine	10 mg/kg	7	MH
Scopolamine	0.3 mg/kg	7	S
Mecamylamine	2.5 mg/kg	8	S+ML
+ Scopolamine	0.3 mg/kg		
Mecamylamine	10 mg/kg	8	S+MH
+ Scopolamine	0.3 mg/kg		

Experiment II: Effects of anticholinergics on the retention of water-maze task. Drug injections were made 30 min before the spatial probe trial.

	Dose	No.	Abbreviation
Saline	—	10	S
Scopolamine	0.8 mg/kg	10	S
Mecamylamine	10 mg/kg	10	M
Mecamylamine	10 mg/kg		
+ Scopolamine	0.8 mg/kg	10	M+S

Experiment III: Effects of anticholinergics on the acquisition of passive avoidance task. Drug injections were made 30 min before the training trial.

	Dose	No.	Abbreviation
Saline	—	7	C
Scopolamine	0.8 mg/kg	7	SL
Mecamylamine	10 mg/kg	7	M
Mecamylamine	10 mg/kg		
+ Scopolamine	0.8 mg/kg	7	MSL
Scopolamine	2.0 mg/kg	7	SH

Experiment IV: Effects of anticholinergics on the retention of passive avoidance task. Drug injections were made 30 min before the retention trial.

	Dose	No.	Abbreviation
Saline	—	7	C
Scopolamine	0.8 mg/kg	7	SL
Scopolamine	2.0 mg/kg	7	SH
Mecamylamine	10 mg/kg	7	M
Mecamylamine	10 mg/kg		
+ Scopolamine	0.8 mg/kg	7	MSL

Experiment V: Peripheral controls. Drug injections were made 30 min before behavioral testing.

	Dose	No.	Abbreviation
Saline	—	6	C
Hexamethonium	0.5 mg/kg	6	H
Methylscopolamine	1.0 mg/kg	6	NMS
Hexamethonium	0.5 mg/kg		
+ Methylscopolamine	1.0 mg/kg	6	HNMS

three or four animals. Room temperature was +20°C, humidity was 50–60% with a light period of 14 hours (lights on 0700–2100). Food and water were given ad lib.

Drugs

The drug treatment consisted of the muscarinic antagonist, scopolamine hydrobromide (0.3 mg/kg, 0.8 mg/kg, 2.0 mg/kg), or the nicotinic antagonist, mecamylamine hydrochloride (2.5 mg/kg or 10 mg/kg), or combinations of the two drugs. All the centrally active drugs were dissolved in 0.9% saline and injected (IP, 4 ml/kg) 30 min before behavioral testing. Saline injections in equal volume served as controls. Subcutaneous injections of hexamethonium (5 mg/kg, SC, 0.75 ml/kg, 30 min before testing) and methylscopolamine (1 mg/kg, IP, 4 ml/kg, 30 min before testing) were used for control purposes. Table 1 shows the experimental groups used in the present study (number of rats, drugs, time schedule of drug administration).

Morris Water-Maze

The water-maze pool was a circular fiberglass tank painted black, 150 cm in diameter, 74 cm deep, and filled to a height of 52 cm with water at room temperature (19 ± 1°C). The platform was made of a Plexiglas tube and the top surface was made of black rubber. The top surface was 1.5 cm below the water line. We have also tested the visibility of the platform in the pool (Sirviö *et al.*, submitted). For this purpose, two groups of rats were trained to find the submerged platform either in clear water or water with wooden chips in the surface of water. During the first day, the rats were trained 16 times. On the second day, the position of the platform was reversed, and the rats were tested 10 times. Escape latency did not differ between the two groups of rats tested (data not shown). The pool was divided into four quadrants and three annuli of equal surface area. The starting locations were called east, north, south and west and they were located arbitrarily at equal distance on the pool rim. The platform was located in the south-west quadrant in all the training trials, but was removed during the probe trial which was used to measure the distance swum in the previous training quadrant. The swim paths were monitored by a video camera linked to a computer through an image analyser. The computer calculated separately the total distance swum as well as the path lengths in all quadrants and annuli. Since the escape latency data is confounded by changes in swimming speed, the measurement of escape distance was used as an index of acquisition performance (the shorter the path lengths, the better the acquisition performance).

