Evidence for Retrograde Degeneration of Epinephrine Neurons in Alzheimer's Disease

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Alzheimer's disease (AD) is associated with a progressive loss of locus ceruleus neurons. These noradrenergic neurons receive a major afferent projection from epinephrine neurons in epinephrine cell groups in the brainstem. The epinephrine neurons have a specific enzymatic marker, phenylethanolamine *N*-methyltransferase (PNMT), which allows them to be identified chemically and immunohistochemically. We have previously reported a decrease in PNMT in brains of patients with AD. We now report that the decrease in PNMT activity in projections to the locus ceruleus is not due to the loss of epinephrine neurons, although up to 33% of these neurons are atrophic. The decrease in presynaptic PNMT does, however, correlate with the loss of postsynaptic locus ceruleus neurons in brains from AD patients. The percentage of degenerating neurons in the epinephrine nuclei also correlates significantly with the amount of loss of locus ceruleus neurons in AD. In addition, there is a 55% decrease in mitogen activity, a nonspecific measure of growth or maintenance factors, in dialysed locus ceruleus extracts from the AD patients compared to those from control subjects. The mitogen activity in the locus ceruleus was significantly correlated with PNMT activity and with the density of locus ceruleus neurons in all cases examined. These findings provide evidence for the hypothesis that retrograde degeneration is a mechanism of neuronal degeneration in AD and suggest that trophic factors may play a role in this process.

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Although deficits in several neurotransmitter enzymes and peptide neuromodulators have been reported in Alzheimer's disease (AD) [4, 7, 13, 14, 30, 37], little is known about the mechanisms producing these deficits. Recent studies suggest that loss of choline acetyltransferase (Chat), a specific marker for the cholinergic transmitter system, may precede loss of neurons that synthesize this enzyme [19]. We have shown that phenylethanolamine *N*-methyltransferase (PNMT), the rate-limiting enzyme in epinephrine (Epi) synthesis [17] and the specific enzymatic marker for the Epi neurotransmitter system, is decreased in AD brains [7]. This decrease occurs in brain areas affected by AD, i.e., the locus ceruleus, frontal cortex, hippocampus, and amygdala, but not in the cerebellum [7, 35] or motor cortex [9], areas little affected by the disease. This finding suggests that the loss of postsynaptic neurons may trigger changes in their afferent neurons which eventually lead to secondary degeneration of these afferent neurons. Retrograde degeneration has been defined as neuronal atrophy or degeneration following the death of cells upon which they project. This concept includes not only death of the presynaptic neuron but all other situations in which the reaction of the cell falls short of its death [11, 12]. This includes chemical changes, which are the inevitable precursors of structural changes. Ross and colleagues [33], for instance, have demonstrated that one of the earliest chemical changes in the retrograde reaction in central noradrenergic neurons is the loss of catecholamine synthesizing enzymes. Similar enzymatic changes have also been noted in the cholinergic system in experimental retrograde degeneration [24].

To study this process more carefully, we examined the afferent projection to norepinephrine neurons in the locus ceruleus from the C-1, C-2, and C-3 Epi cell groups in the brains of patients with AD and control subjects [2, 13, 21]. It has been demonstrated that the locus ceruleus receives its main afferent projections from regions that contain the Epi nuclei [3]. These

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regions contain a high percentage of Epi neurons [2], and recent retrograde tracing studies have demonstrated that these Epi neurons project to the locus ceruleus [31]. We chose to study this system because there is a well-known loss of locus ceruleus neurons with increasing severity of AD [5]. This fact allowed us to examine the effect of a progressive loss of locus ceruleus neurons on afferent projections from neurons in the Epi nuclei (C-1, C-2, C-3) [3, 21].

It has been proposed that neurodegeneration in AD results from the reduced efficacy of growth factors in the target tissue [1, 19, 20]. It has also been shown that growth factors can induce enzyme synthesis. For instance, nerve growth factor induces catecholamine enzymes in peripheral sympathetic neurons [20, 36] as well as Chat activity in the central nervous system (CNS) [20]. Although nerve growth factor is not trophic for the central adrenergic system, other growth factors with neurotrophic activity have been identified within neurons in the CNS [23, 28]. In this article, we examine the effect of loss of postsynaptic locus ceruleus neurons on the Epi neurons in its major afferent projection area. The goals of this study were to: (1) determine if the decrease in PNMT in AD brain is due to the loss of Epi neurons; (2) determine if there is a relationship between loss of postsynaptic locus ceruleus neurons and deficits in PNMT in the synaptic terminals and structural changes in the neuronal cell bodies of Epi neurons; (3) determine if mitogen activity present in locus ceruleus extracts is affected in AD; and (4) determine if alterations in trophic factors in the locus ceruleus are related to changes in PNMT.

