Pharmacology Biochemistry & Behavior, Vol. 24, pp. 1287–1292, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Behavioral Recovery Following Bilateral Lesions of the Nucleus Basalis Does Not Occur Spontaneously

RAYMOND T. BARTUS,*† MICHAEL J. PONTECORVO,* CHARLES FLICKER,† REGINALD L. DEAN* AND JOANNE C. FIGUEIREDO*

**Department of Central Nervous System Research, Medical Research Division of American Cyanamid Company Lederle Laboratories, Pearl River, NY 10965 and †New York University Medical Center, 550 First Avenue, New York, NY 10016*

Received 31 January 1986

BARTUS, R. T., M. J. PONTECORVO, C. FLICKER, R. L. DEAN AND J. C. FIGUEIREDO. *Behavioral recovery following bilateral lesions of the nucleus basalis does not occur spontaneously.* PHARMACOL BIOCHEM BEHAV 24(5) 1287–1292, 1986.—Recent studies have shown that rats given bilateral ibotenic acid lesions of the nucleus basalis (NBM) exhibit significant impairments on tasks requiring recent or trial-specific memory. However, despite the persistence of cholinergic deficiencies in the cortical projection area, the memory impairments gradually recover over a period of several months of training. Moreover, in one study, the behavioral recovery on a radial arm maze retention task was shown to generalize to a completely different behavior paradigm (passive avoidance) on which the animals had received no prior experience. The present study was performed to determine the extent to which this generalized recovery of performance on memory tasks is dependent upon extensive post-lesion training. Rats were given ibotenic acid lesions of the NBM and were then passively detained in their home cages for six months. Contrary to animals which had received post-surgical radial arm maze experience, the animals detained in their home cages displayed a significant retention impairment when tested on the passive avoidance task, suggesting that the experience the animals receive is an important factor for whether post-lesion functional recovery occurs. This study also confirms that the loss of cholinergic markers following bilateral, NBM lesions persists for at least several months, or longer.

Nucleus basalis Memory Cholinergic neurons Recovery of function Alzheimer's disease Cholinergic hypothesis Neurochemical correlates of behavior Dementia

IN recent years increased attention has been given to a diffuse cluster of large neurons whose parenchyma lie in the mammalian basal forebrain and whose axons project to the neocortex. These neurons, defined as the nucleus basalis magnocellularis (NBM) in the rat, provide a major source of extrinsic cholinergic innervation to the frontal, temporal and parietal cortices [12]. The increased interest in this formerly obscure brain region is, in part, related to recent observations that the homologous region in humans exhibits marked cell loss in patients suffering from certain prevalent neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease). Moreover, the identification and characterization of this cholinergic projection has permitted empirical investigation of a number of problems involving anatomical/neurochemical/behavioral relationships [1, 5, 7, 16, 17b].

Many experiments with animals have studied the effects of artificially destroying the parenchyma comprising the NBM. Neurochemical analysis has revealed a substantial loss of conventional cholinergic markers in the neocortex. Thus, marked decreases in choline acetyltransferase (CAT) activity, high affinity choline uptake (HACU) and acetylcholinesterase (AChE) histochemical staining have been consistently reported following damage to this brain region. Furthermore, regarding the topography of this projection, the greatest loss in cholinergic markers occurs in the more anterior half of the neocortex and little or no effect on cholinergic markers is observed in the posterior neocortex or in archi- or paleo-cortical areas such as the hippocampus.

Behavioral studies following NBM lesions demonstrate impairments in lesioned animals on a number of tasks, with some selectivity for tasks having learning/memory requirements. While the effects of lesions of the NBM on multiple-trial, active avoidance learning tasks have been mixed [7, 15, 16, 17], robust deficits have been reported on the reversal of previously learned tasks [5b, 11b, 18b]. Moreover, clear and consistent deficits have been found on retention of a single-trial passive avoidance paradigm [1, 5, 6b, 7, 9, 16, 17]. Subsequent studies testing NBM-lesioned rats on the passive avoidance paradigm have demonstrated a steep, temporal retention gradient [1,17], suggesting that the deficit may be partly due to accelerated forgetting or some similar disturbance in memory.