The rats were placed in the water with their noses pointing toward the wall at one of the four starting points that were ordered in a semirandom manner. The first swim of the day was always started from one of the points located farthest from the platform (north, east) and the starting location for the second swim of the day was a random point chosen between the south and east. Testing consisted of 7 consecutive days of training (2·80 sec trials per day) and a 50 sec probe trial on the 8th day. If the rat found the platform, it was allowed to stay there for 5 seconds. Rats that failed to find the platform within 80 seconds were placed on it for 5 seconds. A 20-second recovery period was used between the 2 daily trials. During the probe trial the platform was removed. The spatial bias was calculated as the percentage of the total distance swum in the previous training quadrant during the probe trial.

Passive Avoidance

The passive avoidance apparatus consisted of a rectangular

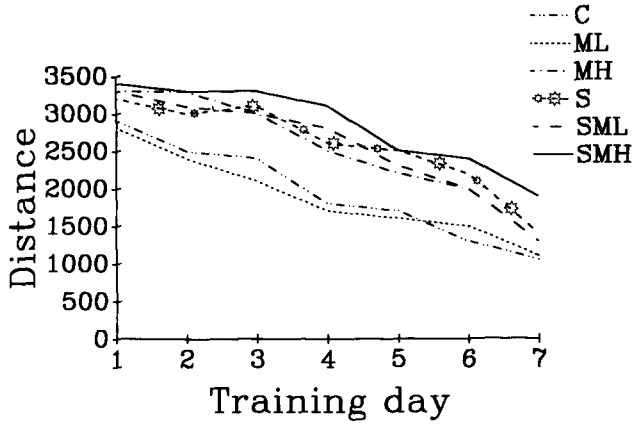

FIG. 1. Effects of chronic administration of centrally active muscarinic and nicotinic antagonist on water-maze acquisition. All the drug injections were performed 30 min before daily behavioral training. Path lengths (Y-axis, arbitrary computer units) during the training days (X-axis) of the first experiment. Scopolamine 0.3 mg/kg = S; scopolamine 0.3 mg/kg and mecamylamine 2.5 mg/kg = SML; scopolamine 0.3 mg/kg and mecamylamine 10 mg/kg = SMH.

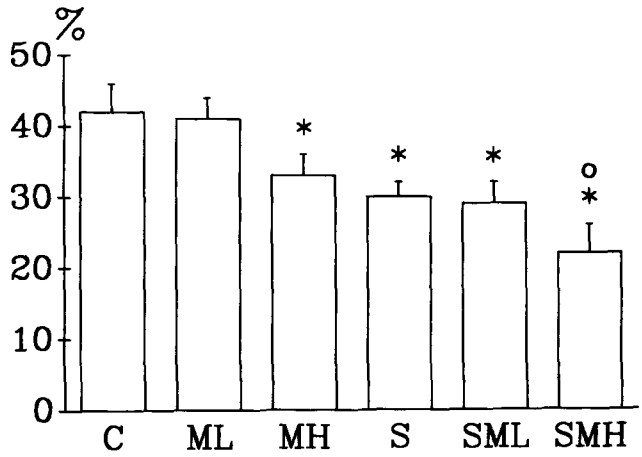

FIG. 2. Effects of chronic administration of centrally active muscarinic and nicotinic antagonist on the spatial bias [the percentage (%) of the total distance swum in the training quadrant during the spatial probe trial]. Values are expressed as mean ± SD. Duncan's post hoc multiple group comparison: *$p<0.05$ vs. controls, O*$p<0.05$ vs. all the other groups. See group abbreviations from Table 1.

Plexiglas box (length: 90 cm, length of the bright compartment: 30 cm, length of the dark compartment: 60 cm, height: 15 cm), divided into two compartments by a metal wall. One of the two compartments in the box was illuminated, the other was dark. The dark compartment had a metal grid floor. A sliding guillotine door was located in the common wall separating the two compartments.

