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Are the Cognitive-Enhancing Effects of Nicotine in the Rat With Lesions to the Forebrain Cholinergic Projection System Mediated by an Interaction With the Noradrenergic System?

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GRIGORYAN, G. A., S. N. MITCHELL, H. HODGES, J. D. SINDEN AND J. A. GRAY. *Are the cognitive-enhancing effects of nicotine in the rat with lesions to the forebrain cholinergic projection system mediated by an interaction with the noradrenergic system?* PHARMACOL BIOCHEM BEHAV **49**(3) 511-521, 1994.—Experiments were conducted to test the hypothesis that the enhancing effect of nicotine on water maze performance in rats with lesions of the forebrain cholinergic projection systems (FCPS) is mediated by an interaction with the noradrenergic system, in particular the ascending dorsal noradrenergic bundle (DNAB) and its projection areas. Three groups of rats received lesions of either: i) the nucleus basalis (NBM) and medial septal area/diagonal band (MSA/DB) by infusion of α-amino-3-hydroxy-4-izoxazole propionic acid (AMPA) (FCPS group), ii) DNAB, by infusion of 6-hydroxydopamine (6-OHDA) (NOR group), or iii) both FCPS plus DNAB (COMB group). Control animals received vehicle. Choline acetyltransferase activity was reduced in the cortex and hippocampus of the FCPS and COMB groups and in the hippocampus of the NOR group. NA level was reduced in the cortex and hippocampus of the FCPS and COMB groups, but not the FCPS group. In a reference memory task, the performance of both the NOR and COMB groups, but not the NOR group, was significantly worse than that of controls; there was no effect of nicotine administration (0.1 mg/kg) on escape latency or other measures in this task. In a working memory task, FCPS and COMB rats took longer to find the submerged platform on the second and following trials, and there was a significant enhancement of performance by nicotine in both groups, but not in controls. These results indicate that the enhancing effects of nicotine in rats with FCPS lesions are not mediated by an interaction with the DNAB.

Water maze Interaction Cholinergic Noradrenergic Lesion Nicotine

LESIONS to the nucleus basalis magnocelullaris (NBM) and medial septal area/nucleus of the diagonal band (MSA/DB) in rats produce memory deficits in a number of tasks (1,3, 8,16,21,28,29,33,39,42,43). Acute systemic nicotine administration has been reported to improve performance in such cognitively impaired animals (14,22,23,48,51). Because nicotine also increases noradrenaline (NA) release in terminal areas of the ascending dorsal noradrenergic bundle (DNAB) (4,34,35), it has been suggested that the cognitive-enhancing effects of nicotine in animals with lesions to the forebrain cholinergic projection system (FCPS) might be mediated by interaction with the noradrenergic system. There is indeed evidence that the noradrenergic system has an important regulatory role in such cognitive processes as learning and memory (2,6,7,15,44), although data opposing this point of view have been also reported (5,19,41,50,55).

Nicotine may also affect performance in FCPS-lesioned animals by interaction of released NA with the residual cholin-

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ergic system. Such an interaction has been demonstrated in a number of electrophysiological (25,54), biochemical (10), and behavioural experiments (11–13,30–32). In most of these studies, the interaction between the noradrenergic and cholinergic systems was synergistic (11–13,20,24,27,30,31). For instance, NA depletion produced by intracerebral injection of the catecholamine-specific neurotoxin, 6-hydroxydopamine (6-OHDA), blocked the catalepsy induced by cholinergic agonists and enhanced the locomotor stimulation caused by anticholinergic drugs (30,31). Deficits in the radial-arm maze (11) and retention of spatial learning in the water maze (12), induced by treatment with the cholinergic antagonist scopolamine, were even more marked in NA-depleted animals than in unoperated control groups. Only combined administration of scopolamine (0.3 mg/kg) and the β-adrenergic antagonist, propranolol (10 mg/kg), has been found to impair performance of spatial memory, but not administration of either scopolamine or propranolol alone (13).

However, there is also evidence to suggest that interactions between noradrenergic and cholinergic systems are either antagonistic or nonexistant (9,36). For example, two research groups have shown that rats with combined noradrenergic and cholinergic lesions perform significantly better in a Morris water maze task than rats with cholinergic lesion alone. Other workers (47) have reported only slight impairments in delayed matching or nonmatching to position tasks following combined lesions of the DNAB and the NBM.

We have previously reported (23) that systemic nicotine ameliorates the performance deficits of FCPS-lesioned rats in the Morris water maze. To examine whether this cognitive-enhancing effect of nicotine in cholinergic-lesioned animals is mediated indirectly by the release of NA, and to examine noradrenergic/cholinergic interactions in these effects of nicotine, the present experiments compared the effect of nicotine on performance in the water maze of animals with FCPS and/or DNAB lesions.

METHOD

Subjects

Eighty-eight male Sprague–Dawley rats were used (Bantin and Kingman Universal Ltd, Hull, England), weighing 250–300 g on arrival. They were housed five to a cage (RC2, North Kent Plastic Cages) and maintained on a 14 L : 10 D cycle (lights off at 2100 h) with free access to food and water.

Surgery

The rats were anesthetized with 3.0 ml/kg equithesin and placed in a stereotaxic instrument. The scalp was incised and retracted, holes were drilled in the appropriate locations, and the lesions were made as follows.

Forebrain cholinergic projection system (FCPS, $n = 22$) lesions of the NBM and MSA/DB were made bilaterally with α-amino-3-hydroxy-4-izoxazole propionic acid (AMPA, Tocris Neuramin, UK; 1.49 μg/μl in phosphate-buffered saline), injected with a microject pump (Bioinvent, Sweden) from a Hamilton microsyringe. The coordinates for the NBM lesions were: AP (anterior-posterior from bregma) +1.0 mm, L (lateral from midline) ±2.6 mm, V (ventral from dura) −7.5 mm; and AP +0.2 mm, L ±3.2 mm, V −7.0 mm; with the incisor bar at 5° above the interaural plane (injection volume 0.2 μl at each site). The coordinates for the MSA/DB lesions were: AP +0.4 mm, L ±0.4 mm, V −7.2 mm, −7.0 mm, and −6.8 mm (injection volume 0.03 μl); and AP +0.4 mm, L 0.0 mm, V −6.5 mm, −6.0 mm, and −5.8 mm (injection volume 0.05 μl); with a horizontal skull. The injections lasted 2 min and the cannula was held in place for an additional 2 min to allow the toxin to diffuse into the tissue.