Methods

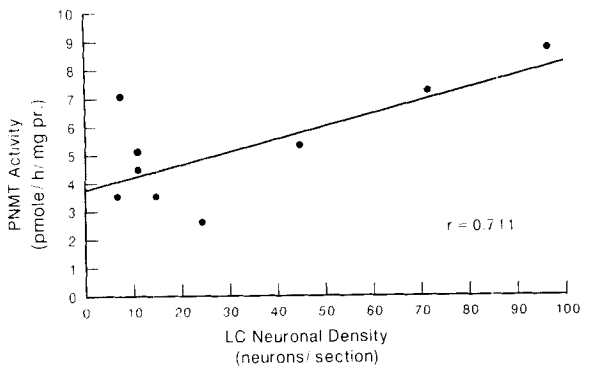
Control samples were obtained from 5 men; 3 had no gross or histological evidence of brain pathology at autopsy and 2 had lacunar infarcts in the globus pallidus. The age at death was 63.2 ± 7.4 years (mean ± SD) and the postmortem interval was 16.5 ± 2.5 hours. On the basis of the clinical history of dementia and the histopathological identification of neuritic plaques, the diagnosis of AD was established in 4 men and 5 women patients with a mean age at death of 75.8 ± 2.2 years; the interval between death and autopsy was 13.9 ± 2.4 hours. There was no correlation between PNMT or mitogen activity and the sex or age [9] of the patient. At autopsy, the locus ceruleus from one-half of the brain was dissected, wrapped in foil, frozen, and stored at −135°C prior to enzyme or mitogen assay. PNMT and mitogen activity were measured in 27,000 *g* supernatants of tissue homogenates, which had been dialysed in tubing with a molecular weight (MW) cutoff of 12,000 daltons. The methods for measuring PNMT [6] and mitogen activity [23] have been described. The mitogen activity of the locus ceruleus dialysates was standardized to that of purified brain-derived growth factor (BDGF) [22].

The locus ceruleus and C-1, C-2, and C-3 nuclei from the other half of the brain were removed, fixed in 10% buffered formalin, dehydrated in graded alcohol, embedded in paraffin, and sectioned serially at 10 μm thickness. Every fifth section was stained with hematoxylin-eosin or, in certain cases, immunocytochemically with PNMT antibody [8]. Slides made from sections at three levels of each nucleus were examined under a microscope at ×125. All neurons containing nuclei were counted in at least seven sections of the locus ceruleus. All neurons in at least 5 sections of C-1, 5 sections of C-2, and 9 sections of C-3 rostral to the area postrema were also counted. The neuronal density is the average number of neurons in the sections examined. Cell counts in a control subject and a severely affected patient with AD were also made in PNMT-stained sections.

The cytoarchitectural boundaries of these regions that contain a large percentage of PNMT-positive neurons have been previously delineated in rat brain using PNMT immunocytochemistry [2, 21]. In addition to using the known boundaries of these nuclei, we verified that the cytoarchitectural boundaries of the Epi nuclei are the same for human brain as for rat brain, by dissecting these areas from an AD and a control case and staining them immunocytochemically with PNMT antibody [8]. To determine the percent of the neurons that were Epi neurons, these regions were fixed, and adjacent sections were stained either immunocytochemically with PNMT or with hematoxylin-eosin. The number of neurons in PNMT-stained sections was then compared to that in adjacent sections stained with hematoxylin-eosin. As a measure of the amount of atrophy in Epi neurons in AD, the cross sectional areas of 11 PNMT-positive neurons containing nuclei in a control subject were compared to 11 neurons in an AD case using a calibrated eyepiece grid. In addition, to determine if structural changes in Epi neurons could be related to the loss of postsynaptic neurons, the percentage of neurons in the Epi cell groups showing degenerative changes (atrophy or ballooning) was determined in 13 pathologically diagnosed AD cases and correlated with the neuronal loss in the locus ceruleus from the same cases. Statistical comparisons of the means of two independent samples were made using Student's *t* test. Correlation coefficients were determined by linear regression analysis.

