ACTA NEUROBIOL. EXP. 1990, 50: 219-223

Symposium "Recovery from brain damage: behavioral and neurochemical approaches"
4-7 July, 1989, Warsaw, Poland

ANIMAL MODELS OF ALZHEIMER'S DISEASE: ARE THEY VALID AND USEFUL?

Gary L. WENK

Department of Psychology, The Johns Hopkins University,
34 Charles St., Baltimore, MD 21218, USA

Key words: Alzheimer's disease, rats, basal forebrain, animal models

Abstract. Animal models of Alzheimer's disease (AD) have been designed to reproduce various components of the pathological, biochemical, and behavioral characteristics of AD in order to understand the consequences of the pathological and biochemical changes that occur as the disease progresses, and investigate the effectiveness of potential pharmacotherapies. An animal model is useful only if it leads to the development of an effective therapy or provides a better understanding of the biological mechanisms that underlie the symptoms of the disease. Animal models of AD have provided much information on the function of the basal forebrain system and have been used to investigate the potential effectiveness of various pharmacotherapies designed to reverse specific symptoms. The validity and usefulness of these models is discussed.

Animal models of Alzheimer's disease have been designed to reproduce various components of the pathological, biochemical, and behavioral characteristics of Alzheimer's disease in order to (1) understand the consequences of the pathological and biochemical changes that occur as the disease progresses, and (2) investigate the effectiveness of potential pharmacotherapies (11, 12). How valid are these animal models (see Table I)? Do they provide an accurate opportunity to investigate the neural mechanisms that underlie the degenerative changes associated

TABLE I

Aspects of animal models of Alzheimer's disease that undermine their potential validity and usefulness

The memory loss observed in rats with NBM lesions recovers; the memory loss in humans with Alzheimer's disease does not
Drugs that are effective in these animal models are not as effective in humans with Alzheimer's disease
Acetylcholinergic cell loss in the NBM does not always impair memory and therefore may not underlie the amnesia seen in Alzheimer's disease

with Alzheimer's disease? Do they provide a useful test that can lead to an effective treatment for Alzheimer's disease? Ultimately, an animal model is useful only if it leads to the development of an effective therapy or provides a better understanding of the biological mechanism that underlie the symptoms of the disease.

Alzheimer's disease is associated with a loss of cells in the nucleus basalis of Meynert (4). This basal forebrain region contains large cholinergic neurons that project to the entire neocortex. The loss of basal forebrain cells is correlated with a decrease in the level of biochemical markers for cholinergic terminals within the neocortex, and with the presence of a severe dementia characterized by a loss of memory for recent events (3). Animal models of Alzheimer's disease involve the production of discrete lesions within the nucleus basalis magnocellularis (NBM, the analog to the nucleus basalis of Meynert). These lesions reproduce the loss of basal forebrain cells, primarily cholinergic, and decrease the levels of cholinergic markers in the brain. Animals with lesions in the NBM have a profound impairment in recent memory (9-11). Therefore, these animal models reproduce a subset of the pathological, biochemical and behavioral changes associated with Alzheimer's disease (11).

Rats with NBM lesions initially show an impairment in tasks that require learning and memory (7). Surprisingly, this memory impairment frequently recovers with continued testing (2). Surviving cholinergic or noncholinergic neurons that were unaffected by the lesions may somehow compensate for the cell loss and produce the behavioral recovery. This recovery of memory is in striking contrast to situation observed in Alzheimer's disease where the amnesia and dementia progressively worsen with time.

Animal models of Alzheimer's disease have provided much information on the function of the basal forebrain system and the effects of lesions within this region on the performance of a variety of behavioral tasks. Frequently, the effects of these lesions have been interpreted in

terms of the loss of cholinergic cells, in spite of the fact that these toxins do not selectively destroy cholinergic cells. Unfortunately, a specific cholinergic neurotoxin does not exist; therefore, the precise role of the basal forebrain cholinergic cells remains a mystery.

Animal models of Alzheimer's disease have been used to investigate the potential effectiveness of various pharmacotherapies designed to reverse specific symptoms associated with Alzheimer's disease (1). Many of these compounds significantly improve the performance of experimental animals in tasks that require learning and memory (1, 12). Because of the documented loss of NBM cholinergic cells, many treatments have been designed to enhance the function of cholinergic neurons (8): these treatments provide precursors for the production of acetylcholine (e.g. lecithin or choline), enhance the lifespan of acetylcholine in the synapse (e.g., phystostigmine), or provide pharmacological agonists to cholinergic receptors in order to mimic the effects of acetylcholine (e.g., arecoline). These treatments consistently lessen the memory impairments observed in animals with basal forebrain lesions. Unfortunately, these cholinergic enhancement therapies do not produce consistent or significant improvements in the behavior of patients with Alzheimer's disease (1). The failure of these cholinergic enhancement therapies may be due to the fact that most of the cholinergic neurons in the basal forebrain of patients with Alzheimer's disease are degenerated. Therefore, there are too few acetylcholine molecules to enhance, or too few terminals to respond to the elevated levels of precursor.