Noradrenergic (NOR, $n = 12$) lesions were produced bilaterally by 6-OHDA (Sigma, UK; 6.0 mg/kg in 0.9% saline and 0.4 mg/ml ascorbic acid) injected into the DNAB at the coordinates: AP −5.2 mm, L ±1.1 mm, V −5.3 mm; horizontal skull, injection volume 1.5 μl in each site, injection duration 3 min.

Combined (COMB, $n = 22$) bilateral lesions included FCPS (NBM and MSA/DB) and DNAB. First, FCPS lesions were made with AMPA. Two weeks later, to allow time for recovery from surgery, lesions of the DNAB were produced by injection of 6-OHDA. This two-stage procedure was adopted to reduce the risk of mortality or seizures that we have found to occur in up to 35% of animals given simultaneous lesions (John Turner, unpublished findings).

Control (CON) rats received the same surgical treatment as the lesioned rats, but the injections were made with phosphate-buffered saline into the FCPS ($n = 10$), ascorbic acid into the DNAB ($n = 12$), or both injections ($n = 10$). These controls are separately reported as CON_1 (comprising FCPS and COMB vehicle groups; as there were no significant differences between either of these control groups on any behavioural or neurochemical measures, these two groups were combined) and CON_2 (DNAB injections) for comparisons with the appropriate lesioned groups. The FCPS, COMB, and CON_1 groups were run together (Experiment 1), followed 2 months later by the NOR and CON_2 groups (Experiment 2). The two experiments were performed with separate batches of rats, from the same supplier. Allocation to lesion and drug condition was random within each experiment.

Postoperative care followed established national (Animal Scientific Procedures Act, 1986) and local guidelines for animal welfare. For example, after surgery the rats were moved to a recovery room and were housed singly (cage RB3) for 7 days to monitor recovery. They were weighed daily, food and water intake was noted, and excretion, urination, and general appearance were checked. The rats were then rehoused in groups of five. After a week they were returned to their home cages, and behavioural testing commenced.

Apparatus

Experiments were conducted in a Morris (38) water maze. The water maze was a circular, black-plastic tank (2 m diameter, 500 mm high), filled with water (at 22–24°C) to a depth of 250 mm. A platform made of Plexiglas tube (100 mm diameter) was placed in the tank. A small amount of milk was added to the water to render the platform invisible. The top of the platform was 20 mm below the water surface. The maze was conceptually divided into three concentric circles (annuli) and four quadrants (40). The platform was centrally located in one of these quadrants within one of these annuli. Four start positions, designated N, S, E, and W, were used in different orders. Objects around the room (posters, diffuse light from windows with blinds, TV monitors, and the experimenter who always returned to the same location after placing animals in the pool) provided extramaze cues for navigation. Inspection of distribution of time in the quadrants over many experiments has provided evidence that rats use these cues to direct their escape. The quadrant most frequented by naive animals is always Quad 3, nearest to the experimenter, and the least visited sector is the minimal cue Quad 2, where the adja-

cent walls are featureless. We have shown (23) that animals with FCPS lesions are particularly disadvantaged if the platform is placed in Quad 2.

Rats were placed in the pool, facing the wall, and allowed to swim for 1 min. If they found the platform within this time, they were allowed to remain there for 10 s; if they failed to find the platform, they were guided to and placed on it for 10 s. After 10 s on the platform the rats were removed either to the holding cage or, after being towelled dry, to the home cage.

The swim path was recorded by an HVS image analysing system (VP112, HVS Image Ltd., Hampton, England). Latency to reach the platform, distance swum, speed (measured as distance swum divided by latency), heading angle (a measure of divergence from the direct path to the platform), and time spent in each quadrant and in each annulus (40) were calculated and saved on disk.

Drug Treatment

Animals were randomly allocated into two groups (to receive saline or nicotine, respectively) within each lesion condition. In Experiment 1, 15 min before each training day in both the reference and working memory tasks (see below), three groups of animals (CON_1-saline, $n = 10$; FCPS-saline, $n = 11$; and COMB-saline, $n = 11$) received an injection of saline (0.9% NaCl, 1.0 ml/kg, SC) and another three groups of rats (CON_1-nicotine, $n = 10$; FCPS-nicotine, $n = 11$; COMB-nicotine, $n = 11$) received an injection of nicotine [(−)nicotine hydrogen tartrate, 0.1 mg/kg (base) in 1.0 ml/kg 0.9% NaCl, SC]. In Experiment 2, all rats were first run in the reference memory task without drug treatment (because no effects of nicotine had been seen in this task in Experiment 1). They were then assigned to two groups within each lesion condition (six rats in each): CON_2-saline and NOR-saline received injections of saline, whereas CON_2-nicotine and NOR-nicotine received injections of nicotine (as above) 15 min before training each day.

Behavioural Procedure

Rats were tested first in the reference memory task, followed immediately by the working memory task.

In the reference memory task, the rats were allowed first to swim for 1 min in the pool with the platform removed (habituation trial). Then they were trained with two trials a day (10-min intertrial interval: ITI) for 15 days using the S and E start positions in reversed order on each day and the platform in the same (NW: Quad 4) location. On day 16 the platform was removed and retention of the platform position was tested in a 1-min probe trial started at the S position.

In the working memory task, the rats were given four trials (S, N, E, W start positions) a day with a 30-s ITI. Rats were run for 5 days with a new platform location and different random order of start positions on each day.

Data Analysis

The data from Experiments 1 (FCPS, COMB, and CON_1 groups) and 2 (NOR and CON_2 groups) were analysed separately, each by a split plot analysis of variance (ANOVA) using GENSTAT (Rothamsted, England). The between-subjects factors were drug (nicotine vs. saline) and lesion; days and trials were within-subjects factors. Separate analyses were conducted for each performance parameter (latency to find the hidden platform, swim path length, percent time spent in each quadrant/annulus, heading angle). Means, and linear and quadratic coefficients (of trends in the days × lesion interaction) were compared using the Newman-Keuls test and the t ratio, based on the appropriate error terms in the ANOVAs. Use of orthogonal polynomials in the analysis of trends allowed us to compare, among the different treatment groups, both the rate of learning and achievement of asymptotic performance over days or trials.

Neurochemical Determinations

Two weeks after behavioural testing was completed, the rats were killed by decapitation and their brains were removed. Sections of the frontal cortex and hippocampus (ca. 30 mg) were dissected from each hemisphere and weighed. All samples were frozen in liquid nitrogen and stored at −70°C until required for assay by high performance liquid chromatography (HPLC) to assess level of noradrenaline concentration and enzymic assay to assess level of choline acetyltransferase (ChAT) activity.

