Pergamon

Brain Research Bulletin, Vol. 36, No. 1, pp. 51–56, 1995

0361-9230/95 $9.50 + .00

0361-9230(94)00162-6

Nucleus Basalis Lesions: Implication of Basoamygdaloid Cholinergic Pathways in Memory

PAUL E. MALLET,* RICHARD J. BENINGER,*[1] SHEERA N. FLESHER,† KHEM JHAMANDAS† AND ROLAND J. BOEGMAN†

*Departments of *Psychology and †Pharmacology and Toxicology, Queen's University, Kingston, Canada K7L 3N6*

[Received 15 October 1993; Accepted 29 June 1994]

ABSTRACT: Previous studies have shown a lack of association between cortical choline acetyltransferase (ChAT) activity and severity of memory impairment following excitotoxic lesions of the nucleus basalis magnocellularis (NBM). It recently has been proposed that the differential effects of NBM injections of various excitotoxins on amygdaloid and cortical ChAT may explain this result. The present study evaluated the mnemonic effect of unilateral intra-NBM infusions of the excitotoxins phthalic acid and quisqualic acid, which decrease ChAT activity primarily in the amygdala and cortex, respectively. Rats were trained in a double Y-maze, lesioned, and allowed to recover for 1 week prior to memory assessment. Behavioral results showed impaired working but not reference memory following phthalic acid lesions, and no significant effect following quisqualic acid lesions. Biochemical analysis in a second group of subjects confirmed that phthalic acid lesions produced a large decrease in basolateral amygdaloid ChAT, but had little effect on cortical ChAT activity. Conversely, quisqualic acid lesions produced a large decrease in cortical, but not basolateral amygdaloid, ChAT activity. These results suggest that the NBM amygdalopetal cholinergic pathways play a role in mnemonic functioning.

KEY WORDS: Acetylcholine, Amygdala, Choline acetyltransferase, Double Y-maze, Nucleus basalis magnocellularis, Phthalic acid, Quisqualic acid, Reference memory, Working memory.

INTRODUCTION

Attempts at modeling age- and neuropathology-related disorders of memory using excitotoxic lesions of the nucleus basalis magnocellularis (NBM) recently have come under criticism, due in part to the finding that lesion-induced decreases in cortical choline acetyltransferase (ChAT) activity failed to correlate with the extent of memory impairment in spatial and nonspatial tasks [8,19,25]. For example, ibotenic acid lesions of the NBM produced a greater impairment in the acquisition of a water maze task than quisqualic acid lesions of the NBM, even though quisqualic acid produced a larger decrease in cortical ChAT activity [5].

These findings have led to the suggestion that memory impairments following excitotoxic lesions of the NBM may not be due to damaged corticopetal cholinergic cells, but instead, may be related to the extent of damage to noncholinergic cells in the region of the NBM [7]. Alternatively, some evidence suggests that other cholinergic basal forebrain pathways may be affected differentially by different excitotoxins. Thus, our previous work has shown that lesions of the NBM made with different neurotoxins produce different effects on cholinergic projections to the cortex and amygdala [2,3]. Various excitotoxins (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid, ibotenic acid, quisqualic acid, quinolinic acid, or *N*-methyl-D-aspartic acid) were infused into the NBM of rats 7 days prior to assessment of cortical and amygdaloid ChAT activity [3]. Each neurotoxin produced a unique dose-dependent decrease in cortical and amygdaloid ChAT activity. Although mnemonic function was not assessed, it was noted that excitotoxins that produced the greatest ChAT decrease in the amygdala had been reported in previous investigations to produce the largest impairments of memory [5,19,25].

In these neurochemical experiments, one excitotoxic compound was particularly interesting. Phthalic acid [1,2-benzenedicarboxylic acid] is a quinolinic acid analogue that has been shown to excite cortical neurons [24] and to evoke acetylcholine release from striatal slices [15]. Infusions of phthalic acid into the NBM produced a large decrease in amygdaloid but not cortical ChAT activity, a profile opposite that seen with quisqualic acid [2]. Hence, if the NBM amygdalopetal pathways play a role in memory, it follows that phthalic acid lesions of the NBM should lead to mnemonic deficits.

