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Effects of THA on Passive Avoidance Retention Performance of Intact, Nucleus Basalis, Frontal Cortex and Nucleus Basalis + Frontal Cortex-Lesioned Rats

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RIEKKINEN, P., JR., J. SIRVIÖ, M. RIEKKINEN AND P. RIEKKINEN. *Effects of THA on passive avoidance retention performance of intact, nucleus basalis, frontal cortex and nucleus basalis + frontal cortex-lesioned rats.* PHARMACOL BIOCHEM BEHAV **39**(4) 841–846, 1991.—Unilateral quisqualic acid lesions of the nucleus basalis magnocellularis (NBM) produced marked choline acetyltransferase depletion (−67% ipsilateral to lesion) and impaired passive avoidance (PA) retention at 24 hours. Pretraining injections of tacrine (THA: 1, 3 and 5 mg/kg), an anticholinesterase, failed to facilitate PA retention in intact rats. However, the retention performance of NBM-lesioned rats was improved by pretraining administration of THA at 3 mg/kg but not at either 1 or 5 mg/kg. Frontal cortex lesioning did not impair PA retention, and THA at 3 mg/kg had no effect on the PA retention of frontal cortex-lesioned rats. THA at 3 mg/kg failed to improve retention performance of NBM + frontal cortex-lesioned rats. After 10 days of chronic treatment with THA, NBM lesion-induced PA retention deficits were partially restored at both 3- and 5-mg/kg doses. The results suggest that 1) the insult to cholinergic neurons in the NBM may be involved in the PA memory consolidation deficit induced by nonselective quisqualic acid lesioning; 2) the beneficial effects of THA on NBM lesion-induced PA retention deficit occur in a narrow dose range; 3) the alleviating effects of THA on NBM lesion-induced PA memory deficits are blocked by frontal cortex lesions; and 4) the dose-response window for THA-induced PA retention performance improvement is broadened by repeated treatment.

THA Dose-response NBM Frontal cortex Passive avoidance Alzheimer's disease

THE severity of loss of cholinergic neurons in the nucleus basalis of Meynert (NBM) is related to the degree of clinical dementia in patients with Alzheimer's disease (AD) (10,12). These findings have led to the development of cholinergic replacement strategies. The increase of central cholinergic activity by the administration of cholinesterase inhibitors to prevent the breakdown of acetylcholine constitutes one pharmacological strategy to ameliorate cognitive deficits in AD patients (18, 19, 21).

Several lines of evidence suggest that the "NBM to cortex" cholinergic pathway has an important role in passive avoidance (PA) behavior in rats. Quisqualic or ibotenic acid NBM lesions produce PA performance deficits similar to those observed after injection of antimuscarinic drugs (4, 5, 13). Indeed, the alleviation of NBM lesion-induced PA deficits by physostigmine (an anticholinesterase) or intracortical grafts of fetal ventral forebrain tissue can be cited as further evidence in support of the hypothesis that these deficits are induced by loss of cholinergic NBM fibers in the frontal cortex (3,7). Therefore, it is reasonable to suggest that NBM lesion-induced PA retention deficit may be used as a pharmacological model for testing the cholinomimetic efficacy of drugs aimed at reversing age- or AD-related functional deficit of the "NBM to cortex" pathway. Indeed, Haroutunian et al. (7,8) have shown that physostigmine, an anticholinesterase drug, may improve PA retention performance of rats subjected to NB lesioning.

However, clinical pharmacological treatment trials using cholinesterase inhibitors [e.g., tacrine (THA) and physostigmine] have resulted only in partial rehabilitation of cognitive symptoms of AD patients (21).

The pathology of either neocortical association areas (e.g., frontal cortex) or noncholinergic subcortical regulatory systems (e.g., serotonin and noradrenaline neurons) may also be intimately involved in the cognitive deficits found in AD patients and may partly account for the failures of cholinergic replacement strategies to induce marked amelioriations of cognitive functions (1, 11, 16, 20).

Therefore, in the present study, we investigated whether 1) THA could restore an NBM-lesion-induced PA retention deficit; 2) whether THA could reverse a PA retention deficit induced by combined NBM and frontal cortex lesion; and 3) whether tolerance develops to THA-induced PA memory effects in NBM-lesioned rats.