ChAT activity. The samples of 50 rats were used for measurement of the ChAT activity (the samples of 10 rats were spoiled and samples of four rats were lost). ChAT activity was assessed by measuring (in duplicate) the rate of formation of acetylcholine ([^{14}C]ACh) from [^{14}C]acetyl coenzyme A by a method derived from Fonnum (17). Samples were homogenized in 1% NP-40 (Sigma) in phosphate buffer (pH 7.4) using 8.3 μl/mg tissue wet weight. Tissue homogenate (10 μl) was incubated in duplicate at 37°C with 10 μl incubation medium containing 0.75 M NaCl, 135 mM NaH_2PO_4, pH 7.4, 20 mM choline, 50 mM ethylenediaminetetracetic acid (EDTA), 1 mM acetyl coenzyme A, 0.4 mA physostigmine sulphate, and 10 μl of 2 μCi[^{14}C]acetyl coenzyme A (New England Nuclear). Incubation was for 5 min and was stopped with 5 ml of cold 10 mM NaH_2PO_4, pH 7.4. [^{14}C]ACh was extracted with acetonitrile containing 20 mg/ml tetraphenylboron and counted in a PPO-POPOP toluene scintillant. Tissue- and incubation-zero controls produced low values both at the beginning and end of each assay.

HPLC with electrochemical detection. Samples of 57 rats (samples of four rats were lost) were sonicated in 500 μl 0.1 M perchloric acid (containing 1 mM EDTA) and centrifuged at 13,000 × g for 10 min at 4°C. Supernatants were decanted, frozen in liquid nitrogen, and stored at −70°C.

The HPLC system consisted of an ACS 351 series pump (ACS Ltd.) and an on-line degassor (ERMA, Inc.) coupled to a Chromspher C18 cartridge column (5 μm particle size; 10 cm in length, 3 mm internal diameter) protected by a guard column and saturation precolumn (Chrompack UK Ltd.). Detection was accomplished with an LC4-A detector (BAS, Inc.); working electrode was maintained at +0.75 V with respect to an Ag/AgCl reference electrode. The mobile phase consisted of a 0.1 M citrate/0.2 M phosphate buffer containing 1.5 mM octane sulphonic acid, 1 mM EDTA, and 12% methanol, pH 2.70; flow rate was 0.6 ml/min. Peaks were displayed, integrated, and stored using a Shimadzu CR-3A coupled to an FDD-1A disk drive (Dyson Instruments, Ltd.).

RESULTS

Neurochemical Results

Means and SEs for all the neurochemical measures are presented in Table 1 for ChAT and Table 2 for NA. As shown in these tables, there were differences between the CON_1 and CON_2 groups in both frontal cortex and hippocampus for ChAT and in frontal cortex for NA; however, lesion effects

TABLE 1

ChAT ACTIVITY IN THE FRONTAL CORTEX AND HIPPOCAMPUS IN THE LESIONED AND CONTROL GROUPS

	Frontal Cortex	Hippocamus
Groups	CON_1 532 ± 37.8	852 ± 57.7
(df = 2, 47)	FCPS 319 ± 37.8	547 ± 57.7
	COMB 269 ± 37.8	450 ± 57.7
	$F = 24.73, p < 0.001$	$F = 24.48, p < 0.001$
CON_1 vs. FCPS	$t = 5.63, p < 0.001$	$t = 5.28, p < 0.001$
CON_1 vs. COMB	$t = 6.95, p < 0.001$	$t = 6.96, p < 0.001$
FCPS vs. COMB	NS	NS
Groups	CON_2 406 ± 35.1	449 ± 31.2
(df = 1, 22)	NOR 375 ± 35.1	356 ± 31.2
	NS	$F = 8.9, p < 0.01$
Groups	CON_1 532 ± 48.3	852 ± 51.48
	CON_2 406 ± 48.3	449 ± 51.48
	$F = 6.83, p < 0.05$	$F = 51.48, p < 0.001$

Data were analysed by ANOVA followed by a t-test for a comparison of means. They are expressed in pmol/min/mg wet weight and represent the mean ± SEM. NS, nonsignificant value of groups comparison.

were statistically evaluated (Tables 1 and 2) against each control group within the two experiments.

ChAT activity. ChAT was significantly decreased ($p < 0.001$; Table 1) in the frontal cortex in the FCPS (by 40% vs. CON_1) and COMB (50%) groups. The ChAT loss in the hippocampus for these groups was 36% and 47% ($p < 0.001$) relative to the CON_1 group. The FCPS and COMB groups did not differ significantly on these measurements. There was no significant difference between the NOR group and CON_2 animals in ChAT activity in the frontal cortex; but, unexpectedly, the difference between these two groups was significant ($p < 0.01$) in the hippocampus, ChAT being decreased by the DNAB lesion (by 20% vs. CON_2).

Noradrenaline levels. For both brain areas, ANOVA revealed significant effects of the lesions (Table 2) on levels of NA. These effects were due to significant (t-test, $p < 0.0001$) reductions in NA in both COMB (for hippocampus, by 92.4% vs. CON_1, 92.3% vs. FCPS; for frontal cortex, 91.5% vs. CON_1, 91.9% vs. FCPS) and NOR groups (for hippocampus, 94.6%; for frontal cortex, 92.8%; both vs. CON_2).

TABLE 2

LEVELS OF NORADRENALINE IN THE FRONTAL CORTEX AND HIPPOCAMPUS IN THE LESIONED AND CONTROL GROUPS

	Frontal Cortex	Hippocampus
Groups	CON_1 384.9 ± 10.2	CON_1 385.8 ± 15.7
(df = 2, 57)	FCPS 409.6 ± 20.0	375.5 ± 15.6
	COMB 32.8 ± 3.2	29.9 ± 5.1
	$F = 243.8, p < 0.0001$	$F = 238.1, p < 0.0001$
CON_1 vs. FCPS	NS	NS
CON_1 vs. COMB	$t = 5.82, p < 0.0001$	$t = 6.05, p < 0.0001$
FCPS vs. COMB	$t = 6.23, p < 0.0001$	$t = 5.91, p < 0.0001$
Groups	CON_2 283.6 ± 10.9	410.8 ± 13.0
(df = 1, 22)	NOR 20.9 ± 1.6	22.11 ± 1.2
	$F = 290.4, p < 0.0001$	$F = 511.8, p < 0.0001$
Groups	CON_1 384.9 ± 10.2	385.8 ± 15.7
	CON_2 283.6 ± 10.9	410.2 ± 13.0
	$t = 6.07, p < 0.001$	NS

Data were analysed by ANOVA followed by a t-test for a comparison of means. They are expressed in ng/g tissue wet weight and represent the mean ± SEM. NS, nonsignificant value of groups comparison.