The purpose of the current study was to investigate the effects of phthalic acid lesions of the NBM on working and reference memory. It was predicted that phthalic acid lesions of the NBM would produce a larger impairment of working memory than quisqualic acid lesions of the NBM, because the former affects primarily amygdalopetal pathways, and the latter affects primarily corticopetal pathways. It also was predicted that there would be no difference between groups in reference memory performance. The double Y-maze, an apparatus that consists of two Y-mazes joined at the stem, was used to assess mnemonic functioning for two reasons. First, every trial has a distinct reference and working memory component. Second, if lesioned animals

[1]To whom requests for reprints should be addressed.

showed a working but not a reference memory deficit, then nonmnemonic factors such as deficits in motivation, perception, and motor functioning could be ruled out as potential factors affecting performance. This was possible because the reference and working memory components of the double Y-maze task are identical in all respects, except for the type of memory required for accurate performance.

METHOD

Subjects

Treatment of the subjects used in the present experiment was in accordance with the guidelines of the Canadian Council on Animal Care, the Animals for Research Act, and relevant University policies, and was reviewed and approved by the Queen's University Animal Care Committee.

Forty-six experimentally naive male Sprague–Dawley rats, weighing approximately 200–225 g (Charles River Breeders, St-Constant, Quebec), were housed in groups of three or four during training, and were maintained in a temperature-controlled environment (approximately 20°C) with a 12 L:12 D cycle (lights on at 0700 h). Twenty-nine animals were used in the behavioral experiment, and 18 were used for biochemical verification of lesion effects. All animals received free access to water and were maintained at 85–90% of their free-feeding weights (increased by 5 g/week for growth) by daily feeding with measured rations of dry food (Purina rodent laboratory chow #5001). Following training, animals were caged singly in preparation for surgery, and they remained individually housed until the conclusion of the experiment.

Apparatus

A wooden double Y-maze was used (Fig. 1). Each arm was 35 cm long and extended from the central stem (45 cm long and 17 cm wide) at 120° angles. The floor was constructed of parallel stainless steel bars, spaced approximately 9 mm apart, except for the junction where the arms met the stem, which was constructed of Plexiglas triangles. Removable wooden doors were used to permit or restrict entry into each half of the maze. The doors and maze walls (26 cm high) were painted flat gray. Small pieces of Froot Loops cereal were used as reward, and were also scattered beneath the floor to prevent the animals from using food odor cues to find the baited arms. The central stem, as well as the distal end of each arm, contained a metal food cup. The entire maze was supported on a table (70 cm above floor level) in a room where various visual cues could be readily viewed (e.g., experimenter, door, light fixture, electrical panel).

Training

Animals were food deprived to 85–90% of their free-feeding weights, and were given Froot Loops cereal (3 g) in their home cages 5 days prior to introduction to the maze. Each animal received 3 days of habituation during which they were placed in the maze with all doors removed and were allowed to collect cereal from all food cups for a total of 10 min per day.

Training trials consisted of two parts: a reference memory component and a working memory component. In the reference memory component, animals were placed at the end of one of the arms of the first Y (A or B in Fig. 1) and were rewarded for going down the stem (C in Fig. 1), the end of which was blocked, thereby restricting access to the second Y. If the animal chose the stem, the door was removed and another door was placed behind the animal, permitting access to the second Y and restricting access to the first Y. Failing to choose the stem was scored as a reference memory error and resulted in the termination of the trial.

