The Cholinergic Deficit in Alzheimer's Disease

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The history of the discovery of cholinergic deficit in Alzheimer's disease is briefly reviewed, focusing on the cholinergic basal forebrain. The anatomy of the structure is discussed, and the clinical implications of pathology in this population of nerve cells are presented.

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Two medications, tacrine and donepezil, have been approved in the United States and some European countries for the treatment of Alzheimer's disease. Although their effects are modest, we can celebrate the application of basic science discoveries to the development of medications that offer the promise of benefiting millions of people affected by dementias characterized by cholinergic basal forebrain neuronal loss.[1]

HISTORY

Approximately 30 years ago, our understanding of neurodegenerative diseases increased dramatically when classic neuropathologic studies could be combined with neurochemical analyses of neurotransmitter markers in the brain. Perhaps the greatest early success was to correlate the loss of cells in the substantia nigra in Parkinson's disease with the loss of dopaminergic markers in striatum. This discovery led to therapeutic interventions, namely, the use of L-dopa. It is noteworthy that the Lewy body (the principal pathologic feature of Parkinson's disease) was first described in the substantia innominata, a part of what we now call the basal forebrain, and not the substantia nigra.

In the 1960s, a reduction in cholinergic markers in cortex was identified in the brains of patients with Alzheimer's disease.[1,2] The earliest discovery was the recognition of acetylcholinesterase reduction. However, acetylcholinesterase is a nonspecific marker for cholinergic neurons. In the mid-1970s, reductions in choline acetyltransferase concentration were identified and led to a search for the damaged cholinergic cell bodies. It took approximately another 5 years to characterize the loss of cells in the basal forebrain, particularly the nucleus basalis of Meynert as the principal pathologic hallmark underlying the loss of cholinergic markers in cortex. Ironically, the nucleus basalis of Meynert was the name given to the substantia innominata, which was first implicated in the pathology of Parkinson's disease.

Although earlier studies[3] had characterized cell loss in the nucleus basalis of Meynert in small samples of patients, it took until the 1980s to recognize that these cells in the nucleus basalis of Meynert were, in fact, cholinergic and that loss of these cells was the substrate for the loss of choline acetyltransferase in Alzheimer's disease and other related diseases. Moreover, it became clear that the nucleus basalis of Meynert is only one part of an extensive sheet of cells constituting the frontal and basal cholinergic portions of the brain.

ANATOMY

The cholinergic basal forebrain is composed of cells in a variety of classic nuclear structures that include the medial septum, the diagonal band, and the nucleus basalis of Meynert proper. These cells are large Nissl-positive cells that can be identified by either immunocytochemistry for choline acetyltransferase or the presence of nerve growth factor receptor.[4,5] Anatomical tract tracing studies[2] demonstrated that these cells project widely to telencephalon. Moreover, there appear to be topographically organized projections such that, for example, cells in the medial septum and diagonal band project more to the hippocampus while those in the basal forebrain project to the cortex.

Subsequent studies have shown that there are also noncholinergic neurons in the basal forebrain, some of which project to telencephalon and likely play a role in cognition.[6] Moreover, the basal forebrain is not the only anatomical substrate for the cognitive impairment of dementia; a variety of other cell populations are affected, including subcortical nuclei such as the locus ceruleus and raphe.[2] Neuritic plaques are not commonly seen in a nucleus basalis of

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Meynert, but intracellular and extracellular neurofibrillary tangles can frequently be found in this structure.

NEUROCHEMISTRY OF THE BASAL FOREBRAIN

Cholinergic Aspects

After the characterization of the cell loss in the basal forebrain, neurochemical studies[2] attempted to identify the neurotransmitters associated with afferents and efferents of the basal forebrain system. High density of nicotinic receptors and muscarinic, particularly M_2 subtype, cholinergic receptors were found in the nucleus basalis of Meynert. The observation that these receptors are found in the cell bodies was consistent with the idea that these were presynaptic receptors produced in the soma and transported to the distal axons. Although lesion studies in animals were somewhat inconsistent, these receptors are presynaptic receptors. Some of this receptor binding in the nucleus basalis of Meynert may represent cholinergic input to the basal forebrain.

Noncholinergic Aspects

The understanding of the basal forebrain neurochemistry connectivity and function was of course advanced by the development of specific lesion techniques. Electrolytic lesions of the basal forebrain in animals damaged not only cell bodies but also axons in transit; thus, it was difficult to differentiate the specific aspects of basal forebrain anatomy and function. A variety of excitatory amino acid toxins were developed that more specifically damaged cell bodies rather than axons. However, these toxins were nonspecific and damaged all nerve cells without regard to their cholinergic nature.