Rats were placed in the lighted side of the passive avoidance box. After 60 sec a door opened into the dark side. The time to enter the dark chamber was measured (1st entry latency). Five sec after entry into the dark side a 1.0 mA shock was delivered to the rat's feet. The shock was maintained till the rat remained on the lighted side for 60 sec. The number of reentries was measured. Testing was done 24 hours later. The rat was put on the lighted side, and the door opened 60 sec later. The latency to enter into the dark chamber was again measured (2nd latency) The session continued until the rat entered the dark side, or remained on the lighted side for 600 sec.

Data Analysis

Passive avoidance data (1st and 2nd entry latency, number of reentries) and water-maze probe trial results (spatial bias, path length, swim speed) were analysed using one-way ANOVA, followed by a Duncan's post hoc multiple group comparison. Main group effect and group comparisons on the training trial data (path length, swim speed) were analysed with the ANOVA test.

RESULTS

Experiment I

Analysis of the path lengths of the training trials (Fig. 1) revealed a significant group effect, $F(1,643)=12.1$, $p<0.001$. The groups that were injected with scopolamine (0.3 mg/kg), $F(1,223)=4.7$, $p<0.05$, or with mecamylamine (10 mg/kg), $F(1,223)=4.0$, $p<0.05$, were impaired compared with controls. The groups receiving combined injections of scopolamine (0.3 mg/kg) and mecamylamine [2.5 mg/kg: $F(1,237)=4.5$, $p<0.05$; 10 mg/kg: $F(1,237)=8.9$, $p<0.001$] were also impaired. The swimming distances of rats injected with scopolamine (0.3 mg/kg) and high mecamylamine dose (10 mg/kg) were the longest of all the groups ($p<0.05$, in all comparisons).

The main group effect in the spatial probe test of the first experiment (Fig. 2) was significant, $F(5,40)=6.5$, $p<0.01$. The group receiving injections of mecamylamine 2.5 mg/kg was not impaired compared with controls ($p>0.05$). However, the groups that were injected with scopolamine 0.3 mg/kg and mecamylamine 10 mg/kg were more impaired than the controls ($p>0.05$ in both comparisons). The group injected with scopolamine 0.3 mg/kg in combination with mecamylamine 2.5 mg/kg also was more impaired than the controls ($p<0.05$).

In the first experiment, the main group effect in swim speed was significant, $F(1,643)=11.9$, $p<0.001$. Comparison between the groups revealed significant differences between the control group and 4 experimental groups. These 4 groups included the following ones: scopolamine 0.3 mg/kg, $F(1,223)=6.3$, $p<0.01$, alone or in combination with mecamylamine [scopolamine 0.3 mg/kg + mecamylamine 2.5 mg/kg: $F(1,237)=3.7$, $p<0.05$; scopolamine 0.3 mg/kg + mecamylamine 10 mg/kg: $F(1,237)=4.5$, $p<0.05$, and mecamylamine 10 mg/kg alone: $F(1,223)=3.1$, $p<0.05$]. No differences were found between these four groups ($p>0.1$).

Experiment II

The path length analysis revealed that the overall group effect was not significant, $F(1,559)=0.2$, $p>0.1$, and no two groups differed significantly during the training trials ($p>0.05$) (data not shown). As shown in Fig. 3, drug-induced impairments in spatial bias were observed in the second experiment. There was a significant overall group effect, $F(4,45)=4.3$, $p<0.05$. Comparison between the groups revealed that only the rats receiving a combination of mecamylamine (10 mg/kg) and scopolamine (0.8 mg/kg) were significantly impaired compared to controls ($p<0.05$). Scopolamine 0.8 mg/kg and mecamylamine 10 mg/kg did not impair retention performance ($p>0.05$).