More sophisticated behavioral paradigms have convincingly demonstrated that destruction of the NBM significantly impairs performance on memory tasks, especially in situations requiring use of recent, short-term, or trial-specific types of information [5b, 11b, 14b, 17b]. For example, rats with NBM lesions exhibit a profound, time-dependent deficit in their ability to remember which arms of a radial

maze have been entered several minutes or hours earlier in the test session [5]. In contrast, memory for arms entered only moments earlier, as well as more general skills learned in the maze (involving the availability of food and the reinforcement contingencies related to obtaining the food) were not impaired.

Because paradigms such as the radial arm maze procedure above permit unconfounded, multiple testing of the same subject, it has also been possible to study the longer term behavioral effects of NBM lesions. These studies on the longer term effects of the lesion indicate that (despite persistence of the lesion-induced neurochemical deficiencies) the major deficits on memory function eventually recover over the course of several months of continued testing [5]. It was discovered that when rats received training and testing on the radial arm maze task, the performance of the lesioned rats on the delay conditions gradually improved. By six months after surgery, the previously robust deficit in recent memory had apparently recovered, and retention of the lesioned rats on the task was no longer different from that of the sham controls. Following the occurrence of this functional recovery, the rats were trained and tested on the same passive avoidance task which had revealed a profound effect on NBM lesions in previous experiments [5,7]. Although control rats with short-term NBM lesions exhibited a profound retention deficit on the passive avoidance task, the long-term lesioned rats that had previously recovered recent memory ability on the radial arm maze task exhibited no retention deficit on the passive avoidance task [5]. Thus, the recovery of recent memory, which occurred over a period of several months of training and testing on the radial arm maze, apparently generalized to the passive avoidance task, on which no post-lesion practice had been received.

As noted earlier, this recovery of behavioral function occurred in the absence of a corresponding neurochemical recovery of CAT activity, HACU and muscarinic receptor binding in the innervated tissue, or compensatory changes in other cholinergic brain areas. In contrast, there have been scattered reports suggesting that, following *unilateral* lesions of the NBM, a gradual recovery of CAT activity and HACU may occur in the cortex, with levels returning to normal within four to twelve weeks [18b,21]. However, the neurochemical deficiencies following the *bilateral* NBM lesions administered in these behavioral studies do not display similar recovery, and persisting reductions have now been documented for durations exceeding seven months [5].

In summary, this study demonstrated that although severe and selective deficits in recent memory were observed following destruction of basal forebrain cholinergic neurons, complete recovery of the memory loss gradually occurred over the course of several months, while no cholinergic or neuroanatomical correlate of this recovery was identified. Several clear differences in task parameters between the radial arm maze and the passive avoidance procedure allowed one to exclude a number of salient variables from consideration as relevant to the recovery of function which was observed. These included the type of reinforcement used (food vs. shock), response requirement (active, discriminatory response vs. passive, inhibitory avoidance), and specific post-lesion task experience (several months on the radial arm maze vs. none on the passive avoidance task). What clearly remains unanswered is whether the dramatic recovery of function could occur spontaneously over a period of time or alternatively whether the recovery is dependent upon general stimulation and/or activation of memory-related neurological systems (as occurred during the course of handling the animals and routinely testing them on the radial arm maze for six months following NBM destruction). The present study was conducted to address this question.

Contrary to the preceding experiment, NBM-lesioned rats in the present study received no training or task experience during the six-month interval between surgery and behavioral testing. In fact, experimenter interaction during this time was limited to weekly cleaning and weighing, and daily feeding. The results of this study clearly show that when the NBM-lesioned rats were passively detained for six months following surgery, the deficit in the passive avoidance task persisted. Thus, the dramatic functional recovery observed on both the radial arm maze and the passive avoidance procedures in the prior study [5] apparently did not occur spontaneously, but rather was dependent upon the stimulation and/or experience gained from the routine, post-surgical training and testing on the radial arm maze task.

METHOD

Subjects

Sixteen male Sprague-Dawley rats (10 months of age) were divided into two equal groups and given either sham or NBM lesions. The rats were housed individually in standard plastic cages (with corn cob bedding) maintained on a 12 hr light/dark cycle, and given food and water ad lib.