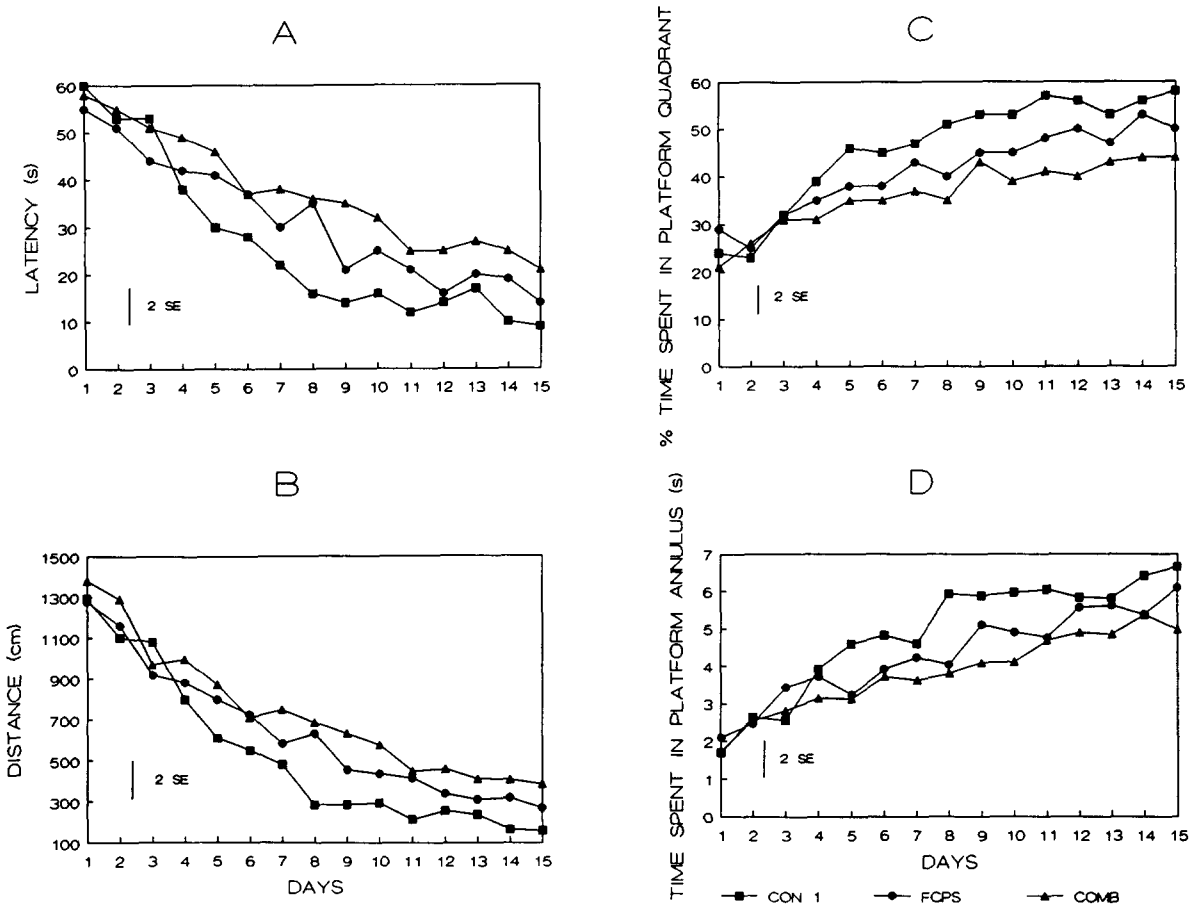

FIG. 1. Effects of FCPS and combined (COMB: FCPS + DNAB) lesions on water maze performance (reference memory task). COMB- and FCPS-lesioned animals learned the task significantly slower than controls (CON 1) on escape latency (A), swim path length (B), time spent in the platform quadrant (C), and time spent in the platform annulus (D). SEM derived from the ANOVA for the lesion × days interaction.

Reference Memory Task

Figure 1 shows that the FCPS- and COMB-lesioned groups were both impaired in learning the location of the hidden platform compared to the control group. They had longer latencies to reach the safe platform (Fig. 1A), showed an increased swim path length (Fig. 1B), and spent less time in the platform quadrant (Fig. 1C) and annulus (Fig. 1D) than controls. These overall effects were significant in the COMB-lesioned group, as shown by substantial differences from controls (see Table 3), contributing to significant main effects of lesion in all four measures. The FCPS group was not as impaired as the COMB group, and did not differ overall from the controls' level of performance. However, the effects of double lesion were not additive, as there were no differences between the two lesion groups on any measure, so that although the COMB group was significantly impaired relative to controls, it was not significantly worse than the FCPS group.

Significant days × lesion interactions, with both linear and quadratic components, demonstrated differences in learning rates for the two lesion groups relative to controls (Table 3). As seen from Fig. 1 and Table 3, the FCPS and COMB groups deviated from the rapid initial phase of learning shown by controls (the linear component) and were slower than controls to level off at asymtotic performance (the quadratic component). Although the COMB group showed larger differences than the FCPS group in comparison with controls, evidence for an impaired rate of learning in the FCPS group in terms of trend interactions was robust (Table 3) and the two lesion groups did not differ. There was no overall Lesion effect on swim speed (i.e., distance swum/escape latency), suggesting that the differences in performance of control and lesioned groups were not likely to reflect motor or motivational effects.

The data from Experiment 2 (NOR vs. CON_2 groups) are shown in Fig. 2. This figure shows that lesion effects were apparent mainly during the first 5 days of training. The data were therefore analysed both for the entire 12 days of training and separately for the first 5 and final 7 days; the results of these analyses are presented in Table 4.