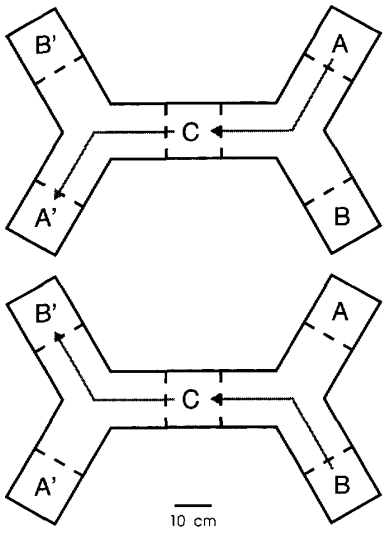

FIG. 1. Schematic diagram of the double Y-maze. Arrows represent the two possible correct paths. Dashed lines represent the locations where wooden barriers could be placed to permit or restrict access to certain parts of the maze.

In the working memory component, the animal had to choose the opposite direction chosen in the reference memory component to be rewarded. That is, if the trial began at A (Fig. 1, top), then the correct working memory choice was to choose A′. If the trial began at B (Fig. 1, bottom), the correct working memory choice was to choose B′. Choosing the correct arm was scored as a correct working memory choice and constituted a complete trial. Failing to choose the correct arm was scored as a working memory error. Following a working memory error, the animal was allowed to proceed to the correct arm to collect the reward (previous experiments using this task found that this served to reduce the number of training trials during acquisition). Each animal received one session of between 24 and 50 trials per day, at approximately the same time each day, 7 days per week. A random half of the trials began in each arm of the first Y except that no more than three trials in a row began in the same arm. Training continued until a score of at least 88% was obtained on the first 24 trials (21 correct out of the first 24 trials), on each of 3 consecutive days, for both the reference and working memory components.

Drugs

Quisqualic acid (Sigma) was dissolved in phosphate-buffered saline (0.9%) in a concentration of 60 nmol/0.5 μl. Phthalic acid (Sigma) was dissolved in saline (0.9%) in a concentration of 300 nmol/0.5 μl. The pH of both solutions was adjusted to 7.0 using 1 N NaOH. All drugs were prepared before the commencement of the study and were kept frozen in aliquots at −20°C until needed. Once thawed, the unused portions of solutions were discarded.

Preoperative Preparation and Surgeries

Once the acquisition criterion was reached, rats were prepared for surgery. Because phthalic acid lesions of the NBM normally produce an acute state of aphagia and adypsia that can last up to 1 week (unpublished observations), all subjects were given food and water ad lib beginning a few days before surgery to maximize survival rates. Normal diet was also supplemented with sweet foods such as chocolate milk and chocolate chip cookies so that they would not be novel when given postoperatively.

Animals were anaesthetized using an oxygen flow containing 4% halothane (Halocarbon, Malton, Ontario), which was reduced to 2% during surgery. Animals then were mounted in a stereotaxic apparatus with the incisor bar set at −3.3 mm, and a small hole was drilled through the skull directly above the infusion site. A 0.31-mm diameter cannula was lowered into the ventral globus pallidus-substantia innominata region (1.3 mm posterior to bregma, 2.6 mm lateral to the midline, and 7.5 mm ventral to the surface of the skull) through which was delivered a 0.5-μl microinjection of either phthalic acid (300 nmol), quisqualic acid (60 nmol), or vehicle (0.9% saline). The infusion took place over a 2.25-min period, and the cannula was left in place for an additional period of 2.0 min before being withdrawn to allow for diffusion. Unilateral lesions were chosen because previous work in our laboratory has demonstrated that bilateral lesions of the NBM, using the dose of phthalic acid needed in the present investigation, is often fatal. Half of the subjects received left side lesions, and half received right side lesions. The skull hole was filled with bone wax, the wound was sutured with surgical silk, and the animal was removed from the stereotaxic apparatus. Animals were housed in plastic single cages with wood chip bedding during the postoperative recovery period. Behavioral testing began 7 days later.

Behavioral Testing

Each animal was given 24 double Y-maze test trials each day for 12 days. Test trials were identical to training trials. The total number of reference and working memory errors was recorded for each day. Of the initial 29 subjects trained, one did not reach the acquisition criterion and was not lesioned, and one died postoperatively. Behavioral assessment was conducted blind to the experimental condition; that is, the maze operator was not informed of the subjects' group membership.