The development of toxins specific to cholinergic neurons advanced our understanding of the function of the forebrain neuron further. AF64A was the first widely used compound; however, the selectivity of this toxin for cholinergic neurons is dose sensitive.[7] Recent studies indicate that a specific antibody, 192-IgG-saporin, appears to produce a nearly complete and specific lesion of neocortical and hippocampal cholinergic afferents.[7–9] This method works by attaching a monoclonal antibody to the low affinity nerve growth factor receptor, which is present on cholinergic neurons, to a toxin, saporin. Intraventricular administration or direct injection of this compound can damage cholinergic neurons in the basal forebrain. However, this toxin damages any nerve cell with low affinity nerve growth factor receptors, and, when administered intraventricularly, this toxin causes some noncholinergic cell damage to, for example, cerebellar Purkinje cells. Moreover, alcoholic intake may damage basal forebrain neurons in animals[10] and perhaps in man.[11]

Noncholinergic neurons are also found in the basal forebrain.[7] For example, a number of GABAergic neurons appear to be present and to project to cortex and play a role in cognition. Other neurotransmitters and neuropeptides such as neurotension and galanin have been implicated as playing a role in cognition in association with loss of cells in the basal forebrain.[7] Moreover, other growth factors play a role in the nucleus basalis of Meynert.[12] Lesion studies in animals suggest a role for the cholinergic basal forebrain in control of electroencephalographic rhythms.[13] Such an effect on brain electrical activity may relate to a functional role in memory and/or attention.[8,14]

Neuropathology

As mentioned above, isolated studies of individuals with Parkinson's disease and dementia demonstrated pathology in the basal forebrain.[3] In fact, in Parkinson's disease, Whitehouse[15] suggested that the clinical syndrome of bradyphrenia, slowness of mentation, was associated with loss of cells in the nucleus basalis of Meynert. However, it was not until the 1980s that cell loss in the structure was identified as a common occurrence in several "cholinergic" dementias.[15]

Arguments have been made that change in cell size or a loss of synapses correlates better with dementia. Whatever the case, however, it is clear that damage and dysfunction of the basal forebrain neurons are part of the pathologic substrate of the cognitive impairment.[2]

Although most Alzheimer's disease studies have focused on the cholinergic basal forebrain, it is important to recognize that many dementias may have a cholinergic component. Often, patients with Parkinson's disease have a mild degree of cognitive impairment that may be associated with a slight degree of cell loss. Frank dementia can also occur in Parkinson's disease and is associated with more profound cell loss.[16] Occasionally, Parkinson's disease–related dementia is associated with plaques and tangles consistent with coexisting Alzheimer's disease. However, other forms of dementia, including Lewy body dementia, can occur in association with parkinsonism and are accompanied by cell loss in the nucleus basalis of Meynert.[15] While cell loss occurs in progressive supranuclear palsy, it does not occur in Huntington's disease. Alcoholic dementia and perhaps Korsakoff's psychosis may also involve loss of neurons in the nucleus basalis of Meynert.[10]

Whether cell loss occurs in Pick's disease and other frontal lobe dementias is less clear. Moreover, some evidence has suggested that cholinergic loss may occur in vascular dementia. Part of the reason for the lack of clarity about the role of cholinergic basal forebrain in other dementias may be that there is also age-related change in this structure. Thus, one of the pathologic substrates for aging-related cognitive impairment (also called benign senescent forgetfulness) may be some degree of cell loss in the cholinergic basal forebrain.

As expected, based on an understanding of the normal neurotransmitter systems associated with basal forebrain,

a loss of nicotinic cholinergic receptors is one of the most consistent receptor alterations in Alzheimer's disease. This receptor loss in the cortex and hippocampus is most likely due to dysfunction of cholinergic basal forebrain cells associated with the loss of presynaptic nicotinic cholinergic receptors. Similar observations have been made suggesting selective M_2 muscarinic receptor loss in Alzheimer's disease and relative sparing of the M_1 postsynaptic receptor.[17] Moreover, the nucleus basalis of Meynert innervates blood vessels in animals and man, which contain nicotinic and muscarinic receptors.[18] Loss of these receptors occurs in Alzheimer's disease and may underlie some of the vascular components of Alzheimer's disease and possibly play a role in the vascular dementias.[17]

