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RAPID COMMUNICATION

Effects of Tetrahydroaminoacridine on Spatial Navigation of Nucleus-Basalis- and Frontal-Cortex-Lesioned Rats

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RIEKKINEN, P. JR., M. RIEKKINEN AND J. SIRVIÖ. *Effects of tetrahydroaminoacridine on spatial navigation of nucleus-basalis- and frontal-cortex-lesioned rats.* PHARMACOL BIOCHEM BEHAV 41(3) 637-641, 1992.—The present study investigates the effects of tetrahydroaminoacridine (THA: 1 and 3 mg/kg) on water maze (WM) spatial learning performance of intact, nucleus-basalis- (NB) lesioned, frontal-cortex- (FR) lesioned, or NB+FR-lesioned rats. NB lesions did not impair WM learning and had no effect on the WM performance deficit in FR-lesioned rats. THA at 1 or 3 mg/kg did not improve WM spatial memory of intact, NB-, FR-, or NB+FR-lesioned rats. These results suggest that 1) the cholinergic NB system is not a prerequisite for frontally mediated acquisition of WM performance, 2) THA treatment does not enhance spatial memory, and 3) THA is not effective in alleviating cognitive deficits indued by degeneration of the frontal cortex.

Acetylcholine Nucleus basalis Frontal cortex Spatial learning THA

SOME early clinical features in Alzheimer's disease (AD) patients include memory defects (16,18,20). For example, spatial memory processing is impaired at early stages of the disease.

One of the most consistent pathological changes in AD is the loss of cholinergic neurons in the nucleus basalis of Meynert (NBM) (3,18,19). Interestingly, the degree of cholinergic deficit has been shown to correlate with the severity of AD-related memory deficits (18,19). Indeed, the "cholinergic hypothesis" of age-related memory deficits proposed that the loss of basal forebrain cholinergic neurons is importantly involved in the memory loss found in old age and that pharmacological restoration of cholinergic activity may alleviate memory defects (3). This cholinergic hypothesis has been supported by experimental studies demonstrating that cholinergic drugs may improve avoidance test performance of intact rats (2,10,13). Furthermore, cholinergic drugs may alleviate the memory loss induced by lesions of the basal forebrain neurons (23a). However, more recent studies have questioned the importance of NBM neuron loss for the AD- and age-related memory deficits (5). It has also been suggested that the cholinergic system may not be primarily involved in memory processing, but may be involved in mechanisms underlying arousal, attention, and information processing capacity (4,5). Indeed, clinical pharmacological treatment trials using cholinesterase inhibitors [e.g., tetrahydroaminoacridine (THA)] have resulted at best in only partial stabilization of memory deficit of AD patients (12,21,28).

It is important to note that degeneration of the association neocortex is importantly involved in AD-related memory loss (6,8,30). Human patients who have undergone surgical excision of the frontal cortex (FR) exhibit a dramatic deficit in learning spatial tasks (7). Moreover, the severity of frontal cortex pathology correlates with the degree of cognitive deficits in AD patients (8). Therefore, these results may both imply a degree of structural change in the brain not likely to be affected by cholinergic drug therapies to induce marked alleviation of memory loss and also suggest that AD-related memory deficits may be due to concurrent degeneration of cholinergic NBM and the association neocortex.

A logical approach in the study of memory and the pharmacological consequences of AD-related pathology of cortical association areas and cholinergic neurons is to lesion those brain areas in experimental animals. It has been demonstrated that lesions of the FR impair performance in the water maze

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(WM) spatial learning test (29). Interestingly, earlier studies have demonstrated that quisqualic acid lesions of the cholinergic "NBM to FR" projection do not impair WM performance (9,22). However, the spatial memory consequences of combined NBM + FR lesions and the efficacy of THA, an anticholinesterase, in reversing FR-lesion-induced spatial memory defects have not been investigated.