Biochemical Analysis

To verify the extent of ChAT depletion, ChAT assays using the method of Fonnum [9] were carried out in a second group of animals. Although it would have been preferable to obtain biochemical data from the same animals that generated the behavioral data, this was prevented by technical difficulties with the ChAT assay when the brains of the subjects used in the behavioral experiment became available. Rats (n = 18) were lesioned in the same manner as that described above. Seven days later, rats were sacrificed by decapitation and their brains were rapidly removed and placed in ice-cold saline for 15 s. Samples of frontal and parietal cortex were obtained from a coronal slice taken 3 mm caudal to the posterior aspect of the optic chiasm. The amygdala, including the basolateral nucleus, was prepared from a 2-mm thick coronal slice cut caudal to the optic chiasm by a free-hand dissection of the tissue lateral to the optic tract, medial to the extension of the corpus callosum, ventral to the rhinal fissure, and dorsal to the piriform cortex. Tissue was dissected on ice and homogenized in ChAT homogenizing buffer before being stored at −75°C. Protein assays [16] were carried out within 1 week of freezing, and the amount of ChAT activity was expressed in nmol of acetylcholine formed per mg of protein per hour in each brain sample.

RESULTS

Reference Memory

The mean percentage correct reference memory postoperative test trials averaged into four blocks of three sessions each are shown in Fig. 2A. As can be seen, performance was very accurate across blocks in all three groups.

A two-factor analysis of variance (ANOVA) (group by block) with one factor repeated (block) was conducted on the mean percentage of correct reference memory trials. Geisser–Greenhouse [10] corrected degrees of freedom were used to correct the positive bias that could result from violating the sphericity assumption of within-subjects ANOVA designs [13]. The analysis did not produce a significant main effect of group, $F(2, 24) = 2.99$, $p > 0.05$, or a significant group by block interaction, $F(4.53, 54.33) = 2.30$, $p > 0.05$. However, the block effect was significant, $F(2.26, 54.33) = 3.10$, $p < 0.05$. It should be noted that this represents a general improvement of performance over sessions and not a difference among groups. Post hoc Tukey tests comparing each of the four levels of block to the remaining three levels were conducted to further isolate the significant effects. None of the comparisons was found to be significant ($p > 0.05$).

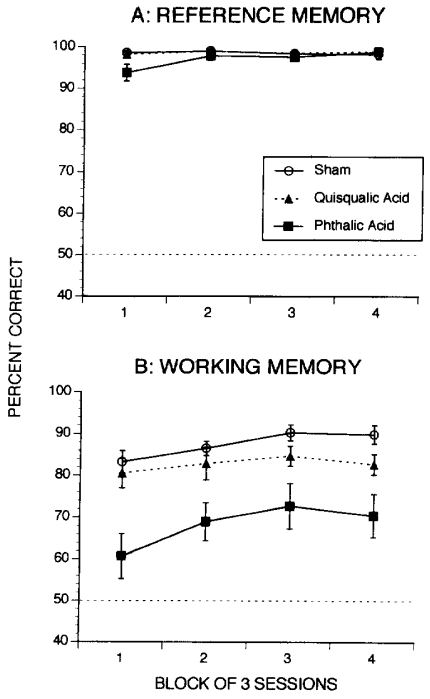

FIG. 2. Mean ± SEM percentage of correct postoperative reference memory (A) and working memory (B) test trials as a function of blocks of three sessions for subjects receiving sham, quisqualic acid, or phthalic acid lesions of the NBM. The broken horizontal lines at 50% represent chance performance.

Working Memory

The mean percentage correct working memory postoperative test trials averaged into four blocks of three sessions can be seen in Fig. 2B. Accuracy was highest in the sham-operated controls, and lowest in the phthalic acid group. The performance of the quisqualic acid group fell between that of the other two groups. Figure 2B also shows that the percentage of correct working memory trials increased over blocks of sessions in all groups.

