Alzheimer's Disease: A Disorder of Cortical Cholinergic Innervation

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Summary. Great emphasis is being placed on identification of neurotransmitter systems involved in the symptomatic manifestations of neurological and psychiatric disorders. In the case of Alzheimer's disease, which now seems to be one of the most common causes of mental deterioration in the elderly, compelling evidence has been developed that acetylcholine-releasing neurons, whose cell bodies lie in the basal forebrain, selectively degenerate. These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory. These advances reflect a close interaction between experimental and clinical neuroscientists in which information derived from basic neurobiology is rapidly utilized to analyze disorders of the human brain.

One of the most feared and devastating aspects of aging is the deterioration of memory and other mental processes that occurs with increasing frequency in advancing years. About 5 percent or more of the population above the age of 65 years suffers from dementia, a severe impairment in cognitive functions; an additional 10 percent of individuals exhibit mild-to-moderate abnormalities in their cognitive abilities (*1*). Mental infirmity is the major reason for confinement of elderly individuals in nursing homes; and, in the United States, the present cost of nursing home care for patients whose chief symptom is dementia is estimated to exceed $6 billion per year (*2*).

Generally, the onset of senile dementia is heralded by impairments in recent memory. Affected individuals may be able to recall in considerable detail life events from the distant past, but they cannot remember what occurred just minutes earlier (*3*). Inevitably, higher cognitive functions deteriorate and the patients lose the ability to read, write, calculate, or use language appropriately. The loss of cognitive abilities may be accompanied by psychiatric symptoms such as irritability, emotional lability, paranoid delusions, and hallucinations. Affected individuals remain alert until the terminal stages; and the dementia occurs commonly in the absence of focal neurological deficits, such as paralysis or sensory loss, which frequently accompany cerebrovascular disease. Although many individuals remain intellectually adept and lead productive lives into their eighth and ninth decades, it has long been thought that senile dementia is a normal consequence of the aging process.

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Alzheimer's Disease

Presenile dementia of the Alzheimer's type is a rare disorder in which individuals, typically in their fifth decade, develop a progressive deterioration of cognitive functions clinically indistinguishable from senile dementia. The demonstration that the pathological alterations in the brains of more than half of elderly demented individuals are similar to those found in the brains of patients suffering from the presenile form of Alzheimer's disease (AD) (*4*) suggests that these are related disease processes. In both the presenile and senile forms of the disease, neuropathological examination of the brains disclose characteristic abnormalities (Fig. 1) such as neuritic plaques, which consist of abnormal neurites (primarily axon terminals) associated with a core of extracellular amyloid; neurofibrillary tangles, comprised of bundles of paired helical filaments, such as cross-linked polypeptides (*5*), which accumulate within the cell bodies of neurons; and granulovacuolar degeneration, that is, intracellular vacuoles in hippocampal pyramidal neurons. Further evidence that the presenile and senile forms of AD may have a common basis (*6*) comes from genetic studies indicating that the disease may occur as an autosomal dominant in some families. In this article, these two disorders are considered as a single entity, AD.

The cognitive deficits of AD have been attributed to abnormalities in the cerebral cortex and hippocampal formation in that neurofibrillary tangles and senile plaques are prominent in these brain regions. In fact, the density of neuritic plaques in the cortex of AD patients at autopsy correlates with the severity of their cognitive defects (*7*). Since normal aging is associated with a reduction in the number of cortical nerve cells (*8*), it has been difficult to clearly demonstrate that the loss of nerve cells in AD is more severe than in age-matched controls (*9*). However, over the past 10 years, substantial evidence has accrued to indicate that excessive nerve cell loss does occur in the cerebral cortex of AD patients (*10, 11*), with the majority of investigators now affirming that the frontal and temporal cortices are most affected.

Cholinergic Neurons and Alzheimer's Disease

In that neurotransmitter-specific neuronal systems have been shown to have a role in the pathophysiology of disorders like Parkinson's disease (*12*) and Huntington's disease (*13*), investigators have begun to examine the role of neurotransmitters in the symptoms of disorders of cognition and memory. One strategy used in clinical neuropsychopharmacology is to administer drugs that selectively alter central neurotransmission and then determine whether these manipulations produce symptoms similar to those seen in the disorder.