Therefore, in the present study we investigated whether quisqualic acid NBM lesions aggravate FR-lesion-induced WM spatial learning deficit and whether THA improves the WM spatial memory performance of naive, NBM-, FR-, or NBM + FR-lesioned rats.

METHOD

Animals

Young male KUO:Wistar rats (3 months old) (n = 96, 8/group) were used. Food and water were freely available.

Drugs

Tacridine (THA) (1 and 3 mg/kg; volume 4 ml/kg) was dissolved in saline and injected IP 30 min before daily behavioral training. It has been shown that brain acetylcholinesterase activity is decreased with these doses (26). Saline injections of equal volume were used for control purposes.

In the first experiment, naive rats were used: saline, THA 1 mg/kg, THA 3 mg/kg. In the second experiment, NBM-sham-lesioned (saline) and three groups of NBM-lesioned rats were used (saline, THA 1 mg/kg, THA 3 mg/kg). In the third experiment, rats were subjected to either FR lesions or combined FR and NBM lesions: NBM + FR sham lesioned (saline), FR lesioned (saline), FR lesioned (THA 3 mg/kg), NBM + FR lesioned (saline), NBM + FR lesioned (THA 3 mg/kg).

Surgery

Animals were anesthetized with chloral hydrate (350 mg/kg IP) and placed in a stereotaxic frame with the bregma and lambda in the horizontal plane. Intracerebral injections of quisqualic acid were made by means of a 5-μl syringe with a 31-ga needle at a speed of 0.25 μl/min. Unilateral quisqualic acid (0.12 M, 1.0 μl, in phosphate-buffered saline, pH 7.4) infusions were used to lesion the NBM (AP: −0.8 mm; ML: 2.6 mm, the left NBM was lesioned in half of the rats and the right NBM in the other half; DV: −7.4 mm relative to the bregma). NBM-sham-lesioned rats received vehicle infusions of equal volume into the NBM. The lesion coordinates for the FR were: AP 3.5 mm and ML 1.9 mm; AP 1.5 mm and ML 1.9 mm, DV −2.0 mm relative to the dura (the left FR was lesioned in half the rats and the right FR in the other half). Half the rats subjected to combined NBM + FR lesioning received all infusions into the left hemisphere and the other half received all infusions into the right hemisphere.

WM Testing

Our computer-based WM testing apparatus (San Diego Instruments) has been described in detail previously (22). Escape distance was used as an index of spatial memory acquisition during training trials (3 consecutive days, 4 60-s trails in a day, 10 reinforcement on the platform, 30-s recovery period). During the spatial probe trial (fifth day), the spatial bias (total distance/distance in the previous training quadrant) was measured. Swimming speed was analyzed to evaluate drug- and lesion-induced changes in motor behavior.

TABLE 1

WM SPATIAL BIAS (DISTANCE IN THE TRAINING QUADRANT/TOTAL DISTANCE × 100%) DURING THE SPATIAL PROBE TRIAL

Group	Spatial Bias (%)
First experiment	
C	34 ± 5
T 1	36 ± 5
T 3	31 ± 6
Second experiment	
C	35 ± 8
NBM	34 ± 7
NBM T 1	38 ± 8
NBM T 3	33 ± 6
Third experiment	
C	34 ± 5
FR + NBM	21 ± 5*
FR + NBM T 3	23 ± 5*
FR	24 ± 7*
FR T 3	23 ± 6*

The platform was withdrawn during the spatial probe trial and rats were allowed to swim 50 s in the pool. Drugs were injected 30 min before daily behavioral Training. Values are expressed as mean ± SD. (C), controls; (NBM), NBM lesioned; (FR), frontal cortex lesioned; (NBM + FR), NBM + frontal cortex lesioned; (T 1 and T 3), THA 1 and 3 mg/kg.

*$p < 0.05$ vs. controls, Mann-Whitney U-test.