A two-factor ANOVA (group by block) with one factor repeated (block) using Greenhouse-Geisser (10) corrected degrees of freedom for the repeated factors was conducted on the mean percentage of correct working memory trials. The analysis resulted in a significant main effect of group, $F(2, 24) = 8.42$, $p < 0.01$, a significant main effect of block, $F(2.34, 56.11) = 6.79$, $p < 0.01$, but did not result in a significant group by block interaction, $F(4.68, 56.11) = 0.84$, $p > 0.05$.

Post hoc Tukey tests comparing each of the three groups (averaged over blocks) with the remaining two were conducted to further isolate the significant effects. Results indicated that the phthalic acid-lesioned animals showed an impairment when compared to each of the other two groups ($p < 0.05$). No significant difference was observed between the sham-lesioned controls and the quisqualic acid-lesioned subjects ($p > 0.05$).

Post hoc Tukey tests comparing each of the four blocks of three sessions (averaged over groups) with the remaining three resulted in a significant difference when the first block was compared with either the third or fourth block ($p < 0.05$). This confirms that working memory performance improved over blocks of sessions. None of the other comparisons was found to be significant ($p > 0.05$).

Biochemical Analysis

Table 1 shows the results of the ChAT assays. Some variability among groups can be seen in the absolute values of ChAT activity on the nonlesioned side for both the cortex and amygdala. However, sham values for percent decrease on the lesioned side were consistently within the range seen in our previous studies, as were the profiles for quisqualic and phthalic acids. As can be seen, phthalic acid lesions of the NBM produced a large decrease in basolateral amygdaloid, but not cortical, ChAT activity. The opposite was observed in rats that received quisqualic acid lesions of the NBM; cortical ChAT, but not amygdaloid ChAT, showed a large decrease in activity. Two single-factor ANOVAs were conducted on the percent decrease in ChAT activity, one comparing cortical and one comparing amygdaloid ChAT activity in the three groups of subjects. Results indicated a group main effect for both cortical ChAT activity, $F(2, 15) = 9.80$, $p < 0.01$, and amygdaloid ChAT activity, $F(2, 15) = 7.70$, $p < 0.01$.

Post hoc Tukey tests comparing the percent of cortical ChAT activity decrease for each of the three groups with the remaining two revealed a significant difference in activity between the sham-lesioned and quisqualic acid-lesioned animals ($p < 0.01$). In addition, a significant difference was observed between the phthalic acid-lesioned and quisqualic acid-lesioned subjects ($p < 0.05$). No difference was noted between the phthalic acid-lesioned and sham-lesioned subjects ($p > 0.05$).

Post hoc Tukey tests also were conducted to compare amygdaloid ChAT activity for each of the three groups to the remaining two. A significant difference in ChAT activity between the sham-lesioned and phthalic acid-lesioned animals was found ($p < 0.01$). Moreover, a significant difference was observed between the phthalic acid-lesioned and quisqualic acid-lesioned subjects ($p < 0.05$). No difference was observed between the quisqualic acid-lesioned and sham-lesioned subjects ($p > 0.05$).

DISCUSSION

The present study demonstrated that phthalic, but not quisqualic acid, lesions of the NBM led to a selective disruption of working memory performance in the double Y-maze. Animals undergoing the same lesions as those used in the behavioral investigation revealed that phthalic acid produced a large decrease in amygdaloid, but not cortical, ChAT activity relative to the unoperated side. This is the opposite of what was found in those animals that received quisqualic acid lesions of the NBM. A large decrease in cortical, but not amygdaloid, ChAT activity was found in these subjects. Biochemical results are in good agreement with our previous reports [2,3]. It is noteworthy that the animals used in the biochemical investigation had not received maze experience and were not food deprived. However, previous work in our laboratory suggests that this should not have affected our results. It also should be noted that all of our biochemical results from cortical ChAT assays are based on a slice of frontoparietal cortical tissue. We assume that ChAT would be affected similarly in other sections of the cortex as described by Johnston et al. [12].