Drugs that block central acetylcholine (ACh) muscarinic receptors have long been known to disrupt higher cognitive functions and induce transient amnestic states (*14*). When low doses of scopolamine, a centrally active muscarinic receptor blocker, were administered to young adult volunteers, the drug caused selective deficits in recent memory but

did not impair immediate registration or long-term memory (*15*). The scopolamine-treated young adults exhibited a profile on the Wexler adult inventory scale (WAIS) similar to that seen in elderly, drug-free individuals with a significant reduction in performance IQ (intelligence quotient) but not verbal IQ resulting in a comparable "organicity index." The important role played by cholinergic neurons in memory has been substantiated by the findings that drugs which potentiate central cholinergic function enhance recent memory and reverse the performance deficits induced by anticholinergics (*16*). Thus, central cholinergic neurotransmission may play a role in the processing of recent memories, and abnormalities of this system may underlie some of the symptomatic manifestations of AD.

Evidence further implicating the cholinergic system in AD is derived from neurochemical studies of brain tissue obtained from affected patients. Since neurons have highly specialized biochemical processes for the synthesis, storage, and inactivation of their neurotransmitter (Fig. 2), these specialized chemical properties can be used as "markers" for quantifying the innervation of a brain region by transmitter-specific neurons (*17*). The most stable and specific neuronal markers are the enzymes responsible for the synthesis of the neurotransmitter. These enzymes appear to be restricted, in most cases, to the neurons that release the neurotransmitter; their activity remains relatively stable in brain for many hours after death (*13*).

In the cerebral cortex and hippocampal formations of patients who have died with AD, the activity of choline acetyltransferase (CAT), the enzyme that synthesizes ACh, is significantly reduced (by 60 to 90 percent) as compared to age-matched controls that died of unrelated causes (Table 1) (*18–22*). In contrast, muscarinic cholinergic receptors, which are concentrated on neurons receiving cholinergic innervation, have generally not been found to be decreased in the cortex of patients with AD (*20, 23*). Although some reductions in CAT activity have been observed in subcortical structures such as the basal ganglia, these changes are less severe and more variable than those occurring in the hippocampus and cerebral cortex. The activity of acetylcholinesterase (AChE), the enzyme that hydrolyses ACh, was considerably redued in the cortex and hippocampal formation of patients with AD (*19–22, 24–25*). Although AChE is enriched in cholinergic neurons, it is also present in some nerve cells which do not utilize ACh; for this reason, AChE is not considered a marker specific for cholinergic neurons (*26*).

Source of Cortical Cholinergic Innervation

Interpretation of the reduction of the markers for the cholinergic neurons in cerebral cortex in AD presented problems because the location of the cell bodies providing cortical innervation was uncertain. The decrements in CAT activity in AD appeared much greater than the degree of neuronal loss in the cerebral cortex (*27*). Nevertheless, a loss of a subpopulation of cortical neurons, which are cholinergic, might not be appreciated with cell counting techniques that cannot distinguish neurotransmitter characteristics of neurons.

Early studies demonstrated that undercutting the cerebral cortex caused a marked reduction in the activity of CAT in the overlying cerebral cortex (*28*). This finding was consistent with the conclusion that cortical cholinergic innervation came from neurons located outside the cortex; however, an alternative explanation, that the enzyme reduction reflected a retrograde degeneration of cortical cholinergic neurons whose axons projected out of cortex, could not be dismissed. Subsequently, Shute and Lewis (*29*), using a histochemical method for AChE, traced the axons stained for this enzyme from the cortex to large neuronal cell bodies in the basal forebrain and concluded that these neurons were the source of cortical cholinergic innervation. However, this interpretation was challenged when noncholinergic neurons, which utilize other neurotransmitters including dopamine and norepinephrine, were also observed to stain intensely for AChE activity (*26*). More recently, immunocytochemical studies have been used to localize CAT-containing neurons innervating the cortex; however, even this method has yielded conflicting results (*30*) which may reflect the exceptional difficulty in purifying this enzyme to homogeneity in order to produce monospecific antiserum (*31*).

A useful approach for identifying the source of transmitter-specific innervation is to ablate discrete regions of the