Dissection, Biochemistry, and Histology

After decapitation of the NBM-lesioned/control rats, the rostral FR (30–35 mg) and the hippocampi (60–80 mg) were bilaterally dissected and stored at −70°C. Next, a piece of brain, cut coronally three mm anterior and posterior to the needle tract, was put into 3% formalin (phosphate-buffered saline, 0.1 M, pH 7.4) for 10 h and subsequently immersed in 30% sucrose. Serial sections (40 μm) were cut and neighboring sections were stained with cresyl violet (CV) and acetylcholinesterase (AChE) histochemistry. Half the rats injected with quisqualic acid into the FR or both FR and NBM were used for histological verification of the lesions. The other half of the NBM + FR- or FR-infused rats were dissected, as were the NBM-lesioned rats. Choline acetyltransferase (ChAT) activity was measured according to the method of Fonnum (11).

Statistics

The mixed-model analysis of variance (ANOVA) was used to analyze group and group × training day effects on WM memory acquisition (escape distance). The Mann–Whitney U-test was used to analyze group differences in biochemical and spatial bias data.

RESULTS

First Experiment: Naive Rats, THA at 1 and 3 mg/kg

WM performance. THA at 1 or 3 mg/kg did not affect WM escape distance values measured during the training days

[group: $F(2,21) = 0.6$, $p > 0.05$; group × training day: $F(6,63) = 0.1$, $p > 0.05$] (data not shown). Furthermore, THA at 1 or 3 mg/kg did not improve spatial bias ($p > 0.05$) (Table 1).

Group effect was significant in the analysis of swimming speed, $F(2,21) = 8.9$, $p < 0.05$. Group × training day effect was not significant, $F(6,63) = 0.4$, $p > 0.05$. THA at 3 mg/kg [group: $F(1,14) = 11.4$, $p < 0.05$], but not at 1 mg/kg [group: $F(1,14) = 0.7$, $p > 0.05$], decreased swimming speed (data not shown).

Second Experiment: NBM-Lesioned Rats, THA at 1 and 3 mg/kg

WM performance. Figure 1 shows the effects of THA on the WM escape distance values of NBM quisqualic-acid-lesioned rats. Group, $F(3,28) = 0.4$, $p > 0.05$, and group × training day, $F(9,84) = 0.8$, $p > 0.05$, effects on escape distance were not significant. Furthermore, overall group effect was not significant in the analysis of spatial bias data ($p > 0.05$ in all group comparisons) (Table 1).

A significant group, $F(3,28) = 6.7$, $p < 0.05$, effect was found in the analysis of swimming speed data. THA-3 mg/kg-injected, NBM-lesioned rats significantly differed from controls, $F(1,14) = 8.8$, $p < 0.05$.

Biochemistry. ChAT activity of NBM-lesioned rats was decreased in the ipsilateral frontal cortex (64% decrease, $p < 0.05$). Frontal ChAT activity ipsilateral to the lesioned NBM did not differ between the different NBM lesion groups ($p > 0.05$).

Histology. Analysis of the CV- and AChE-stained sections revealed that quisqualic acid NBM lesions produced gliosis and loss of AChE-positive neurons in the ventral pallidum (Fig. 2).

Third Experiment: NBM+FR-lesioned rats, THA at 3 mg/kg

WM performance. Figure 3 shows the escape distance values measured during WM training. Group, $F(4,35) = 9.9$, $p < 0.05$, effect was significant. FR- [group: $F(1,14) = 9.1$, $p < 0.05$] and NBM+FR- [group: $F(1,14) = 12.1$, $p < 0.05$] lesioned rats were impaired in the acquisition of WM compared with controls. The acquisition performance of FR- and NBM+FR-lesioned rats did not differ significantly [group: $F(1,12) = 0.6$, $p > 0.05$]. THA at 3 mg/kg did not improve the WM performance of NBM+FR- [group: $F(1,12) = 1.0$, $p > 0.05$] or FR- [group: $F(1,12) = 0.5$, $p < 0.05$] lesioned rats. Spatial bias was decreased by FR and NBM+FR lesions ($p < 0.05$). NBM lesioning was not aggravate FR-lesioning-induced spatial bias deficit ($p > 0.05$). THA at 3 mg/kg did not stabilize the spatial bias decrease induced by NBM+FR or FR lesioning ($p > 0.05$).