Results

PNMT activity in projections from Epi neurons onto the locus ceruleus was decreased by 58% in the brains of patients with AD (control, 311.6 ± 28.6 pmol/hr/gm wet weight; AD, 131.0 ± 20.6; $p < 0.001$). To determine whether this decrease was due to a loss of Epi neurons, we identified the Epi cell groups in human brain and counted the neurons in these regions. Immunocytochemical staining revealed that 88.5% of neurons in the Epi nuclei were PNMT-positive in a control subject. This was not significantly different from the 85.2% PNMT-positive neurons in Epi nuclei in an AD patient. The boundaries for these nuclei and the high percentage of PNMT-positive neurons were the same in human brain as has been described for rat brain [2, 21]. There was no loss of neurons in C-1, C-2, or C-3 in AD patients (control C-1, 59.7 ± 3.3 neurons/section, vs AD, 52.1 ± 1.9; control C-2, 23.2 ± 1.1, vs AD, 22.5 ± 1.2; control C-3, 6.9 ± 0.6, vs



Correlation between phenylethanolamine N*-methyltransferase (PNMT) activity in afferent projections to the locus ceruleus (LC) and the number of neurons in the locus ceruleus from the same AD brains. PNMT activity was measured in dialysed supernatants of the locus ceruleus. The neuronal density was determined as described in the text. The correlation coefficient was determined by linear regression analysis;* p = *0.029 as calculated by Z transformation of the correlation coefficient. (pr. = protein.)*

AD, 6.8 ± 0.4). This was confirmed when only PNMT-positive neurons were counted in a control subject and a severely affected AD patient (control C-1, 45.4 ± 1.3 neurons/section, vs AD, 39.6 ± 6.0; control C-2, 15.8 ± 1.4, vs AD, 22.2 ± 2.8). However, hematoxylin-eosin–stained sections revealed that from 0 to 33% of C-1 and from 0 to 32% of C-2 neurons, but no C-3 neurons, were atrophic in all 9 AD brains examined. Photomicrographs of PNMT-positive neurons have demonstrated that the atrophy occurs in PNMT-positive neurons, which make up over 85% of the Epi nuclei [7]. The cross sectional areas of the 11 PNMT-positive neurons from an AD brain were 42% smaller than those from a control subject (control, 721 ± 104 μ^2, vs AD, 414 ± 47 μ^2; $p < 0.015$), demonstrating that the atrophy in the Epi neurons was significant.

In contrast to Epi neurons, locus ceruleus neurons were decreased 65% in patients with AD (control 94.3 ± 5.0 neurons/section; AD, 32.6 ± 10.1). In addition, the loss of these postsynaptic neurons correlated significantly ($r = 0.711$; $p = 0.029$) with the decrease in PNMT activity in projections to the locus ceruleus from Epi neurons (Figure). There was also a significant correlation between the percentage of neurons showing degenerative changes in the Epi cell groups and the loss of locus ceruleus neurons ($r = -0.610$; $p < 0.05$).

To determine whether a growth or maintenance factor is involved in this process, we measured mitogen activity in locus ceruleus extracts. Mitogen activity was significantly reduced by 55% in the locus ceruleus from the AD cases compared to control subjects

Mitogen Activity[a] *in the Locus Ceruleus of Control Subjects and Patients with Alzheimer's Disease*

Group	Mitogen Activity
Control subjects	91.8 ± 12.4
Alzheimer's disease	40.8 ± 5.7[b]

[a]Activity is reported as pg equivalent/mg protein. Mitogen activity in locus ceruleus samples was normalized to the activity of 1 pg brain-derived growth factor (BDGF) standard. One pg of BDGF added to the incubation mixture resulted in the incorporation of 3×10^3 cpm of [^{3}H] thymidine into the DNA of monolayers of Swiss mouse 3T3 fibroblasts during a 20-hour culture period. Values represent the mean ± SE from 5 control subjects and 9 patients with AD.
[b]$p < 0.001$ (Student's t test).

(Table). The mitogen activity correlated significantly with the PNMT activity in all the cases examined ($r = 0.752$; $p < 0.01$). However, in the AD group there was no significant correlation between mitogen activity and PNMT. Mitogen activity was also significantly correlated with the density of locus ceruleus neurons ($r = 0.742$; $p < 0.01$). Again, the correlation was no longer significant when the control cases were removed from the analysis.

Discussion

We have previously reported a decrease in PNMT in areas of AD brain where there is loss of postsynaptic neurons [7, 9]. This loss of PNMT activity in AD brain was due to a decrease in the amount of enzyme protein [7]. The present study indicates that this deficit in PNMT protein is not due to a loss of the Epi neurons that synthesize this enzyme because the large decrease of PNMT in axon terminals occurs prior to significant neuronal loss in the C-1, C-2, and C-3 nuclei. Although neuronal counts in these regions were made with hematoxylin-eosin stain, immunocytochemical staining with PNMT antibody shows that almost all the neurons in this region are Epi neurons. This finding of almost exclusive PNMT-positive neurons in the rostral C-1, C-2, and C-3 regions of human brain corresponds to a similar finding in these regions in rat brain [2, 21]. Counts of PNMT-stained neurons from a control subject and a severely affected AD patient confirmed that there is no loss of Epi neurons in these AD cases.