METHOD

Animals

Young male KUO:Wistar rats (3 months old) (n = 128) were

used in the present study. Food and water were freely available.

THA (1, 3 and 5 mg/kg; volume 4 ml/kg) was dissolved in saline and injected IP 30 minutes before behavioral training. Previously, it has been shown that brain acetylcholinesterase activity is decreased with these doses in rats subjected to SC THA injections (18). Saline injections of equal volume were used for control purposes.

In the 1st experiment, naive rats (total n = 40) were used: saline (n = 10); THA 1 mg/kg (n = 10); THA 3 mg/kg (n = 10); THA 5 mg/kg (n = 10).

In the 2nd experiment, NBM-sham-lesioned and 4 groups of NBM-lesioned rats were used (total n = 37): NBM-sham-lesioned saline (n = 7), NBM-lesioned saline (n = 8)/THA 1 mg/kg (n = 8)/THA 3 mg/kg (n = 8)/THA 5 mg/kg (n = 6).

In the 3rd experiment, rats were subjected to either frontal cortical lesions or combined frontal cortical and NBM lesions (total n = 32): NBM + frontal cortex sham-lesioned, saline (n = 8), frontal cortex-lesioned, saline (n = 6); frontal cortex-lesioned, THA 3 mg/kg (n = 6); NBM + frontal cortex-lesioned, saline (n = 6); NBM + frontal cortex-lesioned THA 3 mg/kg (n = 6).

In the 4th experiment, the effects of chronic THA treatment (10 days) at 3 or 5 mg/kg were investigated (total n = 28): NBM sham-lesioned (n = 7), NBM-lesioned saline (n = 7)/THA 3 mg/kg (n = 7)/THA 5 mg/kg (n = 7). The last THA injections were given 30 min before behavioral training.

Surgery

The 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. Toxin and vehicle infusions were made ipsilaterally. Half of the sham-lesioned and lesioned rats received all infusions into the left hemisphere, and the other half of the rats received all infusions into the right hemisphere. Intracerebral injections of quisqualic acid were made by means of a 5-μl syringe with a 31-gauge needle at a speed of 0.25 μl/minute. Unilateral quisqualic acid (quis; 0.12 M, 1.0 μl, in phosphate buffered saline, pH 7.4) infusions were used to lesion the NBM (A: −0.8 mm; M: 2.6 mm; D: −7.4 mm; relative to the bregma). NBM-sham-lesioned animals received vehicle infusions of equal volume into the NBM. Two intracortical infusions of quis (1.5 μl) were used to unilaterally lesion the frontal cortex: rostral infusion = A 3.5 mm and M 1.9 mm relative to the bregma, −2.0 mm relative to the dura; caudal infusion = AP 1.5 mm and ML 1.9 mm relative to the bregma, −2.0 mm relative to the dura. A two-week recovery period was allowed before PA training was started.

Passive Avoidance

The Plexiglas PA box was divided into a dark and lighted compartment by a metal sliding guillotine door. The dark compartment had a metal grid floor. Rats were placed on the lighted side. After 10 s, a door opened allowing entry into the dark side. Five s after entry into the dark chamber, a 1.0-mA shock was initiated and maintained, until the rat escaped from the dark chamber and until a training criterion of avoiding the dark chamber for a 1-minute interval was attained. The latency to enter the dark chamber, the number of reentries and the shock duration (total time spent in the dark compartment during the delivery of 1-mA shock) were measured. Twenty-four hours after the training, rats were placed in the lighted side of the apparatus and the door was opened. The latency to enter the dark chamber was measured during the retention trial.

TABLE 1

DRUG-INDUCED CHANGES ON THE PA TRAINING TRIAL PERFORMANCE

	Training Trial		
Groups	Reentries	Entry Latency (s)	Shock Duration (s)
C	1.6 ± 0.7	23 ± 33	3.3 ± 4.3
T1	1.3 ± 1.2	25 ± 24	2.6 ± 3.2
T3	1.6 ± 2.3	66 ± 21*	4.1 ± 2.6
T5	1.3 ± 1.2	70 ± 13*	3.1 ± 7.5

Values are expressed as mean ± S.D. Abbreviations: see Fig. 1.
*$p<0.05$ vs. controls, Mann-Whitney U-test.