During the probe trial the swim speeds (data not shown) of all

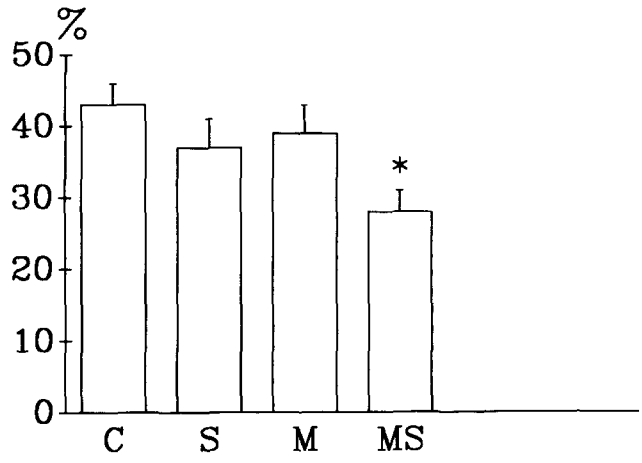

FIG. 3. Effects of preretention test injections of muscarinic and nicotinic antagonist on the spatial bias. [the percentage (%) of the total distance swum in the training quadrant during the probe trial]. The spatial bias values are expressed as mean ± SD. Duncan's post hoc multiple group comparison: *$p<0.05$ vs. controls. See group abbreviations from Table 1.

the groups injected with single or combined injections of scopolamine and mecamylamine were higher than controls [main group effect: $F(3,36)=3.2$, $p<0.05$ vs. controls]. No significant differences were detected between these groups ($p>0.05$).

Experiment III

No significant differences were observed in the passive avoidance entry latencies during the training trial between the groups of rats receiving either vehicle or test drug injections [1st entry: $F(4,30)=0.3$, $p>0.1$] (Table 2A). However, combined injections of scopolamine (0.8 mg/kg) and mecamylamine (10 mg/kg) or single injections of scopolamine 2.0 mg/kg increased the number of reentries [$F(4,30)=3.6$, $p<0.05$; $p<0.05$ in both comparisons] (Table 2A) and decreased passive avoidance retention [$F(4,30)=2.8$, $p<0.05$; $p<0.05$ in both comparisons] (Fig. 4). Scopolamine 0.8 mg/kg or mecamylamine 10.0 mg/kg did not produce any

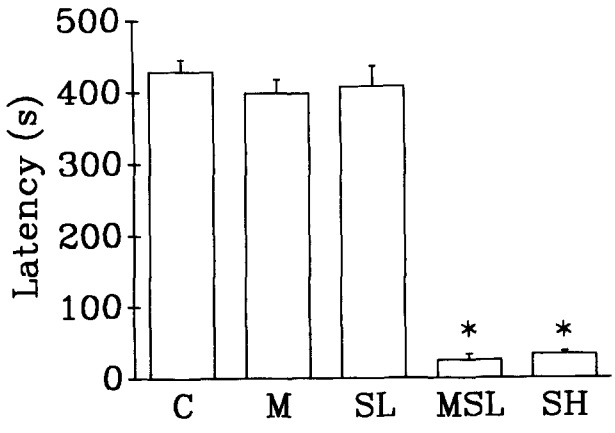

FIG. 4. Effects of centrally acting muscarinic and nicotinic antagonist on the passive avoidance retention (entry latencies, sec). Values are expressed as mean ± SD. All the injections were made before the training trial. See group abbreviations from Table 1. *$p<0.05$ vs. controls, Duncan's post hoc multiple group comparison.

TABLE 2

EFFECTS OF CENTRALLY AND PERIPHERALLY ACTING MUSCARINIC AND NICOTINIC ANTAGONIST ON THE PASSIVE AVOIDANCE ACQUISITION [LATENCY TO ENTER (SECOND, SEC) AND NUMBER OF REENTRIES]

Group	Latency (sec)	Reentries
	Part A	
C	23 ± 5	2.4 ± 0.8
SL	18 ± 8	3.0 ± 0.4
M	30 ± 9	2.2 ± 0.7
MSL	21 ± 6	6.9 ± 0.4*
SH	15 ± 10	8.4 ± 0.8*
	Part B	
C	17 ± 9	1.9 ± 0.6
H	22 ± 9	2.2 ± 0.9
NMS	25 ± 5	1.6 ± 0.7
HNMS	18 ± 7	3.0 ± 0.9

*$p<0.05$ vs. controls, Duncan's post hoc multiple group comparison.

All the drugs were injected 30 minutes before the training trial. See group abbreviations from Table 1. Values are expressed as mean ± SD.

acquisition deficits or subsequent retention deficits ($p>0.05$ in all comparisons).