The largest effect of the lesion was seen in the escape latency data during the first 5 days of training (Fig. 2A), when the NOR group was significantly slower. This effect disappeared during the final 7 days. Furthermore, it may well have been secondary to a reduced speed in the NOR group, also significant over the first 5 days. There was no significant effect of the lesion upon distance swum (Fig. 2B); the apparent in-

TABLE 3

THE ANOVA RESULTS FOR WATER MAZE PERFORMANCE PARAMETERS IN FCPS- AND COMB-LESIONED AND CONTROL ANIMALS IN THE REFERENCE MEMORY TASK

	Latency	Distance	Time Spent in Platform Quadrant	Time Spent in Platform Annulus
Lesion effect (df = 2, 61)	$F = 6.39, p < 0.005$	$F = 4.21, p < 0.025$	$F = 6.59, p < 0.005$	$F = 4.79, p < 0.025$
CON_1 vs. FCPS	NS	NS	NS	NS
CON_1 vs. COMB	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
FCPS vs. COMB	NS	NS	NS	NS
Lesion × days (df = 28, 868)	$F = 2.52, p < 0.005$	NS	$F = 1.92, p < 0.005$	$F = 2.52, p < 0.005$
Lin. Dev. (df = 2, 868)	$F = 7.87, p < 0.005$	NS	$F = 11.57, p < 0.005$	$F = 8.75, p < 0.005$
CON_1 vs. FCPS	$t = 2.68, p < 0.01$		$t = 2.92, p < 0.005$	$t = 2.83, p < 0.01$
CON_1 vs. COMB	$t = 3.76, p < 0.001$		$t = 4.63, p < 0.001$	$t = 4.17, p < 0.001$
FCPS vs. COMB	NS		NS	NS
Quad. Dev. (df = 2, 868)	$F = 12.32, p < 0.005$	$F = 4.56, p < 0.025$	$F = 7.09, p < 0.005$	$F = 7.86, p < 0.005$
CON_1 vs. FCPS	$t = 3.95, p < 0.001$	$t = 2.64, p < 0.01$	$t = 6.5, p < 0.001$	$t = 3.48, p < 0.001$
CON_1 vs. COMB	$t = 4.47, p < 0.001$	$t = 2.5, p < 0.02$	$t = 7.16, p < 0.001$	$t = 3.53, p < 0.001$
FCPS vs. COMB	NS	NS	NS	NS

Comparisons of means were made by the Newman-Keuls test. NS, nonsignificant value of groups comparison. Lin. Dev. and Quad. Dev.: linear and quadratic components of the lesion × days interaction.

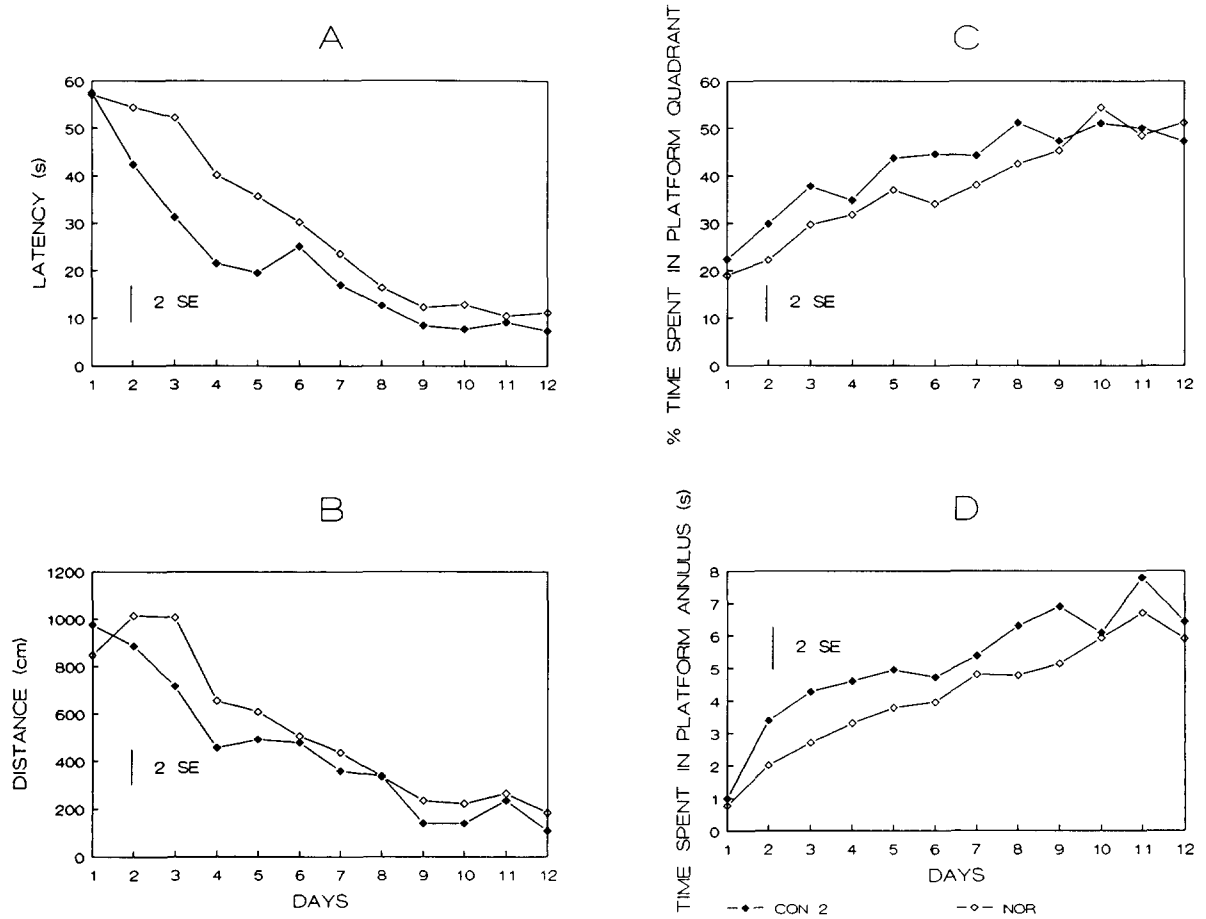

FIG. 2. Effects of the noradrenergic lesion caused by 6-OHDA administration to the DNAB on the water maze performance (reference memory task). NA depletion increased an escape latency (A) and distance swum (B) in NOR group relative to controls (CON 2), but this occurred due to a decrease of swimming speed in NOR group. (C,D) Time spent in the platform quadrant/annulus. SEM derived from the ANOVA for the lesion × days interaction.