Dissection, Biochemistry and Histology

After decapitation [7 days after (last) THA injections were given] of the NBM-lesioned and sham-lesioned rats, the rostral frontal cortex (30–35 mg) was bilaterally dissected and stored at −70°C. Next a piece of brain, cut coronally three millimeters anterior and posterior to the needle tract, was put into 3% formalin (phosphate buffered saline, 0.1 M, pH 7.4) for 10 hours and subsequently immersed in 30% sucrose. Serial sections (40 μm) were cut, and neighboring sections were stained with hematoxylin-eosin (HE) and acetylcholinesterase (AChE) histochemistry. Half of the rats injected with quisqualic acid into the frontal cortex or both frontal cortex and NBM were used for histological verification of the lesions. The other half of the NBM + frontal cortex- or frontal cortex-infused rats were dissected as the NBM-lesioned rats. Choline acetyltransferase (ChAT) activity was measured according to the method of Fonnum (6).

Statistics

The Kruskal-Wallis one-way analysis of variance followed by the Mann-Whitney U-test was used to compare the results of different groups.

RESULTS

First Experiment: Naive Rats, THA at 1, 3 or 5 mg/kg

Passive avoidance. Table 1 shows the effects of THA on the PA training trial performance of young rats. A significant group effect was observed in the analysis of the PA training trial entry latency data ($p<0.05$). THA 3 and 5 mg/kg increased entry latencies during the training trial ($p<0.05$). No differences were detected between these two dosage groups ($p>0.05$). The number of reentries or the duration of the shock period did not differ between the groups ($p>0.05$) (Table 1). No group differences were found in the analysis of the entry latencies during the retention trial ($p>0.05$) (Fig. 1).

Second Experiment: NBM-Lesioned rats, THA at 1, 3 or 5 mg/kg

Passive avoidance. Table 2 shows the effects of THA on the PA training trial performance of NBM-lesioned rats. Again, THA-induced changes were observed in the entry latencies measured during the training trial ($p<0.05$). NBM-lesioned rats injected with THA 3 and 5 mg/kg had longer entry latencies than other groups ($p<0.05$). The number of reentries or the shock

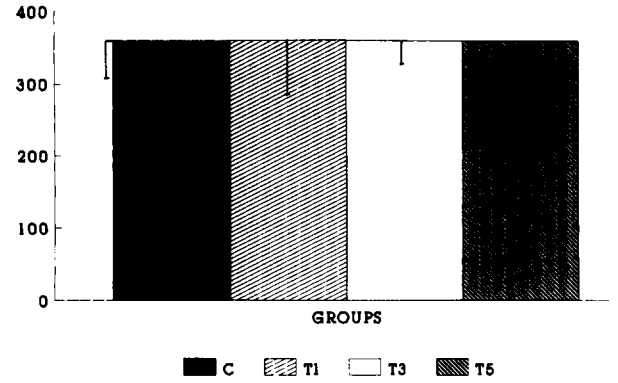

FIG. 1. First experiment: Intact rats, THA 1, 3 or 5 mg/kg. Drug-induced changes in PA retention. Values are expressed as median (+ minimum and maximum values). Abbreviations: C = controls, T1 = THA 1 mg/kg, T3 = THA 3 mg/kg, T5 = THA 5 mg/kg.

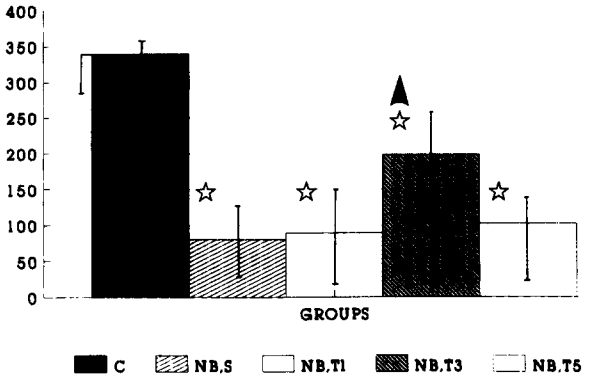

FIG. 2. Second experiment: NBM-lesioned rats, THA 1, 3 or 5 mg/kg. Drug- and NBM-lesion-induced changes in PA retention. Values are expressed as median (+ minimum and maximum values). Abbreviations: C = NBM-sham-lesioned, saline (controls); NB, S = NBM-lesioned, saline; NB,T1 = NBM-lesioned, THA 1 mg/kg; NB,T3 = NBM-lesioned, THA 3 mg/kg; NB, T5 = NBM-lesioned, THA 5 mg/kg. *$p<0.05$ vs. controls, Mann-Whitney U-test. ▲$p<0.05$ vs. other NBM-lesioned groups, Mann-Whitney U-test.