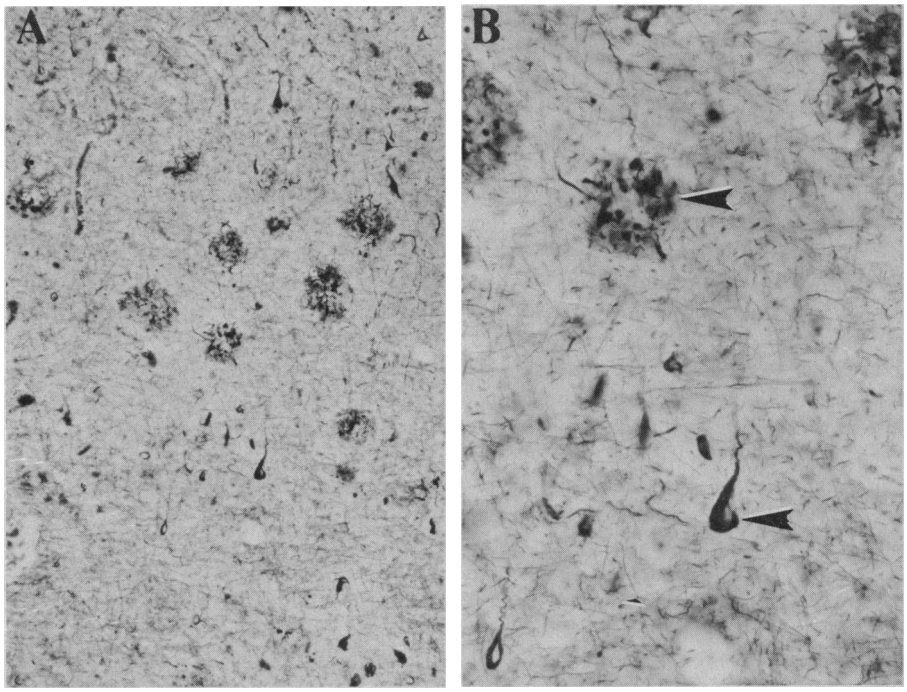


Fig. 1. These photomicrographs, from the brain of an individual with Alzheimer's disease, illustrate, at low (A) and high (B) power, the neuritic plaques and neurofibrillary tangles which are characteristic features of the disorder. This silver impregnation method selectively stains the neurites in plaques and the neurofibrillary tangles in nerve cells, both of which contain abnormal filamentous inclusions. Normal neurons and other elements of the neuropil are not visible in these preparations. (A) The upper layers of the cortex contain several roughly spherical neuritic plaques made up of dark club-shaped processes around a core of amyloid (not stained in this preparation). Several pyramidal neurons contain neurofibrillary tangles impregnated with silver (×40). (B) This micrograph, showing the central part of (A) demonstrates the neurites (axon terminals) forming the corona of the plaque (upper arrow). The cell body and apical dendrite of the layer V pyramidal neuron contain a neurofibrillary tangle (lower arrow); the paired helical filaments are comprised of cross-linked polypeptides, perhaps representing altered neurofilament triplet proteins (×100).

Table 1. Neurotransmitter alterations in the cerebral cortex in Alzheimer's disease. Alterations in the biochemical markers for neurotransmitter specified neuronal systems innervating cortex in AD are summarized. Results were based upon quantitative analysis of markers (enzymes and neurotransmitters) measured in extracts from cortex of postmortem samples obtained from individuals affected with AD and compared to unaffected controls. Extrinsic to cortex refers to the fact that the cell bodies of origin for these neuronal systems are located primarily in the brainstem; intrinsic to cortex indicates that these neurons have their cell bodies primarily within the cortex.

Neuronal type	Level	References
Extrinsic to cortex		
Acetylcholine	Marked reductions	*17–21, 28, 29*
Norepinephrine	Normal to decreased	*18, 57, 58*
Serotonin	Normal to decreased	*57*
Intrinsic to cortex		
γ-Aminobutyric acid	Normal to modest decrease	*19, 20, 27*
Vasoactive intestinal peptide	Normal	*28, 30*
Arginine vasopressin	Normal	*29*
Cholecystokinin	Normal	*29, 30*
Somatostatin	Marked reductions	*21, 53*

brain and then examine the consequences of these lesions on neurochemical parameters at target sites. Because developmental studies (*32*) suggested that cortical cholinergic inputs were derived primarily from subcortical regions, neurochemical mapping studies were undertaken in our laboratory to determine the source of cortical cholinergic innervation. To avoid the interpretational problems associated with nonselective, destructive lesions, excitotoxic analogs of glutamate (kainic acid and ibotenic acid) were injected by stereotaxic methods into specific brain regions. Excitotoxins cause a highly selective destruction of neuronal cell bodies in proximity to the injection site but spare axons of passage (*33*). Excitotoxin lesions of the rat ventral globus pallidus (VGP), the site shown by Shute and Lewis (*29*) to contain neurons staining with AChE, caused a marked reduction in cholinergic markers in the ipsilateral cerebral cortex (*34*). Lesions situated in the thalamus, the internal capsule, dorsal globus pallidus, and zone incerta did not reduce cortical cholinergic markers. Significantly, the VGP lesions did not affect the noradrenergic, serotonergic, or histaminergic inputs whose cell bodies are located in the brainstem and whose axons pass through the VGP. Thus, we noted that excitotoxic lesions in the VGP of the rat resulted in selective cortical cholinergic deficits that mimicked those reported in AD (*34*).