These findings suggest a lack of relationship between cortical ChAT depletion and working memory function following excitotoxic lesions of the NBM. This is in accord with recent experiments [19,22]. However, unlike previous studies that have attributed the lack of correlation between biochemical and behavioral findings to damage to noncholinergic neurons in the region surrounding the NBM [5,7], the present experiment offers

TABLE 1

CHOLINE ACETYLTRANSFERASE ACTIVITY IN THE CORTEX AND AMYGDALA

	Nonlesioned	Lesioned	(%) Decrease
Cortex			
Sham	26.17 ± 1.56	26.45 ± 2.78	−0.15 ± 4.70
Quisqualic acid	27.95 ± 1.75	14.22 ± 2.86	49.77 ± 9.38
Phthalic acid	19.52 ± 1.26	16.04 ± 1.26	16.74 ± 7.47
Amygdala			
Sham	82.17 ± 12.99	69.06 ± 10.52	15.71 ± 5.21
Quisqualic acid	70.84 ± 9.83	52.91 ± 4.33	17.28 ± 12.41
Phthalic acid	65.94 ± 6.22	25.06 ± 1.62	60.69 ± 3.91

ChAT activity levels are expressed as mean ± SEM nmol acetylcholine formed per mg protein per h.

an alternate explanation. That is, excitotoxic lesions of the basal forebrain may produce an impairment in working memory performance due to a loss of NBM amygdalopetal cholinergic neurons. This result is consistent with some recent findings.

First, it has been demonstrated that the cholinergic basal forebrain neurons that project to the amygdala are among the most severely affected in Alzheimer's disease [18,20]. It is possible that a loss of these pathways is a major contributor to the recent memory deficits observed in people afflicted with Alzheimer's disease [see [6] for a description of these mnemonic deficits]. In fact, in an investigation that examined ChAT activity in the brains of people who died of Alzheimer's disease compared to normal controls, it was reported that the only consistent deficiency in the Alzheimer brains was found in the amygdala (ChAT activity was also examined in the hippocampus, thalamus, frontal, temporal, and parietal cortex) [21].

Second, there is evidence that direct cholinergic manipulations of the amygdala can affect working memory. For example, in a recent experiment conducted in our laboratory [11], pretrained rats received bilateral microinfusions of scopolamine into the amygdala before being tested in a double Y-maze. A dose of 24 μg in 0.5 μl produced a selective impairment of working memory. Similarly, working memory impairments have been observed following various treatments (e.g., lesions, electrical stimulation) affecting the amygdala [see [23] for review].

Reference memory was not significantly impaired following lesions of the NBM, although there was a trend in this direction. As can be seen in Fig. 2A, this was most likely due to a transient impairment of reference memory during the first block of three postoperative sessions in the animals lesioned with phthalic acid. However, the impairment did not persist beyond the first block. The lack of reference memory impairment demonstrates that lesion-induced deficits in performance were due to an impairment in mnemonic function and cannot be attributed to nonmnemonic variables (e.g., motivation, motor function, attention, sensory or perceptual ability). That is, a nonmnemonic deficit should affect both the reference and working memory components of the double Y-maze task because both components are identical in all respects except for the type of memory required for accurate performance. Because both components require a spatial discrimination, and both components lead to the same type of food reward, one would expect a deficit in any nonmnemonic variable to affect both components of the task to the same extent [17]. This is an important feature of the double Y-maze task because it eliminates the problem of adypsia and aphagia observed in the phthalic acid-lesioned rats. For example, if the lesioned-induced adypsia and aphagia were still present following the postoperative recovery period, one would expect poor performance on both components of the task. Interestingly, the initial drop in reference memory performance (although statistically nonsignificant) may be explained in this manner.