Surgery

Under Nembutal® anesthesia (50 mg/kg IP), rats were placed in a stereotaxic apparatus with the incisor bar 2.4 mm below the interaural line. Lesioned rats were administered bilateral infusions of the neurotoxin ibotenic acid into the NBM. Ibotenic acid is a neurotoxic glutamate analogue that, like kainic acid, causes selective dendrosomatic degeneration, preferentially destroying dendrites and cell bodies, while sparing axonal processes [19]. Ibotenic acid was used rather than kainic acid because of evidence that it does not produce damage remote from the infusion site, a non-specific effect associated with the epileptogenic actions of kainic acid [10,13]. The ibotenic acid (Regis) was dissolved in saline in a concentration of 6 μg/μl, with the pH adjusted to 7.4. The infusion apparatus consisted of a 10 μl Hamilton microsyringe connected by PE-10 polyethylene tubing (Intramedic) to a 30 gauge stainless steel infusion needle. The infusion site for the NBM lesions was located 1.7 mm caudal to bregma, 3.1 mm lateral to bregma, and 7.7 mm ventral to the surface of the skull. Over a two minute period, 0.4 μl of the ibotenic acid solution was infused, and the needle was removed five minutes later. In sham animals the infusion needle was simply placed 2 mm rostral and 2 mm dorsal to the lesion site for five minutes. All rats received 0.1 ml Bicillin® (30,000 units, IM) immediately post-operatively.

Since NBM lesions have been associated with significant hypophagia [1, 6, 11, 16], rats were given a highly palatable supplemental diet including peanuts, chocolate chips, coconut, cookies and cereal. This supplemental diet was available beginning five days before surgery and was maintained until the animals' body weight returned to pre-surgical levels (usually about two weeks).

Passive Avoidance Task

Following surgery and six months of detention in their

TABLE 1
BIOCHEMICAL DETERMINATIONS

	Choline Acetyltransferase Activity†			High Affinity Choline Uptake‡
	Left Frontal Cortex*	Right Frontal Cortex*	Hippocampus	Cortex*
Sham	0.997 ± 0.020	1.066 ± 0.028	1.323 ± 0.050	6.92 ± 0.327
NBM-Lesioned	0.557 ± 0.028	0.647 ± 0.039	1.410 ± 0.085	4.58 ± 0.259

*$p<0.001$.
†Expressed in nmoles ACh/mg protein/min ± SEM.
‡Expressed in pmoles/mg protein/min ± SEM.

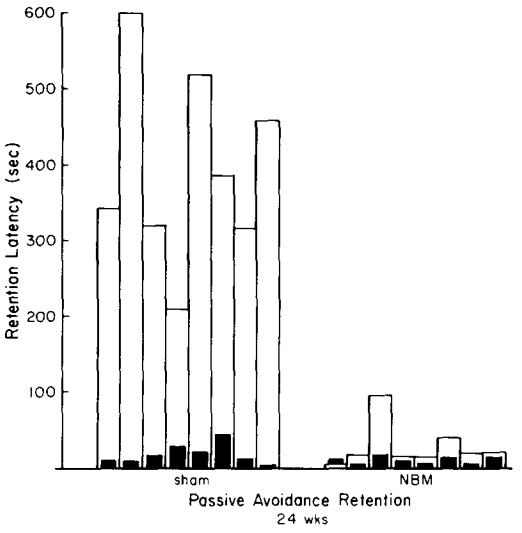

FIG. 1. Effects of sham or nucleus basalis magnocellularis (NBM) lesions on 24 hr passive avoidance retention, 24 weeks subsequent to surgery ($p<0.001$). Small shaded bars within larger open bars depict day 1 training latencies ($p<0.1$).