Group, $F(4,35) = 14.1$, $p < 0.05$, effect was significant in analysis of the swimming speed. FR- [group: $F(1,12) =$

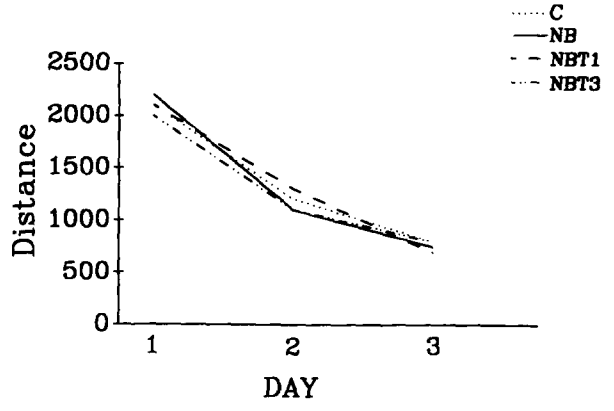

FIG. 1. Daily group mean escape distance values (arbitrary computer units). (C), controls; (NB), nucleus basalis lesioned (saline); (NBT1), nucleus basalis lesioned (THA 1 mg/kg); (NBT3), nucleus basalis lesioned (THA 3 mg/kg).

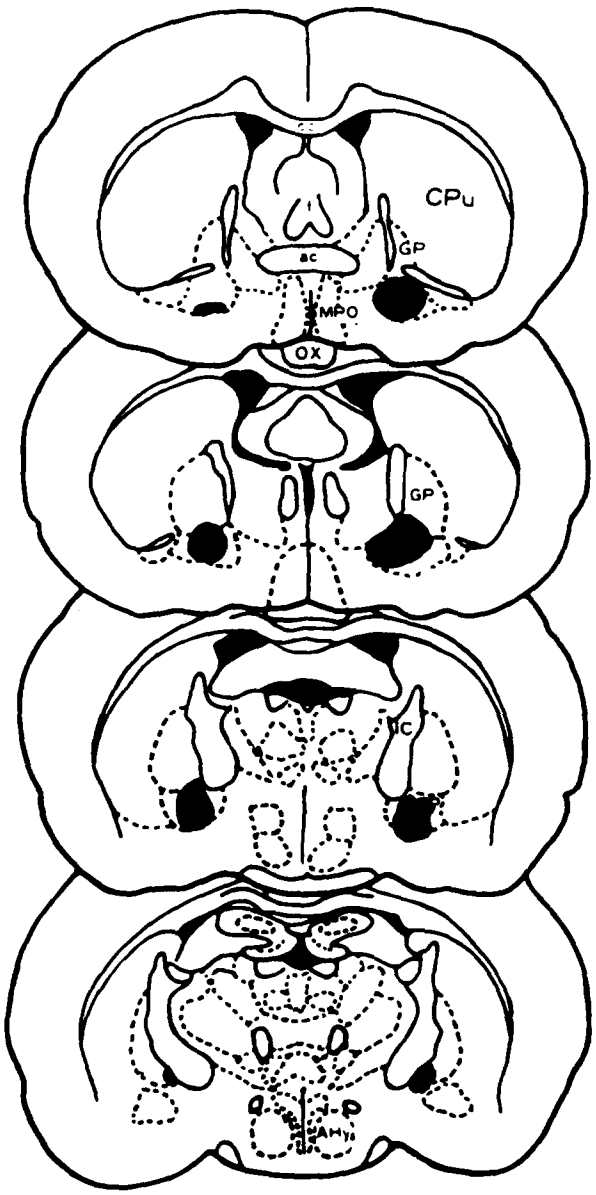

FIG. 2. Coronal reconstructions of largest (reconstructed on the left hemisphere) and smallest (reconstructed on the right hemisphere) nucleus basalis lesions. The black areas indicate gliosis and cell loss. (AC), anterior commisure; (AHy), anterior hypothalamus; (CC), corpus callosum; (CPu), caudate putamen; (GP), glopus pallidus; (IC), internal capsule; (MPO), medial preoptic area; (OX), optic chiasm.