CLINICAL IMPLICATIONS OF THE CHOLINERGIC DEFICIT IN ALZHEIMER'S DISEASE

The evidence that the cholinergic basal forebrain plays a role in producing cognitive impairments extends beyond the pathologic studies in dementia. In animals, selective lesions in the nucleus basalis of Meynert can produce consistent abnormalities in memory and attention tasks.[8] These experiments have led to the use of rats with basal forebrain lesions to screen for cognitive enhancement properties of medications designed to treat human beings. Moreover, clinicians have known for some time that it is possible to produce delirium and amnesia in humans by blocking cholinergic mechanisms with scopolamine or other medications with anticholinergic side effects.[19]

Early studies with physostigmine suggested that in patients with Alzheimer's disease, some degree of cognitive enhancement could be obtained with cholinesterase inhibitors.[14,15] It remained, however, to develop cholinesterase inhibitors with better pharmacokinetic properties, such as a longer half-life, in order to test whether clinical benefit could be achieved with cholinomimetic drugs. Since the original characterization of the loss of cholinergic markers, both chemically and anatomically, the pharmaceutical industry has expended considerable effort to develop animal models and to screen cholinergic drugs for treatment of Alzheimer's disease and related dementias. Since tacrine and donepezil have been approved to treat Alzheimer's disease, cholinesterase inhibitors are the most successful approach to Alzheimer's disease treatment thus far. However, as expected, these drugs produce cholinergic side effects and particularly affect the gastrointestinal system, although donepezil's side affects appear to be minimal, particularly at the lowest dose.

The goal of molecular pharmacology is to develop compounds with more selective positive effects clinically and fewer side effects than drugs with nonspecific actions. Thus, many companies have been attempting to develop selective muscarinic and nicotinic cholinergic agonists that improve cognition with fewer peripheral gastrointestinal and cardiovascular side effects. A variety of muscarinic cholinergic agonists are under investigation and are showing both efficacy and cholinergic side effects. In addition, several companies are developing nicotinic agonists. Some compounds offer the opportunity to develop receptor subtype–specific compounds and perhaps obtain better intellectual performance with fewer side effects.

Interestingly, the clinical benefits of improving the cholinergic deficit may extend beyond purely symptomatic improvement of cognitive systems. Although cholinergic drugs were designed to improve memory and attention, some preliminary evidence suggests that these agents may improve noncognitive symptoms, such as apathy, agitation, and hallucinations.[19] Thus, cholinergic deficits may underlie more of the clinical pathology of Alzheimer's disease than just cognitive impairment. While the usefulness of these drugs in treating behavioral symptoms remains to be seen, it is worthwhile to pursue this observation further, since the behavioral symptoms are important causes of impairment of quality of life in both patients and caregivers.

Cholinergic drugs may also prove beneficial beyond purely symptomatic treatment and provide some degree of neuroprotection. Cholinesterase in the brain exists in several forms and may possess functions that extend beyond acetylcholine hydrolysis. Both acetylcholinesterase and butylcholinesterase are found around senile plaques and may play other chemical roles as peptidases. Thus, it will be important to study whether cholinesterase inhibitors have any effect on slowing disease progression perhaps by affecting neuronal viability. Moreover, muscarinic agonists may alter amyloid processing and thus have neuroprotective effects.

In the future, we hope to develop agents specifically designed to slow progression of disease. Once again, studies of the basal forebrain provide important clues. For example, nerve growth factor has been shown to enhance viability of basal forebrain cells and has been implicated in the pathogenesis of Alzheimer's disease.[5] Intraventricular nerve growth factor has been administered to patients in Sweden to try to slow the progression of Alzheimer's disease. While results are not encouraging, they do offer some guidance for developing approaches to retard nerve cell death and slow clinical progression. Because nerve growth factor must be administered intraventricularly, pharmaceutical companies are working to develop more easily administered small molecules that stimulate nerve growth factor action.

The issue of how to design a study that demonstrates slowing progression of disease is complex. Better biological markers that allow the progression of disease to be tracked are needed. Once again, studies based on an understanding of the neurotransmitter receptors associated with basal forebrain loss in Alzheimer's disease have provided

some clues. The same Swedish group[5] that has administered intraventricular nerve growth factor is tracking the course of the illness and the effects of therapy using positron emission tomography with C-11 nicotine to image nicotinic receptors.

CONCLUSION

The application of basic science knowledge to clinical practice takes considerable time. Loss of chemical cholinergic markers was described in Alzheimer's disease in the 1970s; the anatomical substrate was identified in the early 1980s; and drugs to treat this condition were approved in the early 1990s. We must all work to develop more effective ways to transfer the discoveries of the basic laboratory into clinical practice and to extend our therapeutic armamentarium to include drugs that have more profound effects on disease symptoms and progression than those currently available.

Drug names: donepezil (Aricept), tacrine (Cognex).

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