Experiment IV

The analysis of the acquisition results of the second passive avoidance study showed no marked group effect [1st entry: $F(4,30)=0.1$, $p>0.1$; number of reentries: $F(4,30)=0.5$, $p>0.1$] (Table 3). Moreover, no significant overall group effects were observed in the passive avoidance entry latencies during retention trial, $F(4,30)=0.5$, $p>0.1$ (Fig. 5).

Experiment V

Analysis of passive avoidance training trial data showed no marked group effects [1st entry: $F(3,20)=0.6$, $p>0.1$; number of reentries: $F(3,20)=0.3$, $p>0.1$] (Table 2B). Moreover, no significant group effect was observed in the 2nd entry latency measured during the retention test, $F(3,20)=0.7$, $p>0.1$ (Fig. 6). No significant group effect was observed in the analysis of either path length, $F(1,335)=0.1$, $p>0.1$, and swim speed data measured during the training period, $F(1,335)=0.3$, $p>0.1$ (data not shown) or probe trial data [path length: $F(3,20)=0.4$, $p>0.1$; swim speed: $F(3,20)=0.4$, $p>0.1$; spatial bias: $F(3,20)=0.2$, $p>0.1$] (Table 4).

TABLE 3

LATENCY TO ENTER (SEC) AND NUMBER OF REENTRIES OF DIFFERENT GROUPS DURING PASSIVE AVOIDANCE TRAINING TRIAL

Group	Latency (sec)	Reentries
C	26 ± 8	2.2 ± 0.4
M	16 ± 6	2.4 ± 0.8
SL	29 ± 9	1.8 ± 0.4
MSL	33 ± 12	1.7 ± 0.8
SH	25 ± 9	2.7 ± 0.8

See group abbreviations from Table 1. All the injections were given 30 min before the retention test. Values are expressed as mean ± SD.

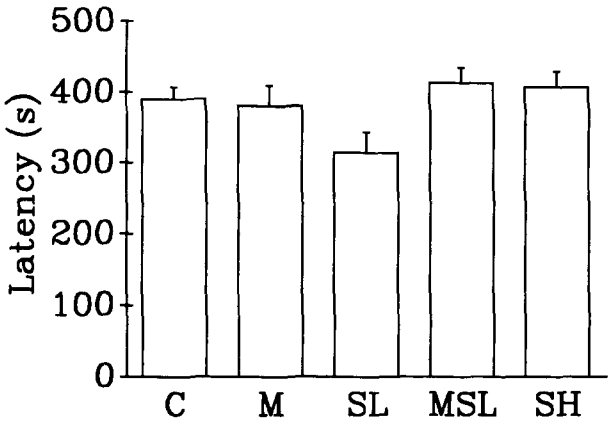

FIG. 5. Effects of peripherally acting muscarinic and nicotinic antagonist on the passive avoidance retention (entry latencies, sec). Latency values are expressed as mean ± SD. All the injections were made 30 min before the training trial. See group abbreviations from Table 1. Duncan's post hoc multiple group comparison revealed no significant differences.

TABLE 4

EFFECTS OF PERIPHERALLY ACTING MUSCARINIC AND NICOTINIC ANTAGONIST ON THE SPATIAL BIAS [THE PERCENTAGE (%) OF THE TOTAL DISTANCE SWUM IN THE PREVIOUS TRAINING QUADRANT DURING THE PROBE TEST]

Group	Spatial Bias (%)
C	31 ± 2
NMS	32 ± 3
H	32 ± 2
NMSH	33 ± 2

Values are expressed as mean ± SD. No significant group effect could be detected (Duncan's post hoc multiple group comparison). See group abbreviations from Table 1.