10.1, $p < 0.05$] and NBM+FR- [group: $F(1,12) = 13.1$, $p < 0.05$] lesioned rats swam faster than controls (data not shown). THA at 3 mg/kg stabilized the swimming speed of FR- [group: $F(1,12) = 1.0$, $p > 0.05$] and NBM+FR- [group: $F(1,12) = 0.4$, $p > 0.05$] lesioned rats (data not shown).

Biochemistry. ChAT activity analysis revealed that only rats subjected to NBM+FR lesioning had lower FR (ipsilateral to the intracerebral infusions) enzyme activity than controls (66% decrease, saline treated: $p < 0.05$; 65% decrease, THA 3 mg/kg treated: $p < 0.05$) (Table 1). ChAT activity of saline and THA 3 mg/kg treated FR-lesioned rats was normal ($p < 0.05$).

Histology. NBM lesions were identical to those described in the second experiment (Fig. 2). Figure 4 shows a reconstruction of a typical FR lesion. Vertically, FR lesions extended from 3.8–1.2 mm relative to the bregma. Mediolaterally, lesions extended from 0.5–2.7 mm relative to the bregma. The loss of normal cell configuration was evident in all cortical layers.

DISCUSSION

In agreement with the previous studies, it was observed that FR lesions impaired WM spatial navigation performance (increase in escape distance) (29). This spatial navigation defect is not likely to be due to motor impairment because FR lesions produced motor hyperactivity (increased swimming speed). Our results also corroborate (9,22) that NBM cholinergic neurons are not importantly involved in spatial learning: Quisqualic acid NBM lesions neither impaired spatial learning nor aggravated FR-lesion-induced WM deficit.

It is also interesting to note that THA did not facilitate spatial memory performance of intact, NBM-, FR-, or NBM+FR-lesioned rats. Our failure to observe a significant facilitation of spatial memory performance data contradicts earlier findings that sought to investigate the effects of cholinergic drugs on memory processing. Baratti et al. (2) and Haroutunian et al. (13) demonstrated that nicotinic and muscarinic receptor agonists and anticholinesterase compounds improve passive avoidance retention. Flood and Cherkin (10) demonstrated that retention of a shock-motivated task was facilitated by THA and arecoline. Therefore, it could be argued that the THA doses were either too high, or too low, to improve spatial memory functions. However, it has been shown that THA inhibits cortical acetylcholinesterase at the doses used in the present study (17,26). Furthermore, only slightly higher doses of THA than used in the present study severely impair motor performance in the test of elevated bridges (designed to measure motor activity), WM, and passive avoidance tasks (2,23a). Importantly, the interpretations of cholinergic drug-induced facilitation of avoidance performance in terms of improved memory functions have been criticized recently because avoidance tasks do not provide good estimates of memory alterations (15,24). Therefore, it is interesting to note that Sahgal et al. (25) were not able to detect any mnemonic improvements caused by cholinergic drugs (nicotine, oxotremorine, and THA) in an appetitively motivated delayed matching or nonmatching to position task in rats (25). The tests used by Sahgal et al. (25) were designed to accurately determine drug-induced changes in memory processing ability of rats. Therefore, it is tempting to propose that differences in the mnemonic demands (avoidance performance vs. spatial memory performance, nonaversively vs. aversively motivated) of the behavioral tasks may underlie some of the discrepancies observed in the effects of cholinergic drugs on performance in tests used to assess learning and memory.