Possibly, the cholinergic enhancement therapies are not effective because NBM cholinergic cell loss does not exclusively underlie the amnesia seen in Alzheimer's disease. Recently, a number of studies have reported that the nearly complete loss of the basal forebrain cholinergic cells in the rat does not always produce an impairment in memory (5, 6, 10). Much of the early research on animal models of Alzheimer's disease used analogues of glutamate, e.g. kainic and ibotenic acid, to produce NBM lesions. Recently, another glutamate analogue, quisqualic acid, has been used to effectively destroy 80-90% of all the cholinergic neurons within the NBM. In spite of the significant loss of cholinergic cells, the memory impairment is either slight or nonexistent, depending upon the particular behavioral task involved. If the loss of cholinergic cells does not produce amnesia in these animal models of Alzheimer's disease, then the loss of the cholinergic cells in humans may not be responsible for the amnesia associated with Alzheimer's disease. If true, this finding might explain why cholinergic augmentation therapy in patients with Alzheimer's disease has not been as effective as predicted.

The loss of basal forebrain cells is correlated with the amnesia asso-

ciated with Alzheimer's disease (3). However, as described above, the loss of cholinergic cells may not be sufficient to produce the amnesia. Ibotenic and kainic acids destroy cholinergic and non-cholinergic cells in the region of their injection, quisqualic acid effectively destroys cholinergic cells but may leave specific non-cholinergic cells intact. The precise identity of these non-cholinergic systems spared by quisqualic acid must be investigated. If we could determine which cell types remain following quisqualic acid injections, but disappear following ibotenic acid injections, it might be possible to target this non-cholinergic system for augmentation therapy. Such a treatment might effectively reverse the amnesia observed in Alzheimer's patients and finally justify the validity and usefulness of this animal model.

REFERENCES

1. BARTUS, R. T., DEAN, R.L., BEER, B. and LIPPA, A. S. 1982. The cholinergic hypothesis of geriatric memory dysfunction. Science 217: 408-417.
2. BARTUS, R. T., FLICKER, C., DEAN, R. L., PONTECORVO, M., FIGUEIREDO, J. C. and FISHER, S. K. 1985. Selective memory loss following nucleus basalis lesions: Long term behavioral recovery despite persistent cholinergic deficiencies. Pharmacol. Biochem. Behav. 23: 125-135.
3. BLESSED, G., TOMLIMSON, B. E. and ROTH, M. 1968. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br. J. Psychiatr. 114: 797-811.
4. COYLE, J. T., PRICE, D. L. and DELONG M. R. 1983. Alzheimer's disease: A disorder of cortical cholinergic innervation. Science 219: 1184-1190.
5. DUNNETT, S. B., WHISHAW, I. Q., JONES, G. H. and BUNCH, S. T. 1987. Behavioral, biochemical and histochemical effects of different neurotoxic amino acids injected into nucleus basalis magnocellularis of rats. Neurosci. 20: 653-669.
6. ETHERINGTON, R., MITTLEMAN, G. and ROBBINS, T. W. 1987. Comparative effects of nucleus basalis and fimbria-fornix lesions on delayed matching and alternation tests of memory. Neurosci. Res. Comm. 1: 135-143.
7. HEPLER, D. J., OLTON, D. S., WENK, G. L. and COYLE J. T. 1985. Lesions in nucleus basalis magnocellularis and medial septal area of rats produce qualitatively similar memory impairments. J. Neurosci. 5: 866-873.
8. NARANG, P. K. and CUTLER, N. R. 1986. Pharmacotherapy in Alzheimer's disease: Basis and rationale. Prog. Neuro-Psychopharmacol. Biol. Psychiatr. 10: 519-531.
9. WENK, G. L., HUGHEY, D., BOUNDY, V., KIM, A., WALKER, L. and OLTON, D. S. 1987. Neurotransmitters and memory: The role of cholinergic, serotonergic and noradrenergic systems. Behav. Neurosci. 101: 325-332.
10. WENK, G. L., MARKOWSKA, A. L. and OLTON, D. S. 1989. Basal forebrain lesions and memory: Alterations in neurotensin, not acetylcholine, may cause amnesia. Behav. Neurosci. 103: 765-769.

11. WENK, G. L. and OLTON, D. S. 1987. Basal forebrain cholinergic neurons and Alzheimer's disease. *In* J. T. Coyle (ed.), Animal models of dementia: a synaptic neurochemical perspective; neurology and neurobiology. Vol. 33. Alan R. Liss, New York, p. 81-101.
12. WENK, G. L. and OLTON, D. S. 1989. Cognitive enhancers: Potential strategies and experimental results. Prog. Neuro-Psychopharmacol. Biol. Psychiatr. 13: (Suppl.). S117-S139.