TABLE 4

THE ANOVA RESULTS FOR THE WATER MAZE PERFORMANCE PARAMETERS IN NOR-LESIONED AND CONTROL ANIMALS IN THE REFERENCE MEMORY TASK

	Latency	Distance	Time Spent in Platform Quadrant	Speed
Lesion effect				
All 12 days (df = 1, 22)	$F = 10.0, p < 0.005$	NS	NS	NS
First 5 days (df = 1, 22)	$F = 10.44, p < 0.005$	NS	NS	$F = 9.85, p < 0.005$
Last 7 days (df = 1, 22)	NS	NS	NS	NS
Lesion × Days				
All 12 days (df = 11, 242)	$F = 2.56, p < 0.005$	NS	NS	$F = 3.66, p < 0.001$
First 5 days (df = 4, 88)	$F = 2.68, p < 0.05$	NS	NS	$F = 6.20, p < 0.001$
Last 7 days (df = 6, 132)	NS	NS	NS	$F = 2.76, p < 0.025$
Lin. Dev.				
All 12 days (df = 1, 242)	$F = 6.56, p < 0.025$	NS	$F = 4.73, p < 0.05$	$F = 5.64, p < 0.05$
First 5 days (df = 1, 88)	$F = 5.93, p < 0.025$	NS	NS	$F = 15.97, p < 0.001$
Last 7 days (df = 1, 132)	NS	NS	$F = 8.73, p < 0.005$	NS
Quad. Dev.				
All 12 days (df = 1, 242)	NS	NS	F = 3.85, $p < 0.05$	F = 8.63, $p < 0.005$
First 5 days (df = 1, 88)	$F = 4.53, p < 0.05$	$F = 5.75, p < 0.02$	NS	$F = 4.71, p < 0.05$
Last 7 days (df = 1, 88)	NS	NS	NS	NS

NS, nonsignificant value of groups comparison. Lin. Dev. and Quad. Dev.: linear and quadratic components of the lesion × days interaction.

crease in the NOR group during the first 5 days did not reach significance ($p > 0.05$). The only clear indication, therefore, of an effect of the DNAB lesion upon learning was for time in the platform quadrant (Fig. 2C): both the linear (12- and final 7-day analyses) and quadratic (12-day analysis) coefficients of the lesion × days effects indicated that the NOR group was slower to attain asymptotic performance than the controls. However, the groups did not differ at asymptote. There were no significant lesion × days effects upon time spent in the platform annulus (Fig. 2D).

There were no significant effects of nicotine upon any reference memory measure [e.g., for escape latency: $F(1, 61) = 2.2$, for drug effect; $F(2, 61) = 0.8$, for lesion × drug interaction; $F(28, 868) = 1.02$, for days × lesion × drug interaction].

Working Memory Task

The FCPS- and COMB-lesioned rats took more time to find the platform and had greater swim path length than controls (Fig. 3 and Table 5); the FCPS- and COMB-lesioned groups did not differ significantly from each other ($t = 0.34$ for escape latency; $t = 0.07$ for distance swum). In neither case was there a significant lesion × trials interaction. However, it is clear from Fig. 3A that, with regard to escape latency, the overall lesion effect was not present on trial 1, but appeared rather to reflect slower learning of the platform position from trial 1 to trial 2. The lesion effect upon distance swum, in contrast, was already present on the first trial (Fig. 3B) and did not change over trials.

There was no difference between the NOR and CON_2 groups in latency to reach the platform [$F(1, 20) = 2.89$, for main lesion effect; and $F(3, 300) = 1.39$, for interaction with trials] or distance swum [$F(1, 20) = 0.89$, and $F(3, 300) = 0.27$].

Nicotine significantly decreased the escape latency as shown by the main effect of drug (Fig. 4B, C; Table 5). Although the interaction between lesion and drug failed to reach significance, reductions in latency over trials were seen only in FCPS- and COMB-lesioned animals, not in controls, and drug-treated lesioned groups differed significantly from their untreated counterparts (on trials 2 and 4 between the FCPS-saline and FCPS-nicotine groups, and on trials 1, 3, and 4 between the COMB-saline and COMB-nicotine groups). Nicotine also decreased distance swum; as shown by the significant lesion × drug × trials interaction (Table 5), this compound had no effect upon the controls, but significantly reduced distance swum on trial 4 in the FCPS group and on trials 1 and 3 in the COMB group (data are not shown). There was no effect of nicotine upon swim speed.

Nicotine had no effect on latency or distance swum in NOR-lesioned (Fig. 5B) or CON_2 (Fig. 5A) animals [$F(1, 20) = 0.99$ and 0.82 for drug effects on latency and distance swum, respectively; $F(3, 300) = 0.29$ and 0.72 for drug interaction with lesion and trials].

DISCUSSION

The neurochemical data (Tables 1 and 2) indicate that the intended lesions to the FCPS and DNAB were achieved. The extent of damage to each of these two structures in the COMB group was quite similar (though with slightly, but nonsignificantly, larger ChAT depletion) to that observed in each of the single-lesion groups (FCPS and NOR). An unexpected feature of the results was that, in the NOR group, the DNAB lesion reduced hippocampal ChAT levels to a small (20%) but significant degree. There were also differences between the results obtained from the two control groups, presumably reflecting sampling error. However, because the assessment of lesion effects was made relative to the controls that served in the same experiment, this variability is unlikely to have biased interpretation of the lesion effects.

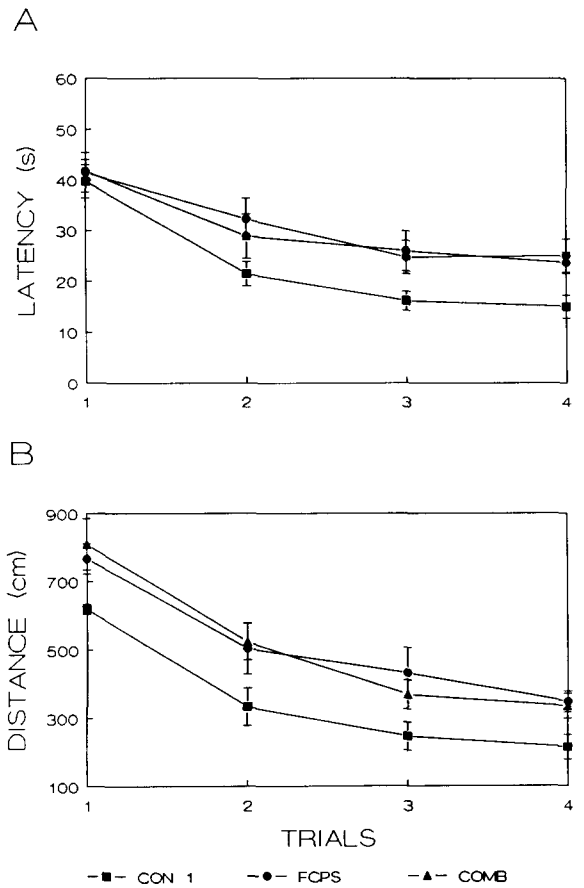

FIG. 3. Effects of FCPS and combined (COMB: FCPS + DNAB) lesions on water maze performance (working memory task). Lesions to the FCPS and FCPS + DNAB systems significantly impaired performance of the rats, assessed by escape latency (A) and swim path length (B). However, the two lesioned groups did not differ substantially from each other.