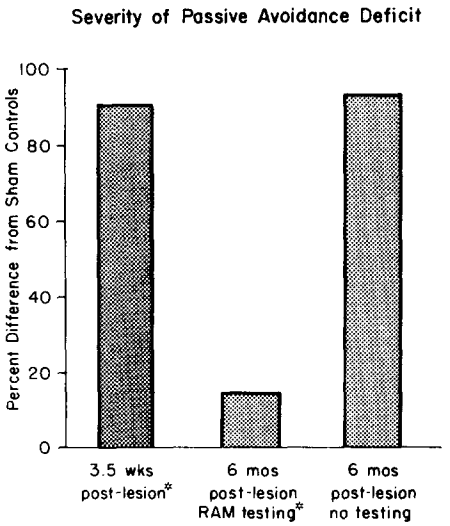

FIG. 2. Relative effects of NBM lesions measured either shortly after recovery from surgery (3.5 weeks post-lesion), following 6 months of radial arm maze (RAM) training and testing, or following 6 months of detention in home cage (i.e., no radial arm maze training and testing). *Adapted from Bartus *et al.* [5].

individual home cages, all rats were trained and tested on a passive avoidance procedure, as reported elsewhere [2, 4, 7].

On the training trial, each rat was placed in the front, illuminated chamber of a two-chambered apparatus. After a 3 second orientation period, a guillotine door was raised, allowing access to the rear chamber. As soon as the rat placed all four paws in the rear, dark chamber, the door was lowered and a 1 mA scrambled shock was delivered to the grid floor for 3 seconds. The rat was removed from the rear chamber 5 seconds later and returned to its home cage. The latency to enter the rear chamber was recorded.

Twenty four hours post-training, the rats were tested for retention of the aversive experience. The rat was placed in the front chamber and the guillotine door was raised 3 seconds later, as in the training trial, except that no shock was delivered. The latency to re-enter the rear chamber was recorded (with a maximum cut-off period of 10 minutes). The higher latencies on the test day presumably reflect greater retention of the prior, passive avoidance training trial.

Histology

Upon completion of behavioral testing, all rats were sacrificed, their brains removed, and tissue samples dissected from the frontal cortex and hippocampus. From the remaining brain, a block of tissue including the needle track was prepared and fixed in 10% formaldehyde. Frozen coronal sections 40 μ thick were mounted on slides and stained with cresyl violet. Under microscopic examination, the area of neuronal degeneration was defined by the total absence of cells with visible nucleoi, in areas where neurons were normally present. Elsewhere, the lesion area was defined by the presence of gliotic activity. Coronal sections showing the maximal neuronal degeneration produced by each lesion were schematically illustrated.

Biochemistry

Choline acetyltransferase (CAT) activity in tissue homogenates (approximately 100 μg of protein) was deter-

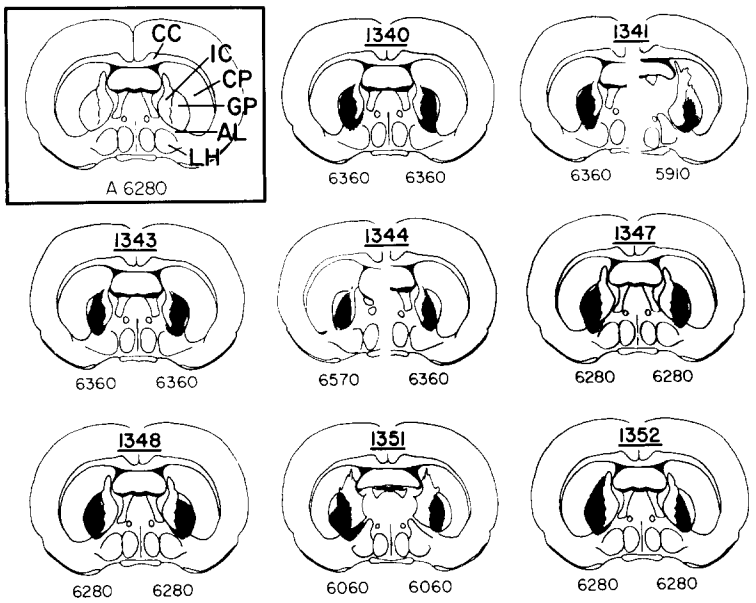

FIG. 3. Schematic representation of neuronal degeneration produced by infusions of ibotenic acid (2.4 μg/0.4 μl) into the NBM. For each of the 16 lesions in the 8 lesioned rats, the coronal section depicted illustrates the rostro-caudal level at which the lesion (stippled area) reached its maximal extent. Section diagrams were modified from König and Klippel [14]. Numbers at the bottom of each section refer to its distance (in microns) anterior to the inter-aural line. Numbers at the top of each pair of sections refer to the individual subject numbers. Neuroanatomical structures are labeled in the diagram on the upper left. Abbreviations: AL, ansa lenticularis; CC, corpus callosum; CP, caudate-putamen; GP, globus pallidus; IC, internal capsule; LH, lateral hypothalamus.