After the VGP lesion, subareas of the cerebral cortex, assayed for CAT activity and stained for AChE, showed reductions in enzyme activity and staining to be greatest in the frontal and parietal cortex but negligible in the occipital cortex and hippocampus (*35*). The most extensive lesions of the VGP, which did not affect GABAergic (GABA, γ-aminobutyric acid) markers within the cerebral cortex, were concomitant with a reduction of up to 70 percent of the CAT activity in the frontal and parietal cortex. Accordingly, the cortex must receive a lesser but significant cholinergic innervation from neurons not contained within the VGP. Direct injection of kainic acid into the lateral neocortex caused a major decrease in the activity of glutamic acid decarboxylase (GAD) and only a very modest reduction in CAT. Cortical laminar analysis (*36*), in conjunction with immunocytochemical studies showing neurons containing CAT in cortex (*30*), indicates that there is a small complement of cholinergic neurons intrinsic to cortex; but that the major cortical cholinergic innervation is derived from nerve cells in the basal forebrain (*34–37*).

The magnocellular neurons of the basal forebrain, the primary source of cortical cholinergic innervation in the rat, are among the largest in the brain. These neurons, which stain intensely for AChE, are located in the ventral and medial aspects of the globus pallidus, extend into the hypothalamus, and range rostrally to include the diagonal band of Broca (dbB) and the medial septal nucleus (*38*). Comparative neuroanatomic studies (*39*) indicate that the major part of this cholinergic system in primates is the nucleus basalis of Meynert (nbM) (*40*). Retrograde tracing techniques (*41*) have provided critical information on the topographical organization of these basal forebrain pathways in the monkey (*42*) and rat (*43*). With this anatomical technique, a small amount of the tracer is injected into a discrete region containing axon terminals; the tracer is taken up by the nerve terminals and transported down the axon and back to the neuronal cell body, thus establishing the existence of neuronal connections between these two regions. The neuronal cell bodies in the medial septum and dbB innervate the hippocampal formation and occipital cortex whereas nerve cells in the nbM project primarily to the frontal, prefrontal, and parietal cortex (Fig. 3). Recently, by means of a combination of histochemical staining for AChE to identify the nbM neurons and quantitative assays of CAT in microdissected adjacent sections, the cholinergic nature of the nbM has been confirmed in the primate (*44*).

Nucleus Basalis in Alzheimer's Disease

The profound reductions in CAT and AChE activities in the cortex and hippocampus of patients dying with AD could result from impaired synthesis of these enzymes, an abnormality of axonal transport of the enzymes from cell bodies to terminals in the cortex, or a degeneration of cholinergic neurons in the basal forebrain. Because several lines of evidence suggested that the primary source of cholinergic innervation to cortex and hippocampal formation was derived from large neurons in the dbB and nbM, we examined these neuronal populations in patients with AD.

The initial case was a 74-year-old man who died after a 14-year history of a progressive loss of memory, impairment of judgment, and deterioration in other cognitive functions. Notably, the patient's father and paternal aunt and uncle suffered from a dementia beginning at approximately 60 years of age (*45*). Histopathological analysis of the brain disclosed neuritic plaques and neurofibrillary tangles diagnostic of AD. Serial histological sections through the forebrain at the level of the anterior commissure were compared with sections from an age-matched control. The patient with AD had a profound and selective loss of neurons within the nbM; whereas nerve cells in the adjacent structures such as the globus pallidus were not affected by the degenerative process.

Because the familial form of AD may represent a separate entity, a subsequent quantitative analysis of neuronal cell loss in the nbM was undertaken in a larger cohort of patients. Five individuals, who suffered from a disorder consistent with AD and who were shown on postmortem examination to have AD, were compared to five similarly aged individuals who had no evidence of dementia (*46*). Nissl-stained sections through the major portion of the nbM were evaluated for the number of neurons in this region. The patients with AD exhibited a highly consistent and marked decrease in neuronal

cell density in the nbM and an absolute reduction in cell number of 75 percent ($P < .001$). No consistent alterations in cell density were observed in adjacent structures contained within the sections such as the dorsal globus pallidus or the hypothalamus. The dbB, present in some sections, also showed loss of nerve cells. Thus, these pathological findings indicate that the cholinergic deficits in the cortex and the hippocampus of patients dying with AD result from a degeneration of nerve cells in the nbM.