duration did not differ between the groups ($p>0.05$). Analysis of the retention test entry latencies revealed a significant group effect ($p<0.05$). NBM-lesioned rats injected with saline, THA 1 or 5 mg/kg were impaired compared with NBM-sham-lesioned rats ($p<0.05$). NBM-lesioned rats injected with THA 3 mg/kg were not impaired compared with the controls ($p>0.05$) (Fig. 2). NBM-lesioned rats injected with THA 3 mg/kg performed better than saline-injected NBM-lesioned rats ($p<0.05$) (Fig. 2).

ChAT activity. Frontal cortex ChAT activity was decreased ipsilateral to NBM lesions ($p<0.05$) (Table 3). No differences were observed between the different groups of NBM-lesioned rats ($p>0.05$ in all comparisons) (Table 3).

Histology. Examination of HE- and AChE-stained sections revealed that quisqualic acid infusions into the NBM produced gliosis and loss of AChE-positive neurons in the ventral pallidum (Fig. 3).

Third Experiment: NBM + Frontal-Cortex-Lesioned Rats, THA at 3 mg/kg

Passive avoidance. Analysis of the entry latencies during the training trial showed a marked group effect ($p<0.05$) (Table 4). The NBM + frontal cortex-lesioned rats and frontal cortex-lesioned rats injected with THA 3 mg/kg entered the dark compartment more slowly ($p<0.05$) (Table 4). The number of reentries and the shock duration did not differ between the groups ($p>0.05$) (Table 4). Analysis of the retention test entry latencies revealed a marked group effect ($p<0.05$) (Fig. 4). NBM + frontal cortex-lesioned rats injected with saline or THA 3 mg/kg were impaired compared with the controls ($p<0.05$) (Fig. 4).

ChAT activity. Analysis of the frontal cortex ChAT activity revealed that only rats subjected to NBM + frontal cortex lesions had lowered ChAT activity in the frontal cortex ($p<0.05$) (Table 5). In all the other groups, ChAT activity remained unchanged ($p>0.05$ in all comparisons).

Histology. Quisqualic acid NBM lesions were identical to those described in the 2nd experiment. The frontal cortex lesions extended from 3.7–1.4 mm relative to the bregma. Loss of normal cell configuration was evident in all layers of the cortex. Mediolaterally, the cortical lesions extended from 0.5–2.5 mm relative to the bregma.

Fourth Experiment: NBM-Lesioned Rats, THA at 3 and 5 mg/kg (Chronic Administration)

Passive avoidance. Analysis of the entry latencies measured during the training trial revealed a marked group effect ($p<0.05$). NBM-lesioned rats treated with THA at 5 mg/kg were slower to enter the dark chamber ($p<0.05$) (Table 6). No group differences were found in the number of reentries or the duration of

TABLE 2

DRUG-INDUCED CHANGES ON THE PA TRAINING TRIAL PERFORMANCE

Groups	Reentries	Entry Latency (s)	Shock Duration (s)
C	1.9 ± 1.5	23 ± 34	4.1 ± 2.5
NB,S	2.5 ± 2.2	33 ± 28	3.5 ± 3.6
NB,T1	1.4 ± 2.1	25 ± 21	4.0 ± 2.6
NB,T3	1.4 ± 0.9	67 ± 12*	2.1 ± 4.0
NB,T5	1.3 ± 2.0	70 ± 19*	3.3 ± 4.4

Values are expressed as mean ± S.D. Abbreviations: see Fig. 2.
*$p<0.05$ vs. controls, Mann-Whitney U-test.