DISCUSSION

Our results support previous evidence revealing that muscarinic and nicotinic systems regulate performance in learning tasks (1, 2, 5–9). Furthermore, the present data corroborate previous evidence revealing additive effects between the nicotinic and muscarinic antagonists in producing anterograde amnesia in spatial learning (radial-arm maze) behavior (7,8). More importantly, our results suggest that the nicotinic-muscarinic joint modulation is important also in acquisition and retention of both spatial reference memory (water-maze) and passive avoidance (passive avoidance) paradigms. Furthermore, the results corroborate previous evidence demonstrating that the effects of anticholinergics are more pronounced on the acquisition as opposed to the performance of previously learned tasks (19) because of the following reasons: higher doses of both mecamylamine and scopolamine were required to impair retention than acquisition performance in water-maze (compare the results of Experiments 1 and 2) and, furthermore, passive avoidance behavior was impaired only by pretraining, but not by preretention test injections of muscarinic and nicotinic receptor antagonist (compare the results of Experiments 3 and 4).

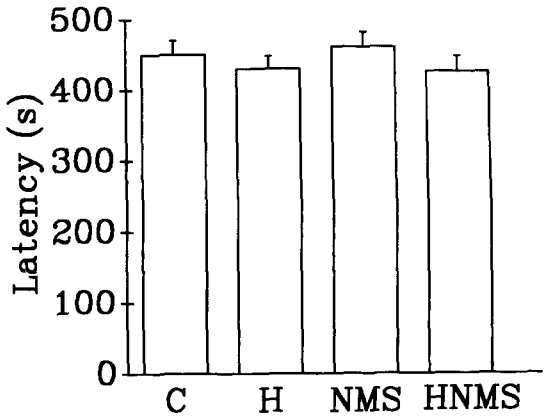

FIG. 6. Effects of centrally acting muscarinic and nicotinic antagonists on the passive avoidance retention (entry latencies, sec). Values are expressed as mean ± SD. All the injections were made before the retention test. See group abbreviations from Table 1. Duncan's post hoc multiple group comparison revealed no significant differences.

It is important to note that the peripherally acting nicotinic and muscarinic blockers did not impair performance in either water maze or passive avoidance tasks. This suggests that the scopolamine- and mecamylamine-induced effects are of central origin.

The central site of interaction between the nicotinic and muscarinic receptors is a matter for speculation, but considering the distribution of muscarinic and nicotinic receptors within the forebrain (15–17) it is reasonable to believe that both hippocampal and cortical sites may be involved in the mediation of scopolamine- and mecamylamine-induced learning and retrieval impairments of spatial and avoidance tasks (3, 4, 12–14).

Since both nicotinic and muscarinic receptors play important roles in cognitive functions (7,8), the understimulation of both of these receptor types may contribute to the cognitive deficits observed in AD. Furthermore, the involvement of nicotinic receptors in AD is supported by the work revealing decreased nicotinic binding in patients with AD (21). Scopolamine-induced amnesia as a model for the age- and AD-related cholinergic deficit and cognitive decline has recently come under criticism (6). Therefore, it is important to note that the concurrent nicotinic-muscarinic blockade may possibly provide a better pharmacological model for testing the effectiveness of drugs aimed at alleviating cognitive deficits induced by generalized cholinergic underactivation. Indeed, Levin *et al.* (8) have shown that radial-arm maze amnesia induced by combined nicotinic and muscarinic blockade is attenuated by D2 agonist. However, the D1 antagonist drug reversed scopolamine-induced amnesia, but not performance deficit induced by combined muscarinic and nicotinic blockade (8).

In conclusion, the present study provides new evidence supporting the interaction of nicotinic and muscarinic receptors in regulation of performance in spatial and passive avoidance learning tasks. Furthermore, our data corroborate previous evidence suggesting that cholinergic antagonists affect acquisition processes more strongly than retention performance.