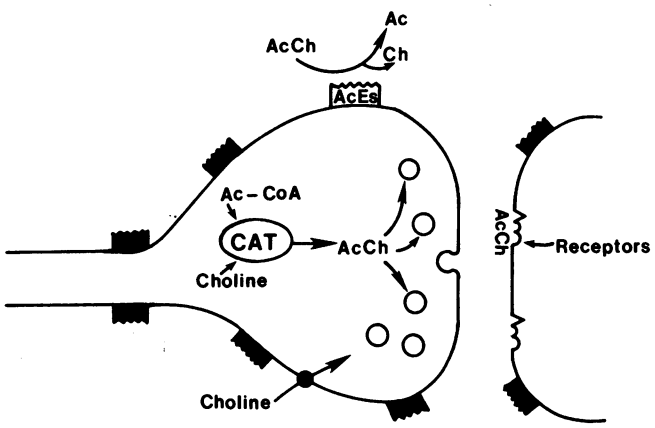
More recently, we have shown that cholinergic innervation is important in the evolution of neuritic plaques. Since aged monkeys, like humans, may develop neuritic plaques with increasing age (*47*), we used silver techniques to reveal the argentophilic neurites, Congo red to stain amyloid, and AChE histochemistry to quantify the number and character of plaques in the frontal cortex of aged monkeys (*48*). Immature plaques were rich in AChE activity but contained little amyloid. Mature plaques showed marked AChE activity and substantial amounts of amyloid. End-stage plaques contained large amounts of amyloid but were devoid of neurites and showed little AChE activity. This investigation suggested that AChE-rich dystrophic neurites, presumably derived from nbM axons, were an early component of the plaque and that loss of these neurites was associated with the formation of burned-out plaques and reduction in AChE activity in the cortex (*48*). One can imagine that this process occurring repeatedly and affecting many cholinergic axons would result in multiple neuritic plaques and profound reductions in AChE and CAT activity in the cerebral cortex (*49, 50*). The fact that plaque density in cortex correlates both with reductions in CAT activity and with the severity of cognitive impairments in AD lends support to this hypothesis (*20*).

Specificity of the Nucleus Basalis Lesion to Alzheimer's Disease

The reductions in the presynaptic markers for the cholinergic neurons in the cerebral cortex and hippocampus in AD appear to be specific rather than reflecting a more global change in neuronal markers. Neurons that use GABA as their neurotransmitter are thought to be intrinsic to the cerebral cortex (*51*); for example, their cell bodies and axons are restricted to the cerebral cortex. The concentration of GABA and the activity of GAD, the enzyme that synthesizes GABA, have not been found to be consistently reduced in the cerebral cortex and hippocampus in AD (*21, 52*). Similarly, cholecystokinin (CCK), arginine-vasopressin, and vasoactive intestinal polypeptide (VIP), neuropeptides that are localized in neuronal cell bodies within the cortex, were not significantly decreased in AD (*22, 53–54*). Thus, markers for several neuronal systems intrinsic to the cerebral cortex exhibit neither the consistent nor the profound reductions demonstrated for the cholinergic systems.

However, it should be noted that concentrations of somatostatin, a neuropeptide believed to be localized in cortical bipolar neurons (*55*), may be significantly decreased in AD (*22*). Because of the growing evidence of the co-localization of neuropeptides in neurons that utilize the amine neurotransmitters (*56*), it seemed possible that the reduction of somatostatin reflected its partial localization in the affected cortical cholinergic fibers derived from the nbM. However, excitotoxin-induced lesions of the rat VGP did not decrease somatostatin levels in the cortex or hippocampal formation whereas excitotoxin lesions of the hippocampus caused a profound reduction in the somatostatin level without affecting CAT activity (*57*). Thus, the reduction in somatostatin levels in the cortex and hippocampus in AD appears to reflect alterations in another neuronal system, probably intrinsic to these regions and distinct from the nbM cholinergic pathways.