TABLE 3

ChAT ACTIVITY IN THE FRONTAL CORTEX IPSILATERAL TO LESIONING

Groups	ChAT (nmol/mg protein/minute)
C	1.11 ± 0.2
NB,S	0.40 ± 0.2*
NB,T1	0.43 ± 0.1*
NB,T3	0.39 ± 0.3*
NB,T5	0.41 ± 0.2*

Values are expressed as mean ± S.D. Abbreviations: see Fig. 2.
*$p<0.05$ vs. controls, Mann-Whitney U-test.

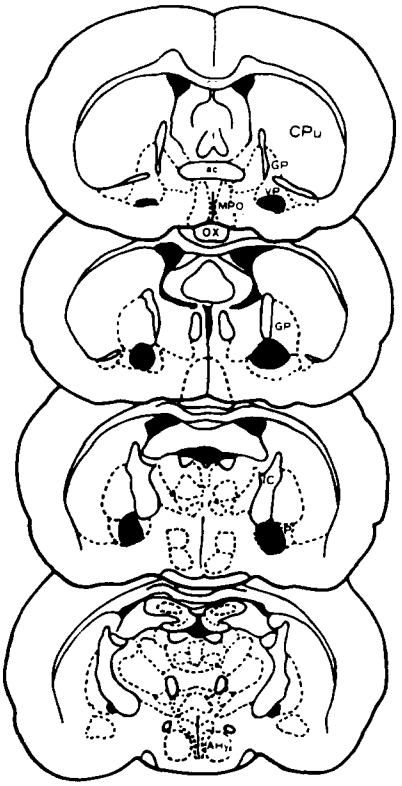

FIG. 3. Reconstructions of maximum (reconstructed on the left hemisphere) and minimum (reconstructed on the right hemisphere) extents of the quisqualic acid-induced lesions. Black areas indicate gliosis and loss of AChE-positive neurons. Abbreviations: AC = anterior commissure, AHy = anterior hypothalamus, CPU = caudate putamen, F = fornix, GP = glopus pallidus, IC = internal capsule, MPO = medial preoptic area, OX = optic chiasma, VP = ventral pallidum.

shock period ($p>0.05$) (Table 6). During the retention test, a significant group effect was found ($p<0.05$). The saline-treated NBM-lesioned group entered the dark compartment faster than the controls ($p<0.05$) (Fig. 5). THA 3- and 5-mg/kg-treated rats were not impaired from the controls ($p>0.05$).

ChAT activity. A significant group effect was found in the analysis of the frontal cortex ChAT activity ($p<0.05$) (Table 7).

TABLE 4

DRUG-INDUCED CHANGES ON THE PA TRAINING TRIAL PERFORMANCE

Groups	Reentries	Entry Latency (s)	Shock Duration (s)
C	1.9 ± 1.5	26 ± 19	3.0 ± 3.1
FX,S	2.6 ± 1.0	12 ± 45	3.6 ± 2.8
FX,T3	2.0 ± 1.3	78 ± 23*	4.3 ± 4.1
NB+FX,S	2.2 ± 0.7	22 ± 34	4.0 ± 3.4
NB+FX,T3	1.5 ± 0.7	80 ± 13*	3.7 ± 2.7

Values are expressed as mean ± S.D. Abbreviations: see Fig. 4.
*$p<0.05$ vs. controls, Mann-Whitney U-test.

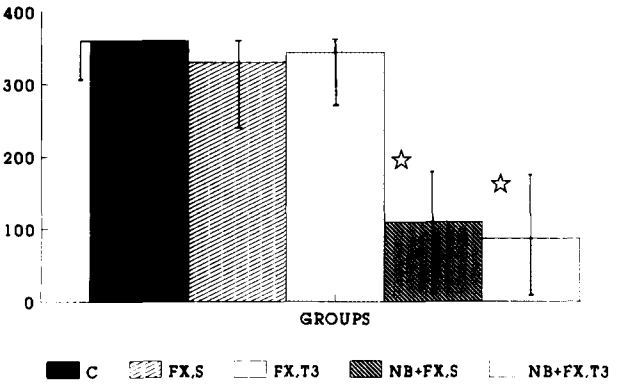

FIG. 4. Third experiment. NBM + frontal cortex-lesioned rats, THA 3 mg/kg. Abbreviations: C = NBM + frontal cortex-sham-operated, saline (controls); FX, S = frontal cortex-lesioned, saline; FX, T3 = frontal cortex-lesioned + THA 3 mg/kg; NB+FX, S = NBM + frontal cortex-lesioned, saline; NB + FX, T3 = NBM + frontal cortex-lesioned, THA 3 mg/kg. Values are expressed as median (+ minimum and maximum). *$p<0.05$ vs. controls, Mann-Whitney U-test.