Confirming results previously obtained (23) in our laboratory using the same behavioural procedures, but after lesions of the nuclei of origin of the FCPS made with two other excitotoxins, ibotenate and quisqualate, lesions of the FCPS made in the present experiment with AMPA led to significant impairment in the rate of learning the location of the hidden platform in the reference memory task (Fig. 1) and in performance during the working memory task (Fig. 3). Taking the present and earlier results together, all three excitotoxins appear to have given rise to similar degrees of cholinergic depletion in the cortex and hippocampus and to similar extents of behavioural impairment. This pattern of results contrasts with other reports (16,45) of dissociations between the effects of these toxins upon cholinergic markers and behaviour, respectively.

Addition of damage to the DNAB in the COMB group led to a more marked impairment, relative to the FCPS group, in the reference memory task (Table 3), where the COMB group showed substantial overall impairment in comparison with controls. However, the COMB and FCPS groups did not differ significantly, and the greater impairment in the COMB than the FCPS group relative to controls may have reflected the slightly greater degree of cholinergic loss in the COMB group, and was not found at all in the working memory task. The failure of the DNAB lesion to add much to the cognitive impairment observed in the COMB group is echoed in the results obtained in the NOR group, in which only the DNAB lesion was made. No effects were seen in the working memory task after this lesion; in the reference memory task, most of the observed changes were confined to the first 5 days of acquisition and are likely to reflect reduced swim speed. Only for time in the platform quadrant was there an indication of impaired cognitive function, the NOR animals taking longer to attain asymptotic performance than controls, but achieving the same asymptote.

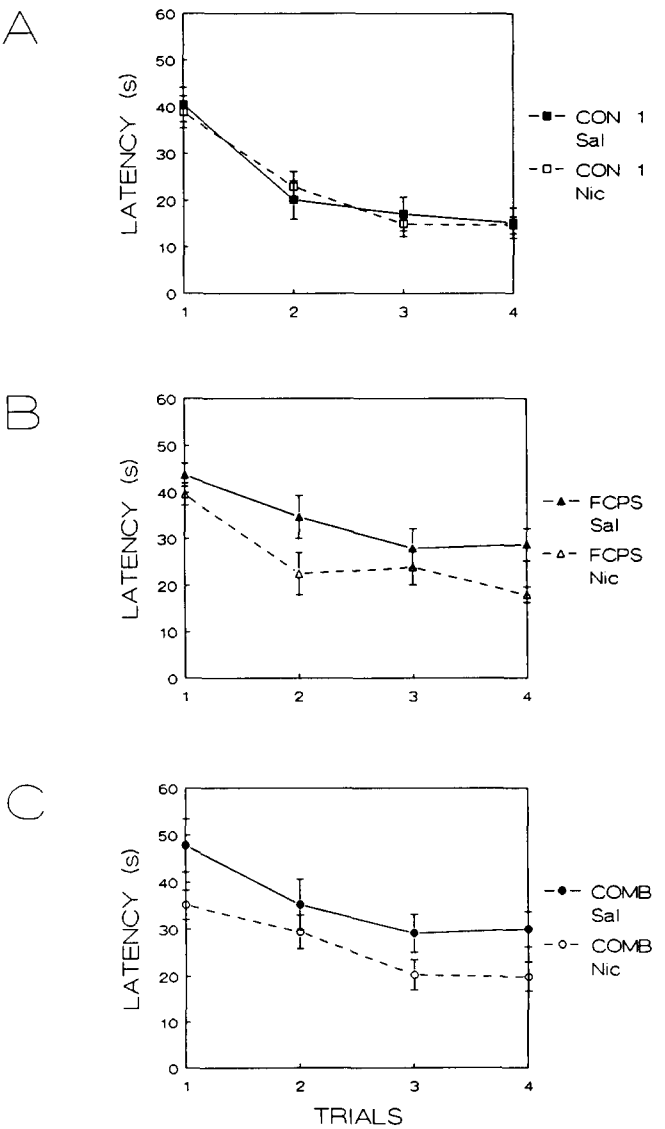

FIG. 4. Effects of nicotine on latency to reach the platform in FCPS-lesioned (B), COMB-lesioned (C), and CON 1 (A) groups (working memory task). Nicotine significantly reduced escape latency in both FCPS- and COMB-lesioned groups but not in controls. Sal, saline group; Nic, nicotine group.

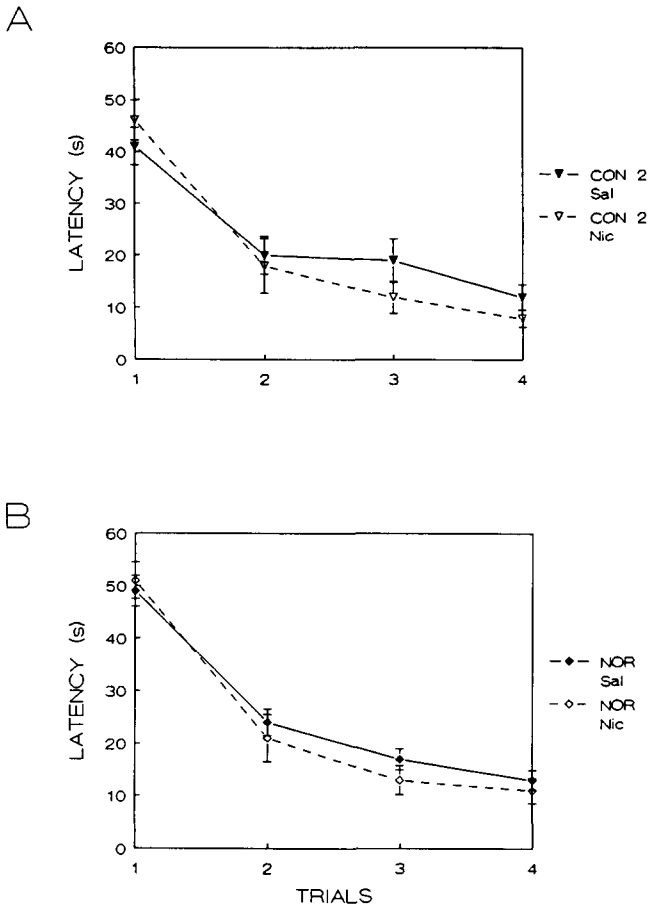

FIG. 5. Effects of nicotine on latency to reach the platform in NOR (B) and CON 2 (A) groups (working memory task). Nicotine had no significant effect on escape latency in either group. Sal, saline group; Nic, nicotine group.