Several studies have been performed on the levels of the presynaptic markers for the noradrenergic neurons in the cerebral cortices of patients who died of AD; and the results have ranged from normal values to significant decrements (*19, 58, 59*). Degeneration of the locus coeruleus, the source of cortical noradrenergic innervation, has been reported to occur in younger patients suffering from AD, whereas this noradrenergic nucleus remains relatively intact in older patients who die with the senile form of the disorder (*60*). This observation points to a possible difference between the early and late age of onset of AD in



AcCh = Acetylcholine
CAT = Choline Acetyltransferase
AcEs = Acetylcholine Esterase

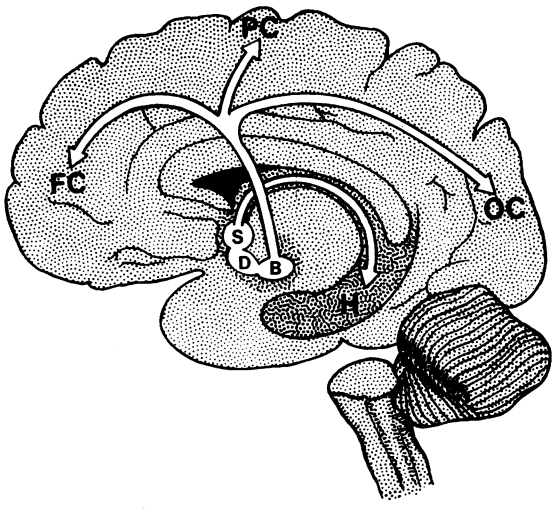


Fig. 2 (left). Schematic representation of a cholinergic synapse. Acetylcholine (*AcCh*) is synthesized from choline and acetyl–coenzyme A (*Ac-CoA*) by the enzyme choline acetyltransferase (*CAT*). Acetylcholine is stored within vesicles in the nerve terminal and released into the synaptic cleft upon depolarization. Acetylcholine diffuses across the cleft to activate muscarinic receptors, the predominant receptor in brain, or nicotinic receptors. The action of acetylcholine is rapidly terminated by hydrolysis by the enzyme acetylcholinesterase (*AcEs*) which is located on the surface of cholinergic neurons as well as neurons receiving cholinergic innervation. Fig. 3 (right). Cholinergic pathways innervating cortex. The cholinergic neuronal cell bodies of the basal forebrain located in the nucleus basalis of Meynert (*B*), the diagonal band of Broca (*D*), and the medial septal nucleus (*S*) send axons that innervate the entire cortex including the frontal (*FC*), parietal (*PC*), and occipital (*OC*) cortex, as well as the hippocampal formation (*H*).

spite of the similarities in the histopathology and cholinergic deficits. Thus, there is compelling evidence of degeneration of other neuronal systems, in addition to the basal forebrain cholinergic projections in AD, which most likely contribute to the symptomatic manifestations of the disorder in, as yet, poorly defined ways.

In a related question, it is important to determine whether the degeneration of dbB and nbM neurons is specific for AD or occurs in other neuropsychiatric disorders. Parkinson's disease (PD), a disorder characterized by degeneration of the nigrostriatal dopaminergic pathway (*12*), is often complicated by a progressive dementia (*61*); and many of these patients show pathological changes (plaques and tangles) of AD (*62*). Nearly 20 years ago, Hassler (*63*) described loss of cells in the nbM in some cases of PD and implicated this lesion in what he termed "bradyphrenia," for example, a slowness of thought, delay in emotional reactions, and difficulty in decision-making. Similar changes were seen in some individuals over 70 years of age. Dementia in PD and lesions in the nbM have not been causally linked, however, until recent quantitative studies of nerve cells in the dbB and nbM have indicated that demented PD patients do have a selective loss of this population of neurons, whereas those PD patients with normal cognitive function do not show damage to the nbM (*64*).

Individuals with Down's syndrome, trisomy 21, often experience a progressive deterioration in their limited cognitive abilities beginning at approximately 30 to 35 years of age (*65*). Brains of affected patients show neuropathological changes virtually identical to those in AD (*66*). Moreover, the activity of CAT is reduced in the cortex and basal forebrain (*67*); and in at least one case, neurons were decreased in the nbM (*49*). Therefore, degeneration of cholinergic neurons in the dbB and nbM is not restricted to AD but occurs in other diseases characterized by deterioration of higher cognitive functions and the histopathological stigmata of AD. In contrast, Huntington's disease (HD) is an autosomal dominant disorder in which there is a profound but relatively selective degeneration of neurons located in the cerebral cortex and striatum, a structure in proximity to the nbM. Although a progressive dementia is a consistent feature of HD, its symptoms differ from those of AD in that apraxias and aphasias generally do not occur (*68*). Notably, neurochemical and histopathological studies do not show neuritic plaques, reduction in the activity of CAT in the cerebral cortex (*13*), or alterations in the population of neurons in the basal nucleus (*69*).