It should be noted that the working memory deficits observed may not be due to the differential effects of phthalic and quisqualic acids on NBM amygdalopetal pathways, but instead may be a product of differential nonspecific damage to the NBM and surrounding neural tissue [7,8]. It is possible that an infusion of phthalic acid into the NBM may cause greater damage to tissue in close proximity to the NBM than does an infusion of quisqualic acid. Some unpublished findings from our laboratory support this notion. Histological examination of the area surrounding the NBM following an intra-NBM infusion of the same doses of quisqualic and phthalic acid as those used in the present investigation revealed that phthalic acid leads to a greater decrease in acetylcholinesterase-positive cells than does quisqualic acid. Possible differential effects on cells that are not acetylcholinesterase-positive have not been investigated.

It is interesting to note that an impairment of working memory following quisqualic acid lesions of the NBM has previously been observed in the double Y-maze [1], an observation that was not replicated in the current investigation. This was likely the result of the relatively smaller neuronal damage induced by unilateral lesions used here, rather than bilateral lesions as were used previously.

Although phthalic acid lesions of the NBM produced an impairment in performance on the working memory component of the double Y-maze task, it is important to note that the working memory component required a very large number of training trials to reach the acquisition criterion relative to the reference memory component. It is possible that the differential effects of phthalic acid on reference and working memory was due to a difference in task difficulty. This is based on the proposition that a positive correlation exists between task difficulty and susceptibility to interference [4]. However, some evidence exists to the contrary. For example, in one study, rats exhibited an impairment in radial maze, but not Stone maze, performance following ibotenic acid lesions of the basal forebrain, even though the Stone maze proved to be a more difficult task to learn [14]. Furthermore, disruption of the high-affinity transport of choline using intracerebroventricular infusions of ethylcholine aziridinium ion produces an impairment of working, but not reference, memory in a split-stem T-maze, even though the rates of acquisition were nearly identical for the reference and working memory components [4]. Nonetheless, the possible involvement of task difficulty in obtaining the present results cannot be completely ruled out.

The results of the current investigation suggest that the NBM amygdalopetal cholinergic pathways may play a role in mnemonic functioning. This may have implications for the development of future strategies for the treatment of Alzheimer's disease. Because it would appear that this system is at least as important as the NBM corticopetal cholinergic neurons, it follows that Alzheimer treatment strategies should investigate the possible benefits gained from the restoration of function to these pathways.

ACKNOWLEDGEMENTS

Funding for this research has been provided by grants from the Natural Sciences and Engineering Research Council of Canada to R. J. Beninger and the Network of Neural Regeneration and Recovery, one of the three networks of Centres of Excellence supported by the Government of Canada.

REFERENCES

1. Biggan, S. L.; Beninger, R. J.; Cockhill, J.; Jhamandas, K.; Boegman, R. J. Quisqualate lesions of rat nbm: Selective effects on working memory in a double y-maze. Brain Res. Bull. 26:613–616; 1991.
2. Boegman, R. J.; Cockhill, J.; Jhamandas, K.; Beninger, R. J. Phthalic acid lesions of rat basal forebrain: Differential effects on choline acetyltransferase in cortex and amygdala. Soc. Neuroci. Abstr. 18:445; 1992.
3. Boegman, R. J.; Cockhill, J.; Jhamandas, K.; Beninger, R. J. Excitotoxic lesions of rat basal forebrain: Differential effects on choline acetyltransferase in the cortex and amygdala. Neuroscience 51:129–135; 1992.
4. Chrobak, J. J.; Hanin, I.; Walsh, T. J. AF64A (ethylcholine aziridinium ion), a cholinergic neurotoxin, selectively impairs working memory in a multiple component T-maze task. Brain Res. 414:15–21; 1987.