The effects of a SC injection of 0.1 mg/kg nicotine also confirmed previous observations (23), made in our laboratory in animals with ibotenate and quisqualate lesions of the MSA/DB and NBM, that this compound improved performance in the working memory task in the FCPS group (Fig. 4). Nicotine also improved working memory performance in the COMB group. Although the detailed pattern of trial-by-trial change induced by nicotine differed between the two groups, the magnitude of the observed effects was very similar. In contrast, nicotine had no effect on working memory performance in either intact controls or in the NOR group (Fig. 5). Thus, the ameliorative effects of nicotine upon cognitive function appear to have been determined entirely by the presence of cholinergic damage. The improved performance in the working memory task induced by nicotine does not appear to reflect an effect principally upon learning or memory processes, because it was apparent on the first daily trial (Fig. 4). Nor was there any effect of this compound in the reference memory task. These data are consistent with a number of previous findings, in both rats (22) and patients with Alzheimer's disease (26,46), suggesting that nicotine is more effective in working than reference memory tasks, and that these effects are more likely related to attentional processes than to memory formation. However, in an earlier experiment (23) with identical procedures, we observed facilitated acquisition of the reference memory task in normal rats and FCPS-lesioned rats given nicotine in the same dose as used here. We are unable to account for this discrepancy, other than to suggest that effects of low doses of nicotine are quite variable (23) and appear to be influenced both by rats and lesion state.

Overall, then, our findings suggest little interaction in performance in the water maze between cholinergic and noradrenergic damage, or between noradrenergic damage and the facilitative effects of the cholinergic agonist, nicotine. This pattern of results contrasts with a number of other reports. According to extensive behavioural, electrophysiological, and biochemical data, the interaction between the noradrenergic and cholinergic systems is frequently synergistic (10,13,20,25, 7,31,54), although there is some evidence suggesting opposing effects (9,36,37,53). It is noteworthy that in a recent paper (9), with lesions to the DNAB in combination with NBM lesions in the water maze task, Connor et al. obtained results opposite to ours. Rats with noradrenergic lesions performed in the reference memory task better than controls, and the rats with dual (noradrenergic and cholinergic) lesions performed better than those with only cholinergic lesions, in tasks employing extramaze cues, comparable to the present experiments. The authors suggested that the ability of the combined lesioned group to perform better than FCPS-lesioned rats was due to the independent ability of the noradrenergic lesion to improve performance, rather than to any direct interaction between the noradrenergic and cholinergic lesions.

The inconsistency between the present findings and those obtained by Connor et al. (9) could be due to a number of factors, including differences in the strain of rats (Fisher 344 vs. Sprague–Dawley in our experiments), site of lesion (NBM/DNAB vs. NBM/MSA/DNAB), size of pool (152 vs. 200 cm), trial duration (90 vs. 60 s), intertrial interval (30 s vs. 10 min), and number of days of training (10 vs. 15). Some of these differences could have an effect on the level of stress and/or anxiety, which appears to be related to the activity of the noradrenergic system (18,52). For instance, Selden et al. (49) showed that local infusion of 6-OHDA into the DNAB enhanced aquisition of the spatial water maze in a stressful condition (cold water: 12°C), but had no effect in warm water (26°C), comparable to the temperature that we used (22–24°C). It is possible that the long trials and short intertrial intervals employed by Connor et al. (9) provided more stressful conditions than those in the present experiments. If so controls may have been more disrupted than the control animals in our experiment. This situation would have persisted until the rats had learned to find a safe platform and climb on it. It is perhaps for this reason that, in both studies, the difference between DNAB-lesioned animals and controls was observed only for the first few days. It is also noteworthy that, once experienced in finding the platform, the rats with noradrenergic lesions were not different from controls in reversal learning with a new platform position (9). This argument also provides a ready interpretation of the present finding that even the small effects observed in animals with DNAB lesions in the reference memory task were no longer apparent in the working memory task: because all rats were well experienced in finding the platform, and presumably therefore under relatively little stress, by the time they entered the working memory phase of the experiment, the noradrenergic system would no longer have a major role to play.

The hypothesis that the enhancing effects of nicotine on performance in cholinergic-lesioned animals might be medi-

TABLE 5

THE ANOVA RESULTS FOR WATER MAZE PERFORMANCE PARAMETERS IN FCPS- AND COMB-LESIONED AND CONTROL ANIMALS IN THE WORKING MEMORY TASK

	Latency	Distance
Lesion effect (df = 2, 56)	$F = 6.05, p < 0.005$	$F = 7.43, p < 0.001$
CON_1 vs. FCPS	$p < 0.05$	$p < 0.05$
CON_1 vs. COMB	$p < 0.05$	$p < 0.05$
FCPS vs. COMB	NS	NS
Drug effect (df = 1, 56)	$F = 9.33, p < 0.005$	NS
Lesion × drug × trials (df = 6, 840)	NS	$F = 2.31, p < 0.05$

Comparisons of means were made by Newman-Keuls test. NS, nonsignificant value of groups comparison.

ated by an interaction with the noradrenergic system predicts a blockade of this effect after lesions to the noradrenergic system. In unpublished experiments (Grigoryan et al., in preparation) we have found that the β-adrenoreceptor antagonist, propranolol (0.5 and 5.0 mg/kg), administered 15 min prior to nicotine injection, was unable to block the effects of nicotine on the performance of FCPS-lesioned animals in a radial-arm maze working memory task. These observations are in agreement with our present findings. In spite of marked NA depletion in the hippocampus and frontal cortex, nicotine administration continued to enhance water maze performance in COMB-lesioned rats. Furthermore, nicotine had no marked effect on water maze performance in the rats with noradrenergic lesions alone. Thus, the data obtained do not support the hypothesis that the enhancing effects of nicotine on water maze performance might be mediated by an interaction with the noradrenergic system.

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