Role of the Nucleus Basalis Lesion in Behavior

The role of the septal-dbB-nbM system in behavior and cognition is poorly defined. As noted above, studies in both man and experimental animals indicate that centrally active drugs, which block muscarinic cholinergic receptors, can cause a relatively selective disruption of recent memory and, at high doses, produce more global impairments of cognitive functions resulting in delirium (*14*). Considerable evidence points to an important role of the hippocampal formation in memory; and lesions of the medial septum or the fimbria, which transect the cholinergic pathways to the hippocampal formation, severely impair learning and recent memory in experimental animals (*70*). Thus, degeneration of neurons in the medial septum and dbB, which project to the hippocampus, may account for the impairments in recent memory that characterize the initial phase of AD.

Thus far, there seem to be no published studies on the behavioral consequences in experimental animals that results from a discrete lesion of the nbM. Studies of the activity of nbM neurons in the primate indicate that many cells exhibit rapid changes in firing in relation to different stimuli and behaviors (*71*). Some neurons in particular respond to the sight of food or to delivery of a food reward, suggesting a role of this structure in feeding behavior. More generally these nuclei may contribute to reward, learning, and attentional mechanisms. In the light of widespread projections from the nbM to all areas of the cerebral cortex, as well as to limbic structures including the amygdala, there is reason to speculate that loss of these cholinergic pathways may account for some of the emotional and cognitive difficulties that develop in the course of AD. The damage to intrinsic cortical neurons or the abnormalities in somatostatin immunoreactivity in AD have not been correlated with clinical abnormalities and are problems for future investigation.

Future Research in Alzheimer's Dementia

The delineation of cholinergic deficits in AD along with the selective degeneration of nerve cells in the dbB and nbM provides the first example of a major disorder of higher cognitive functions in which transmitter-defined neuronal pathways responsible for dementia have been identified. Moreover, this nerve cell population appears to be implicated in two other types of dementia, PD (*64*) and trisomy 21 (*67*), which are associated with AD-type pathology. These findings do not mean that cholinergic projections from neurons in the dbB and nbM are the only systems affected in these types of dementia. However, evidence available to date suggests that this transmitter system is involved most consistently and most severely in AD. The identified cholinergic lesion in AD has important implications for its diagnosis, treatment, and ultimately its prevention.

With regard to diagnosis, we need to know more about the relation between the cholinergic deficits, degeneration of component neurons in the dbB and nbM system, and the variation in the symptomatic manifestations of AD. The degenerative process may result in the appearance of neuronal-specific markers in the cerebrospinal fluid or blood or the development of specific immune responses that could serve as direct diagnostic tests for the disorder. With the development of positron emission tomography (*72*), it seems likely that in the future noninvasive probes of central cholinergic function may be developed that will allow for the assessment of cholinergic neuronal integrity in demented patients with the presumptive diagnosis of AD.

With regard to pathophysiology and treatment, it is interesting to compare AD and PD since both disorders appear to result primarily from the loss of a relatively small population of transmitter-specific neurons with cell bodies located in the base of the brain. In PD, the dopamine utilizing neurons of the substantia nigra, which innervate the striatum, degenerate (*12*). Considerable success has been achieved in reducing the symptoms of PD by treatment with the precursor of dopamine, L-dopa, to correct the deficiency in this neurotransmitter. Several groups have undertaken clinical studies to determine whether treatment with drugs that directly or indirectly potentiate cholinergic neurotransmission might be of therapeutic value for patients with AD. Some of the pharmacologic strategies explored in AD include administration of the precursors for ACh, choline, or lecithin (*73*), treatment with inhibitors of AChE to prolong the synaptic action of ACh (*74*), or treatment with drugs that directly stimulate the postsynaptic muscarinic receptor

(*75*). Thus far, the results have been rather inconclusive although a few reports indicate that some patients, primarily in the early stages of AD, may experience modest improvements in cognitive functions (for review, see *76*).

One possible explanation for relative lack of response to pharmacologic treatment in AD as compared to PD may lie in important differences in the synaptic organization and physiology of the two affected neuronal systems. Whereas the dopaminergic innervation of the striatum appears to be highly arborized and overlapping (*75–77*), the cholinergic fibers innervating the cortex exhibit a topographic, radial distribution (*42, 43*). More importantly, the firing rates of dopamine neurons are very low and show no correlation with specific aspects of movement or behavior, suggesting a more general, modulatory influence on the striatum (*77, 78*). In contrast, nbM neurons discharge at higher rates and are phasically active with rapid alterations in firing in relation to behavior (*71*). The loss of a neuronal system that exerts tonic modulatory influences, like the dopaminergic system, may be more amenable to pharmacologic correction than the loss of a neuronal system, like the nbM, which conveys spatially and temporally coded information. Successful approaches toward the treatment of AD, if feasible, will depend on a better delineation of the synaptic organization, physiology, and function of the cortical cholinergic projections. Animal models with selective lesions of the basal forebrain cholinergic complex may prove to be useful for preclinical testing of potentially therapeutic agents (*79*).