mined by measurement of the rate of formation of acetylcholine from acetyl-CoA using the radiochemical method of Fonnum [8]. High affinity, sodium-dependent choline uptake (HACU) was determined by incubating aliquots of a crude mitochondrial fraction (P_2: approximately 50 μg of protein) in a Krebs-Ringer phosphate buffer (pH 7.4) containing [^{3}H] choline (1.0 μM) for 4 minutes at 37°C, using the method of Simon, *et al.* [20]. Control incubations were maintained on ice (4°C) and the uptake of [^{3}H] choline subtracted to determine net uptake of [^{3}H] choline. Incubation of aliquots of P_2 fractions at 37°C in the absence of Na^+, resulted in values of [^{3}H] choline uptake similar to those obtained in Krebs-Ringer phosphate buffer at 4°C.

RESULTS

Behavioral testing in the passive avoidance procedure demonstrated that while the initial training latencies for the sham and NBM-lesioned rats were equivalent (Fig. 1, $p>0.1$), a robust difference in latencies between the two groups was observed on the 24 hour retention test (Mann Whitney $U=0.00$, $p<0.001$).

Biochemical determinations revealed a significant loss of CAT activity in both the left (approximately 44%; $t(12)=13.34$, $p<0.001$) and right (approximately 39%; $t(12)=9.35$, $p<0.001$) frontal cortices, with no detectable loss in the dorsal hippocampus ($t(11)=0.94$, $p>0.05$). Finally, high affinity choline uptake in the frontal cortex was found to be significantly reduced (approximately 33%; $t(13)=6.00$, $p<0.001$; Table 1).

The neurodegenerative changes produced by these lesions were essentially the same as has been reported previously [5,7]. The lesions were elliptical in shape and covered a little over 1 mm in their rostro-caudal extent. The area of degeneration was maximal at approximately A 6280 of König and Klippel [14], at which level degeneration was usually present throughout the ventromedial two thirds of the globus pallidus. The infusion site was located farther caudal, in or adjacent to the ventromedial corner of the globus pallidus. The lesions produced a limited amount of damage ventral to the globus pallidus and internal capsule, almost always causing some cell loss in the area of the ansa lenticularis and the dorsal part of the lateral hypothalamus or lateral preoptic area (see Fig. 3). Signs of spread of the neurotoxin to the caudate-putamen were rare, although in a few cases there was a slight invasion of the medial caudate adjacent to the ventral or dorsal globus pallidus.

DISCUSSION

The primary finding of this study is that rats detained in their home cage for six months following NBM lesions continue to exhibit a passive avoidance deficit. This result contrasts markedly with that previously found when rats were

routinely trained and tested on a radial arm maze task for six months following NBM lesions. In the previous study, rats given post-surgical experience on the maze task exhibited a gradual and complete recovery of the lesion-induced deficit, and when subsequently tested on the passive avoidance task, showed no deficit on that task either (see Fig. 2). The lack of similar recovery in the present study indicates that the functional recovery following NBM lesions observed by various laboratories [5, 6, 11b, 18b] apparently requires some degree of post-operative stimulation or task exposure.

Although these results confirm an important role of the nucleus basalis magnocellularis (and its cholinergic projection to the cortex) in the mediation of tasks requiring learning and/or memory, many more questions persist. Particularly intriguing is the issue of what conditions or parameters are necessary for the functional recovery to occur. Specifically, is experience on memory-related tasks, per se, required? If so, then how much is required? Or, alternatively, would general (i.e., non-mnenomic) environmental stimulation be sufficient? Another question the present study cannot address is whether the effects of NBM lesions differ between animals which are test-sophisticated (versus test-naive) at the time of surgery.