5. Connor, D. J.; Langlais, P. J.; Thal, L. J. Behavioral impairments after lesions of the nucleus basalis by ibotenic acid and quisqualic acid. Brain Res. 555:84–90; 1991.
6. Coyle, J. T.; Price, D. L.; DeLong, M. R. Alzheimer's disease: A disorder of cortical cholinergic innervation. Science 219:1184–1189; 1983.
7. Dunnett, S. B.; Everitt, B. J.; Robbins, T. W. The basal forebrain-cortical cholinergic system: Interpreting the functional consequences of excitotoxic lesions. Trends Neurosci. 14:494–501; 1991.
8. 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.
9. Fonnum, F. A rapid radiochemical method for the determination of choline acetyltransferase. J. Neurochem. 24:407–409; 1975.
10. Geisser, S.; Greenhouse, S. W. An extension of Box's results on the use of the F distribution in multivariate analysis. Ann. Math. Stat. 29:885–891; 1958.
11. Ingles, J. L.; Beninger, R. J.; Jhamandas, K.; Boegman, R. J. Scopolamine injected into the rat amygdala impairs working memory in the double Y-maze. Brain Res. Bull. 32:339–344; 1993.
12. Johnston, M. V.; McKinney, M.; Coyle, J. T. Neocortical cholinergic innervation: A description of extrinsic and intrinsic components in the rat. Exp. Brain Res. 43:159–172; 1981.
13. Keppel, G. Design and analysis. A researcher's handbook. Englewood Cliffs, NJ: Prentice Hall; 1991.
14. Knowlton, B. J.; Wenk, G. L.; Olton, D. S.; Coyle, J. T. Basal forebrain lesions produce a dissociation of trial-dependent and trial-independent memory performance. Brain Res. 345:315–321; 1985.
15. Lehmann, J.; Fernaky, J. W.; Schaeffer, P.; Coyle, J. T. Dissociation between the excitatory and "excitotoxic" effects of quinolinic acid analogs on the striatal cholinergic interneuron. J. Pharmacol. Exp. Ther. 232:873–882; 1985.
16. Lowrey, O. H.; Rosebrough, N. J.; Farr, A. C.; Randall, R. S. Protein measurement with the Folin-phenol reagent. J. Biol. Chem. 193:265–275; 1951.
17. Mallet, P. E.; Beninger, R. J. The double Y-maze as a tool for assessing memory in rats. Neurosci. Protocol. 93-010-02: 1–11.
18. Mann, D. M. A. The site and nature of the primary lesions in Alzheimer's disease. Prog. Clin. Biol. Res. 317:303–311; 1989.
19. Markowska, A. L.; Wenk, G. L.; Olton, D. S. Nucleus basalis magnocellularis and memory: Differential effects of two neurotoxins. Behav. Neural Biol. 54:13–26; 1990.
20. Mufson, E. J.; Bothwell, M.; Kordower, J. H. Loss of nerve growth factor receptor-containing neurons in Alzheimer's disease: A quantitative analysis across subregions of the basal forebrain. Exp. Neurol. 105:221–232; 1989.
21. Palmer, A. M.; Procter, A. W.; Stratmann, G. C.; Bowen, D. M. Excitatory amino acid-releasing and cholinergic neurones in Alzheimer's disease. Neurosci. Lett. 66:199–204; 1986.
22. Robbins, T. W.; Everitt, B. J.; Ryan, C. N.; Marston, H. M.; Jones, G. ; Page, K. J. Comparative effects of quisqualic and ibotenic acid-induced lesions of the substantia innominata on the acquisition of a conditional visual discrimination: Differential effects on cholinergic-mechanisms. Neuroscience 28:337–352; 1989.
23. Sarter, M.; Markowitsch, H. J. Involvement of the amygdala in learning and memory: A critical review, with emphasis on anatomical relations. Behav. Neurosci. 2:342–380; 1985.
24. Stone, T. W. Excitant activity of methyl derivatives of quinolinic acid on rat cortical neurones. Br. J. Pharmacol. 81:175–181; 1984.
25. Wenk, G. L.; Markowska, A. L.; Olton, D. S. Basal forebrain lesions and memory: Alterations in neurotensin, not acetylcholine, may cause amnesia. Behav. Neurosci. 103:765–769; 1989.