All three NBM-lesioned groups had lower ChAT activity than the controls. No differences were found between the different groups of NBM-lesioned rats ($p>0.05$ in all comparisons).

Histology. The lesions produced by quisqualic acid were again comparable to those described in the 1st experiment.

DISCUSSION

Unilateral NBM or NBM + frontal cortex lesions produced an impairment in passive avoidance retention. Our results are in agreement with the previous data which suggest that the integrity of the NBM is important for normal PA retention (2, 8, 13).

Interestingly, whereas 3-mg/kg acute THA treatment did not alter retention performance of intact control rats, this dose did alleviate NBM-lesion-induced amnesia. Furthermore, we could demonstrate that, after 10 days of chronic THA treatment, the dose-response curve was broadened: not only 3 mg/kg but also 5 mg/kg facilitated retention of NBM-lesioned rats. However, acute administration of THA 3 mg/kg failed to restore memory function of rats subjected to combined NBM + frontal cortex lesions.

A question that inevitably arises is whether or not the deficit in PA performance observed after a 24-hour retention interval is

TABLE 5

ChAT ACTIVITY IN THE FRONTAL CORTEX IPSILATERAL TO LESIONING

Groups	ChAT (nmol/mg protein/minute)
C	1.10 ± 0.2
FX,S	1.00 ± 0.2
FX,T3	0.99 ± 0.3
NB+FX,S	0.42 ± 0.1*
NB+FX,T3	0.43 ± 0.1*

Values are expressed as mean ± S.D. Abbreviations: see Fig. 4.
*$p<0.05$ vs. controls, Mann-Whitney U-test.

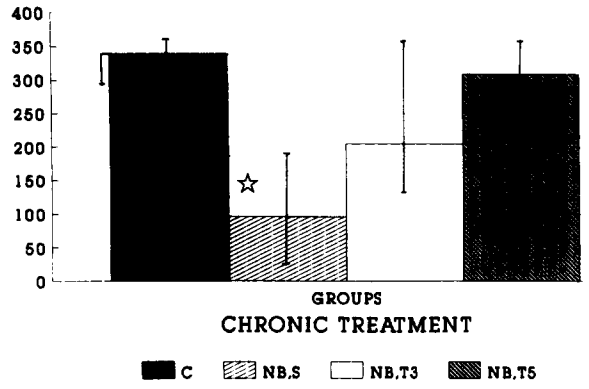

FIG. 5. Fourth experiment: NBM-lesioned rats, THA 3 or 5 mg/kg (chronic administration). The last THA injections were given 30 min before behavioral training. Values are expressed as median (+minimum and maximum). Abbreviations: C = NBM-sham-lesioned, saline; NB, S = NBM-lesioned, saline; NB, T3 = NBM-lesioned, THA 3 mg/kg × 10 days; NB, T5 = NBM-lesioned, THA 5 mg/kg × 10 days. mg/kg; *$p<0.05$ vs. controls, Mann-Whitney U-test.

related to cholinergic deafferentation of cortical areas involved in PA learning (e.g., frontal cortex) or whether it is due to nonspecific subcortical damage. This issue is important because some of the performance deficits induced by NBM lesions may not be related to the loss of cholinergic neurons (2,14). If cholinomimetics (e.g., THA) or fetal grafts rich in cholinergic cell bodies placed in the frontal cortex can reverse amnesia induced by NBM destruction, it is reasonable to believe that the PA impairments may be, at least in part, secondary to cortical cholinergic deafferentation. The present and previous experiments have demonstrated such an effect. Pretraining injections of acute THA at 3 mg/kg could partially reverse NBM-lesioning-induced PA retention deficits. Furthermore, after repeated treatment, THA at 3 mg/kg and also at 5 mg/kg stabilized PA retention performance. Haroutunian et al. (8) have also reported an improvement of NBM-lesion-induced PA deficit by an anticholinesterase, physostigmine. Finally, Dunnett et al. (3) have shown that placement of embryonic forebrain graft into the cortex reversed PA impairment induced by NBM lesioning. Taken together, the present and previous results suggest that the loss of cholinergic fibers in the frontal cortex is at least partially responsible for the PA deficits found in the NBM-lesioned rats. However, with the available nonselective lesion methods, the importance of the noncholinergic neuron loss in the quisqualic acid NBM-lesion-induced PA retention deficit cannot be excluded.