At the same time, certain information from studies of the NBM may have more practical applications. Although it would be dangerous to over-interpret the existing data, the present results, nonetheless, provide direction and encouragement for more careful clinical studies concerned with the impact of the patient's environment on the symptomatology of neurodegenerative disorders, such as Alzheimer's disease. The results from the present study imply that it might be possible to reduce the severity of certain clinical symptoms (which may be partially associated with NBM-cholinergic degeneration) by providing an environment which includes memory-associated tasks and other proper remedial experiences. Indeed, there exist scattered reports in the clinical literature which suggest that activities of this type might be beneficial to Alzheimer's patients [22,23]. The present paper with brain-lesioned rats adds support to this possibility by demonstrating that the long-term functional consequences of artificially-induced degeneration of a brain area (implicated in the pathogenesis and symptomatology of Alzheimer's disease) can be affected by the nature of the post-lesion exposure given to the animals. Finally, although studies with animals are clearly limited in the type of insight they can provide about human-specific neurodegenerative disease, it is also apparent that they can be useful in helping to identify issues that deserve further empirical attention.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical assistance of Kathy Schill and Margaret Marshall, as well as the preparation of figures by Mary Wilfred and the preparation of the manuscript by Rhonda Sheppard.

REFERENCES

1. Altman, H. J., R. D. Crosland, D. J. Jenden and R. F. Berman. Further characterizations of the nature of the behavioral and neurochemical effects of lesions to the nucleus basalis of Meynert in the rat. *Neurobiol Aging* **6:** 125–130, 1985.
2. Bartus, R. T., R. L. Dean, J. A. Goas and A. S. Lippa. Age-related changes in passive avoidance retention: Modulation with dietary choline. *Science* **209:** 301–303, 1980.
3. Bartus, R. T., R. L. Dean, M. J. Pontecorvo and C. Flicker. The cholinergic hypothesis: A historical overview, current perspective and future directions. In: *Memory Dysfunctions, Integration of Animal and Human Research from Clinical and Preclinical Perspectives*, edited by D. Olton, E. Gamzu and S. Corkin. New York: New York Academy of Sciences, 1985, pp. 332–358.
4. Bartus, R. T., C. Flicker and R. L. Dean. Logical principles for the development of animal models of age-related memory impairments. In: *Assessment in Geriatric Psychopharmacology*, edited by T. Crook, S. Ferris and R. T. Bartus. New Canaan, CT: Powley Assoc., 1983, pp. 263–300.
5. Bartus, R. T., C. Flicker, R. L. Dean, M. J. Pontecorvo, J. C. Figueiredo and S. K. Fisher. Selective memory loss following nucleus basalis lesions: Long term behavioral recovery despite persistent cholinergic deficiencies. *Pharmacol Biochem Behav* **23:** 125–135, 1985.

5b Dubois, B., W. Mayo, Y. Agid, M. Le Moal and H. Simon. Profound disturbances of spontaneous and learned behaviors following lesions of the nucleus basalis magnocellularis in the rat. *Brain Res* **338:** 249–258, 1985.

6. Dunnett, S. B. Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria-fornix on delayed matching in rats. *Psychopharmacology (Berlin)* **87:** 357–363, 1985.

6b Dunnett, S. B., G. Tonilo, A. Fine, C. N. Ryan, A. Bjorklund and S. D. Iversen. Transplantation of embryonic ventral forebrain neurons to the neocortex of rats with lesions of nucleus basalis magnocellularis—II. Sensorimotor and learning impairments. *Neuroscience* **16:** 787–797, 1985.

7. Flicker, C., R. L. Dean, D. L. Watkins, S. K. Fisher and R. T. Bartus. Behavioral and neurochemical effects following neurotoxic lesions of a major cholinergic input to the cerebral cortex in the rat. *Pharmacol Biochem Behav* **18:** 973–981, 1983.
8. Fonnum, F. A rapid radiochemical method for the determination of choline acetyltransferase. *J Neurochem* **24:** 407–409, 1975.
9. Friedman, E., B. Lerer and J. Kuster. Loss of cholinergic neurons in rat neocortex produces deficits in passive avoidance learning. *Pharmacol Biochem Behav* **19:** 309–313, 1983.
10. Guldin, W. O. and H. J. Markowitsch. Epidural kainate, but not ibotenate, produces lesions in local and distant regions of the brain: A comparison of the intracerebral actions of kainic acid and ibotenic acid. *J Neurosci Methods* **5:** 83–93, 1982.
11. Hepler, D. J., D. S. Olton, G. L. Wenk and J. T. Coyle. Lesions in nucleus basalis magnocellularis and medial septal area of rats produce qualitatively similar memory impairments. *J Neurosci* **5:** 866–873, 1985.