REFERENCES

1. Buresova, O.; Bolhuis, J. J.; Bures, J. Differential effects of cholinergic blockade on performance of rats in the water tank navigation task and in a radial water maze. Behav. Neurosci. 100:476–482; 1986.
2. Dilts, S. L.; Perry, C. A. Effects of cholinergic drugs on passive avoidance in the mouse. J. Pharmacol. Exp. Ther. 158:279–285; 1967.
3. Dunnett, S. B.; Low, W. C.; Iversen, S. D.; Stenevi, U.; Björklund, A. Septal transplants restore maze learning in rats with fimbria-fornix lesions. Brain Res. 251:335–348; 1982.
4. Dunnett, S. B.; Whishaw, I. Q.; Jones, G. H.; Bunch, S. T. Behavioural, biochemical and histochemical effects of different neurotoxic amino acids injected into nucleus basalis magnocellularis of rats. Neuroscience 20:653–669; 1987.
5. Eckerman, D. A.; Winford, A. G.; Edwards, J. D.; Macphail, R. C.; Gage, M. I. Effects of scopolamine, pentobarbital and amphetamine on radial arm maze performance in the rat. Pharmacol. Biochem. Behav. 12:595–602; 1980.
6. Flood, J.; Cherkin, A. Scopolamine effects on memory retention on mice: A model of dementia? Behav. Neural Biol. 45:169–184; 1986.
7. Levin, E. D.; McGurk, S.; South, D.; Butcher, L. Effects of combined muscarinic and nicotinic blockade on choice-accuracy in the radial arm maze. Behav. Neural Biol. 51:270–277; 1989.
8. Levin, E. D.; Rose, J. D.; McGurk, S. R.; Butcher, L. Characterization of the cognitive effects of combined muscarinic and nicotinic blockade. Behav. Neural Biol. 53:103–113; 1990.
9. Longo, V. G. Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacol. Rev. 18:965–995; 1966.
10. Okaichi, H.; Jarrard, L. E. Scopolamine impairs performance of a place and cue task in rats. Behav. Neural Biol. 35:319–325; 1982.
11. Perry, E. K.; Tomlinson, B. E.; Blessed, G.; Bergman, K.; Gibson, P. H.; Perry, R. H. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br. Med. J. 2:1457–1459; 1978.
12. Riekkinen, P., Jr.; Sirviö, J.; Riekkinen, P. Similar memory impairments found in medial septal-vertical diagonal band of Broca and nucleus basalis lesioned rats: are memory defects induced by nucleus basalis lesions related to the degree of non-specific subcortical cell loss? Behav. Brain Res. 37:81–88; 1990.
13. Riekkinen, P., Jr.; Sirviö, J.; Miettinen, R.; Riekkinen, P. Effects of quisqualic acid nucleus basalis lesioning on cortical EEG, passive avoidance and spatial learning. Brain Res. Bull. 25:147–149; 1990.
14. Riekkinen, P., Jr.; Sirviö, J.; Riekkinen, P. The effects of THA on medial septal lesion-induced spatial memory defects. Pharmacol. Biochem. Behav. 36:237–241; 1990.
15. Spencer, D. G.; Horvath, E.; Traber, J. Coupled (high affinity) and uncoupled (low affinity) M_2 muscarinic receptor distributions in rat brain are identical but distinct from M_1 receptor distributions. Neurosci. Lett. 22:S182; 1985.
16. Swanson, L. W.; Simmons, D. M.; Whiting, P. J.; Lindstrom, J. Immunohistochemical localization of neuronal nicotinic receptors in the rodent central nervous system. J. Neurosci. 7:10:3334–3342; 1987.
17. Wamsley, J. K.; Gehlert, D. R.; Roeske, W. R.; Yamamura, H. I. Muscarinic antagonist binding site heterogeneity as evidenced by autoradiography after direct labelling with (^{3}H)QNB and (^{3}H)pirenzepine. Life Sci. 34:1395–1402; 1984.
18. Watts, J.; Stevens, R.; Robinson, C. Effects of scopolamine on radial maze performance in rats. Physiol. Behav. 26:845–851; 1981.
19. Whishaw, I. Q.; O'Connor, W. T.; Dunnett, S. B. Disruption of central cholinergic systems in the rat by basal forebrain lesions and atropine: Effects on feeding, sensorimotor behavior, locomotor activity and spatial navigation. Behav. Brain Res. 17:103–115; 1985.
20. Whitehouse, P. J.; Price, D. L.; Struble, R. G.; Clark, A. W.; Coyle, J. T.; DeLong, R. M. Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. Science 215:1237–1239; 1982.
21. Whitehouse, P. J.; Martino, A. M.; Antuono, P. G.; Lowenstein, P. R.; Coyle, J. T.; Price, D. L.; Kellar, K. J. Nicotinic acetylcholine binding sites in Alzheimer's disease. Brain Res. 371:146–151; 1986.