Interestingly, memory improvement following cholinomimetic injection has often been observed after performance has been impaired by basal forebrain cholinergic lesions. Riekkinen, Jr. et al. (23a) suggested that THA 3 mg/kg improved WM performance of medial-septal- (MS, the origin of the hippocampal cholinergic system) lesioned rats by stabilizing lesion-induced hippocampal cholinergic hypofunction. However, in the present study NBM-lesion-induced frontal cortical cholinergic hypofunction did not affect WM spatial learning. Therefore, it is reasonable to believe that although THA may have stabilized activity of the lesioned NBM to FR

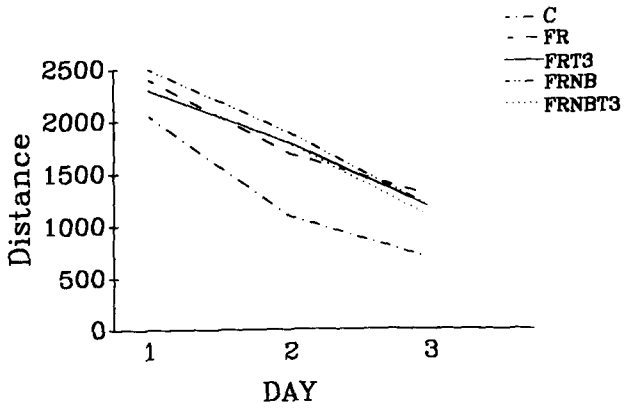

FIG. 3. Daily group mean escape distance values (arbitrary computer units). (C), controls; (FR), frontal cortex lesioned (saline); (FRT3), frontal cortex lesioned (THA 3 mg/kg); (FRNB), frontal cortex + nucleus basalis lesioned (saline); (FRNBT3), frontal cortex + nucleus basalis lesioned (THA 3 mg/kg).

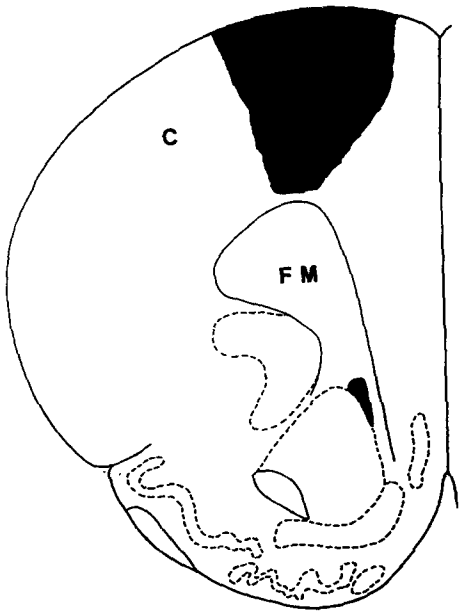

FIG. 4. Coronal reconstruction of a typical frontal cortex lesion. The black areas indicate cell loss and gliosis. (C), cortex; (FM), forceps major.

cholinergic system it did not improve WM spatial memory performance. Furthermore, the failure to observe a THA-induced alleviation of spatial memory defect of FR-lesioned rats suggests that increased cholinergic activity does not reverse cortical nerve-cell-loss-induced functional defects.

The results of present and previous experimental studies may have some relevance for AD-related memory deficits. The present results suggest that the degeneration of FR, but not the loss of the NBM to FR cholinergic system, is importantly involved in the AD-related spatial memory deficit (6, 8,27,30). The present data demonstrating that FR-induced WM spatial learning deficit is not alleviated by THA, and earlier studies showing that FR lesions prevent the passive avoidance memory-stabilizing actions of anticholinesterase drugs (14,23b) in NBM-lesioned rats, suggest that cognitive deficits induced by cortical degeneration may not be alleviated by cholinergic drugs.

In conclusion, the present data demonstrated that 1) quisqualic acid NBM lesions do not aggravate FR-lesion-induced spatial learning deficit and 2) anticholinesterase THA does not facilitate spatial memory performance of intact, NBM-, FR-, or NBM + FR-lesioned rats.

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