11b Hepler, D. J., G. L. Wenk, B. L. Cribbs, D. S. Olton and J. T. Coyle. Memory impairments following basal forebrain lesions. *Brain Res* **346:** 8–14, 1985.

12. Johnston, M. V., M. McKinney and J. T. Coyle. Evidence for a cholinergic projection from neurons in basal forebrain. *Proc Natl Acad Sci USA* **76:** 5392–5396, 1979.
13. Kohler, C., R. Schwarcz and K. Fuxe. Intrahippocampal injections of ibotenic acid provide histological evidence for a neurotoxic mechanism different from kainic acid. *Neurosci Lett* **15:** 223–228, 1979.
14. Konig, J. F. and R. Klippel. *The Rat Brain: A Stereotaxic Atlas*. Baltimore, MD: Williams and Wilkins, 1963.

14b Knowlton, B. J., G. L. Wenk, D. S. Olton and J. T. Coyle. Basal forebrain lesions produce a dissociation of trial-dependent and trial-independent memory performance. *Brain Res* **345:** 315–321, 1985.

15. Lerer, B., J. Warner, E. Friedman, G. Vincent and E. Gamzu. Cortical cholinergic impairment and behavioral deficits produced by kainic acid lesions of rat magnocellular basal forebrain. *Behav Neurosci* **99:** 661–667, 1985.
16. LoConte, G., L. Bartolini, F. Casamenti, I. Marconcini-Pepeu and G. Pepeu. Lesions of cholinergic forebrain nuclei: Changes in avoidance behavior and scopolamine actions. *Pharmacol Biochem Behav* **17:** 933–937, 1982.
17. Miyamoto, M., M. Shintani, A. Nagoaba and Y. Nagawa. Lesioning of the rat basal forebrain leads to memory impairments in passive and active avoidance tasks. *Brain Res* **328:** 97–104, 1985.

17b Murray, C. L. and H. C. Fibiger. Learning and memory deficits after lesions of the nucleus basalis magnocellularis: Reversal by physostigmine. *Neuroscience* **14:** 1025–1032, 1985.

18. Pedata, F., G. LoConte, S. Sorbi, I. Marconcini-Pepeu and G. Pepeu. Changes in high affinity choline uptake in the rat cortex following lesions of the magnocellular forebrain nuclei. *Brain Res* **233:** 359–367, 1982.

18b Ridley, R. M., H. F. Baker, B. Drewett and J. A. Johnson. Effects of ibotenic acid lesions of the basal forebrain on serial reversal learning in marmosets. *Psychopharmacology (Berlin)* **86:** 438–443, 1985.

19. Schwarcz, R., T. Hokfelt, K. Fuxe, G. Jonsson, M. Goldstein and L. Terenius. Ibotenic acid-induced neuronal degeneration: A morphological and neurochemical study. *Exp Brain Res* **37:** 199–216, 1979.
20. Simon, J. R., S. Atweh and M. J. Kuhar. Sodium dependent high affinity choline uptake: A regulatory step in the synthesis of acetylcholine. *J Neurochem* **26:** 909–922, 1976.
21. Wenk, G. L. and D. S. Olton. Recovery of neocortical choline acetyltransferase activity following ibotenic acid injection into the nucleus basalis of Meynert in rats. *Brain Res* **293:** 184–186, 1984.
22. Yesavage, J. A. and T. L. Rose. Concentration and mnemonic training in elderly subjects with memory complaints: A study of combined therapy and order effects. *Psychol Res* **9:** 157–167, 1983.
23. Yesavage, J. A., J. Westphal and L. Rush. Senile dementia: Combined pharmacologic and psychologic treatment. *J Am Geriatr Soc* **29:** 164–171, 1981.