One explanation for the incomplete reversal of NBM-lesion-induced PA memory failure by acute THA may be the lack of an optimal THA dose. In agreement with the previous pharmacological studies investigating the effects of anticholinesterase drugs on memory (8, 9, 15, 21), the PA-retention-improving effects of THA occurred in a narrow dose range. It is reasonable to believe that, at 1 mg/kg, THA may not have restored cholinergic activity of the NBM and therefore, PA retention deficit in lesioned rats was not alleviated. Since THA is not selective for the NBM cholinergic system, acute administration of the highest dose of THA (5 mg/kg) may have overstimulated other central and peripheral cholinergic systems and therefore produced severe side effects, impairing performance in the PA acquisition test. Indeed, in this and a previous study (15), THA at 5 mg/kg induced motor incoordination which may impair PA acquisition performance. Previously, we described that, in a test measuring motor coordination, the test of elevated bridges, acute administration of THA at 5 mg/kg produced severe performance defects (15). Interestingly, after 10 days of repeated THA treatment, both the motor side effect and memory-modulating effect of THA were altered. Whereas both 3 and 5 mg/kg doses of acute THA increased entry latency, only 5 mg/kg had this effect after repeated treatment. Thus indirect comparison across experiments in this study indicates partial tolerance to the motor inhibitory effects even within one week. On the other hand, after repeated administration, THA became more effective in reversing the memory impairment. The 5-mg/kg dose, which was supraoptimal after acute injection, restored performance to control levels after seven days of pretreatment.

Our results described that acute THA at 3 mg/kg did not reverse PA retention defect of rats subjected to NBM + frontal cortex lesions. It is important to note that the degeneration of the association frontal cortex is involved in AD-related memory loss. For example, DeKosky and Sceff (2) described that the degree of pathological changes in the frontal cortex correlated with the severity of cognitive changes in AD patients. Therefore, it is tempting to speculate that THA and other cholinesterase inhibitors [such as physostigmine, (7)] may have only negligible effects on cognitive functions if the frontal cortex has degenerated severely during AD.

In conclusion, THA 1) alleviated, after acute administration, an NBM-lesion-induced PA retention deficit at 3 mg/kg, but not at 1 or 5 mg/kg; 2) alleviated, after 10 days of repeated administration at both 3- and 5-mg/kg doses, an NBM-lesion-induced PA memory deficit; and 3) failed to alleviate NBM + frontal cortex-lesion-induced PA amnesia.

TABLE 6

DRUG INDUCED CHANGES ON THE PA TRAINING TRIAL PERFORMANCE

Groups	Reentries	Entry Latency (s)	Shock Duration (s)
C	2.0 ± 1.2	19 ± 32	3.6 ± 2.6
NB,S	2.2 ± 1.5	23 ± 23	3.0 ± 3.1
NB,T3	1.4 ± 2.3	24 ± 12	2.4 ± 3.2
NB,T5	1.4 ± 1.5	58 ± 23*	4.0 ± 2.5

Values are expressed as mean ± S.D. Abbreviations: see Fig. 5.
*$p<0.05$ vs. controls, Mann-Whitney U-test.
The last THA injections were given 30 min before behavioral training.

TABLE 7

ChAT ACTIVITY IN THE FRONTAL CORTEX IPSILATERAL TO LESIONING

Groups	ChAT Activity (nmol/mg protein/minute)
C	1.21 ± 0.2
NB,S	0.41 ± 0.3*
NB,T3	0.47 ± 0.2*
NB,T5	0.44 ± 0.2*

Values are expressed as mean ± S.D. Abbreviations: see Fig. 5.
*$p<0.05$ vs. controls, Mann-Whitney U-test.

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