The identification of the neuronal systems affected in AD now allows neuroscientists to pose questions concerning mechanisms responsible for the selective degeneration. It is important to determine what features the cholinergic, noradrenergic, somatostatin-containing neurons, and possibly other affected neuronal populations share in common that render them vulnerable to the degenerative process. In other words, is it their size, extent of axonal arbor, type of afferent input or metabolic specialization? The interaction between age and the expression of selective vulnerability remains a critical issue that has relevance not only to AD but other hereditary neurodegenerative disorders such as HD. Insights into the molecular biological mechanisms involved in selective neuronal vulnerability may ultimately lead to the development of treatments that relieve or prevent the degenerative process of AD.

Summary

Alzheimer's disease and senile dementia of the Alzheimer's type, at present distinguished by age of onset, are characterized by progressive abnormalities of memory, behavior, and cognition. The brains of these patients show neurofibrillary tangles, neuritic plaques, and loss of specific populations of nerve cells. Neurochemical studies indicate that presynaptic cholinergic markers are markedly reduced in the cerebral cortex and hippocampus of affected individuals. This cholinergic deficiency appears to be due to a loss of neurons in the medial septum, diagonal band of Broca, and the nucleus basalis of Meynert, a basal forebrain cholinergic system which projects directly to the hippocampus and neocortex. Loss of this cell population also has been implicated in other types of dementia showing features in common with Alzheimer's dementia. The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders.

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The Electric Power Research Institute

Chauncey Starr

Growing awareness of research needs, coupled with the threat of federal intervention, galvanized the leaders of the electric utility industry in the early 1970's. By January 1973, the Electric Power Research Institute (EPRI) was in business—in spite of skepticism from inside and outside the industry.

As EPRI's first president, I began with a budget of $61 million pledged by the industry for 1973 and imputations from many quarters that EPRI was a sham, that the utility industry was not serious about its technical responsibilities, and that this new entity would not get anywhere. This early history of the institute and of the legislation proposed by the Senate Commerce Committee as a result of the 1965 blackout in the Northeast have been recounted elsewhere (*1*).

National investments in research and development (R & D) are indirectly provided by the public through taxation, cost of goods, or direct contribution. EPRI is supported through the cost of electricity and represents a novel form of institutional intermediary between the consuming public, the utilities, and the researchers. Because many scientists in fields outside of energy research have had little contact with EPRI, I shall describe its scope, organization, and philosophy.

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Organization

EPRI is a nonprofit organization whose purpose is to manage a coordinated national R & D program for the electric power industry. EPRI selects and funds research projects designed to develop or improve technologies that will help the utility industry meet present and future electric energy needs in environmentally and economically acceptable ways. EPRI's activities are coordinated with those of government agencies, individual utilities, manufacturers and vendors, and comparable organizations in many other countries.

Of the roughly 3000 electric utilities in the United States, almost all the largest are voluntary supporting members of EPRI. In 1982, the 571 members were 160 investor-owned utilities, including their affiliates and service organizations; 177 municipal or regional government utilities; 232 rural electric cooperatives; and two federal systems—Tennessee Valley Authority and the Bonneville Power Administration. About 150 nonmember utilities also contributed some measure of support. Collectively, the contributors represent about 70 percent of the total electricity generated in the United States. EPRI also has 16 foreign utility associates with which information is exchanged.

In 1982, members paid 0.0236 cents per kilowatt-hour of electricity sold in 1980, or about 0.3 percent of member utilities' gross revenue, of which EPRI manages 80 percent and utilities retain and manage 20 percent for specific R & D needs. EPRI had a total budget of about $300 million in 1982, of which $260 million covered external R & D contract activities. Aside from membership payments from the Tennessee Valley Authority and Bonneville Power Administration, no federal funds come to EPRI, although many joint programs with federal agencies have been undertaken.

EPRI's primary areas of research are organized into six technical divisions (Fig. 1).

Since its founding, EPRI has initiated more than 1800 research projects (*2*). There are currently about 1400 active R & D projects under EPRI management. The 5-year funding plan (1982 to 1986) for these projects totals $1.8 billion. Cofunding and cost-sharing by contractors and other organizations increase