In contrast, however, there was a loss of postsynaptic neurons in the locus ceruleus. Several lines of evidence suggest that loss of postsynaptic cells in AD results in changes in presynaptic neurons. We have shown that the decrease in PNMT occurs in areas of AD brain where there is loss of postsynaptic neurons and not in areas where postsynaptic cells are little affected by the disease [7, 9]. Using immunocytochemistry we have demonstrated a decrease in PNMT-positive axonal projections adjacent to a degenerating neuron but no decrease in PNMT projections adjacent

to viable blood vessel wall cells in the same AD sample [8]. In the present study we show a significant correlation between PNMT activity in presynaptic terminals and the loss of postsynaptic locus ceruleus neurons. There was also a correlation between structural changes of ballooning and atrophy [8] in neurons in the Epi cell group and the loss of locus ceruleus neurons. It is not certain whether all of these atrophying neurons are projecting to the locus ceruleus. It is interesting that, supporting such a direct relationship, the percentage of atrophied C-1 neurons in the most severely affected AD patient is remarkably close to the percentage of PNMT-positive neurons reported to project to the locus ceruleus [31]. Alternatively, the locus ceruleus may be an indicator of general neuronal loss throughout the AD brain [25, 26]. The cholinergic projection to the locus ceruleus [15, 18] appears to be similarly affected. We have reported a significant correlation between decreased Chat activity and the loss of locus ceruleus neurons in AD [6]. In contrast, there is no loss of Chat activity in C-1 or C-2 where there is no loss of Epi neurons (our unpublished observation). These data show for the first time a direct relationship between the loss of postsynaptic neurons and retrograde changes in presynaptic neurons in AD.

We next looked for factors in the locus ceruleus that might explain the decrease in presynaptic PNMT as well as the atrophy in Epi neuronal cell bodies in AD. We used mitogen activity as a nonspecific measure of growth or maintenance factors. Mitogen activity in dialyzed supernatants of the locus ceruleus from patients with AD was significantly less than in control brains. This finding indicates that growth or maintenance factors with MW of at least 12,000 daltons are affected in AD. The data from all cases examined, which show correlation between PNMT and mitogen activity, are consistent with the hypothesis that one or more growth factors may induce neurotransmitter-synthesizing enzymes as occurs in animal models [20, 36]. Some of these factors appear to decrease with neuronal loss. However, in AD the situation may be more complex. Mitogen activity represents an aggregate of growth factors present in the extract. An increase in factors specific for nonneuronal cells may obscure decreases in factors unique to neurons. One explanation for the lack of correlation between PNMT and mitogen activity in AD cases is that other nonneurotrophic growth factors may increase in the disease. Certain growth factors, for instance, are glial mitogens [28]. In this regard, we and others [35] have observed glial proliferation in areas, including the locus ceruleus, in which neuronal loss occurs in AD. Specific growth factors that we are currently examining may correlate better with changes in specific cell populations in AD.

The initial report of retrograde degeneration in AD was based on the finding that there was a loss of Chat activity in the cortex in an AD brain that exhibited atrophy but no loss of neurons in the nucleus basalis [29]. Recently, a topographical study of the loss of neurons from the locus ceruleus has revealed that the neurons that project to regions of the brain most affected by AD are the ones that degenerate, whereas neurons projecting to noncortical areas are relatively spared [25, 26]. It was concluded that the loss of locus ceruleus neurons was also due to secondary retrograde changes. Our earlier findings that plaque counts in the CA-1 region of the hippocampus are correlated with the loss of locus ceruleus neurons [9] support this hypothesis [25, 26]. However, other factors may contribute to the loss of these neurons. Our present study is the first to provide direct evidence for retrograde degeneration in AD by correlating both enzymatic changes in presynaptic terminals and structural changes in Epi neuronal cell bodies with the decrease in number of postsynaptic neurons. The Epi neurotransmitter system is thus the third system reported to be affected by retrograde changes, suggesting that secondary and tertiary retrograde degeneration may be more widespread than previously recognized in AD [16, 32]. The finding of decreased mitogen activity in locus ceruleus dialysates from AD patients favors the hypothesis that alterations in trophic factors may play a role in retrograde degeneration in AD [1, 6, 19, 20]. However, the possibility that growth inhibitory factors [27] or toxins transported in a retrograde manner [34] may be involved in this process has not been excluded.

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