Effects of Alzheimer's Disease Severity on Cerebrospinal Fluid Norepinephrine Concentration

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Objective: Although loss of noradrenergic neurons in the locus ceruleus has been consistently demonstrated postmortem in Alzheimer's disease, several small studies suggest that indices of central noradrenergic activity increase with the severity of Alzheimer's disease in living patients. The authors estimated the effect of Alzheimer's disease severity on central noradrenergic activity by comparing the CSF norepinephrine concentrations of subjects with Alzheimer's disease in earlier and advanced stages. The effect of normal aging on CSF norepinephrine also was determined. Method: Lumbar punctures were performed in 49 subjects with Alzheimer's disease of mild or moderate severity, 25 subjects with advanced Alzheimer's disease, 42 normal older subjects, and 54 normal young subjects. Advanced Alzheimer's disease was defined prospectively by a Mini-Mental State score of less than 12. Norepinephrine was measured by radioenzymatic assay. Results: CSF norepinephrine concentration was significantly higher in the patients with advanced Alzheimer's disease (mean=279 pg/ml, SD=122) than in those with mild to moderate severity (mean=198 pg/ml, SD=89), normal older subjects (mean=219 pg/ml, SD=88), or normal young subjects (mean=154 pg/ml, SD=53). CSF and plasma norepinephrine levels and mean arterial blood pressure all were higher in the older subjects than in the young subjects. Conclusions: Despite the loss of locus ceruleus neurons in Alzheimer's disease, the aging-associated high concentration of CSF norepinephrine is retained in the earlier stages of Alzheimer's disease and increases further as the disease progresses. Increased brain noradrenergic activity may contribute to the agitated behaviors or cognitive deficits of patients with advanced Alzheimer's disease.

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The status of central nervous system (CNS) noradrenergic activity in Alzheimer's disease has potentially important implications for the pharmacologic management of this disorder (1–3). In a previous study comparing indices of CNS noradrenergic activity in patients with Alzheimer's disease and in normal older subjects (4), we unexpectedly demonstrated high CSF concentrations of norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in advanced Alzheimer's disease. We also demonstrated high plasma norepinephrine levels and high mean arterial blood pressure in advanced Alzheimer's disease in that study. Although the CSF norepinephrine results were counterintuitive given the marked loss of locus ceruleus noradrenergic neurons demonstrated in postmortem brain tissue from Alzheimer's disease patients (5–8), they have received independent confirmation from two studies (9, 10). Because the generalizability of these in vivo studies (4, 9, 10) is potentially compromised by the small numbers of subjects and because not all studies have had consistent results (11), we measured CSF norepinephrine concentrations in much larger groups of previously unreported patients with Alzheimer's disease, normal older subjects, and normal young subjects. CSF norepinephrine was chosen as the index of CNS noradrenergic activity because a substantial body of evidence suggests that CSF norepinephrine is primarily derived from the CNS rather than from the peripheral sympathetic nervous system (12). Norepinephrine does not cross the blood-brain barrier (13). In the rat, chemical sympathectomy has no effect on CSF or brain tissue

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norepinephrine (14). Furthermore, destruction of the locus ceruleus substantially reduces the CSF norepinephrine concentration, whereas destruction of the superior cervical ganglion (the source of sympathetic nervous system noradrenergic fibers that innervate cerebral vasculature) has no effect on the CSF norepinephrine concentration (15). On the basis of the previous studies (4, 9, 10), it was hypothesized that CSF norepinephrine concentrations would be highest in Alzheimer's disease patients with advanced disease.

METHOD

Subjects

This study was approved by the University of Washington Human Subjects Review Committee. After the procedures had been fully explained, written informed consent was obtained from all subjects and, in addition, the legal representatives of the Alzheimer's disease patients. The subjects were 74 persons with Alzheimer's disease (56 men and 18 women; mean age=69 years, SD=6), 42 cognitively normal healthy older volunteers (26 men and 16 women; mean age=68 years, SD=7), and 54 healthy young men (mean age=26 years, SD=3). The ages of the patients with Alzheimer's disease and the normal older subjects did not differ significantly (t=0.73, df=114, p=0.47). All subjects resided in the community except for 10 subjects with Alzheimer's disease who were residents of a long-term care Alzheimer's disease clinical research unit at the American Lake Division of the Department of Veterans Affairs (VA) Puget Sound Health Care System. These 10 subjects had resided in this unit for at least 3 months. The community-dwelling subjects were recruited through the University of Washington Alzheimer's Disease Research Center and were demographically representative of the samples recruited for university-affiliated Alzheimer's disease research, which are generally middle socioeconomic class (16). All of the 10 long-term care subjects with Alzheimer's disease were male, but otherwise they were demographically similar to the community-dwelling subjects with Alzheimer's disease. Studies were physically performed at the Seattle and American Lake Divisions of the VA Puget Sound Health Care System.

None of the subjects smoked, they were all in good general health, and they had been free of medications (except occasional nonprescription analgesics or laxatives) for at least 1 month before the lumbar puncture. All were normotensive (systolic blood pressure, <135 mm Hg; diastolic blood pressure, <90 mm Hg) and were within 125% of ideal body weight (Metropolitan Life Insurance Tables, 1983). The subjects were screened by means of medical history, semistructured psychiatric interview, physical and neurologic examinations, ECG, and laboratory evaluations; the laboratory tests included measurement of serum electrolytes and glucose, tests of renal, hepatic, and thyroid function, and a complete blood count. Both the young and older healthy volunteers were free of past or present major psychiatric disorders, neurologic disorders, renal or hepatic disease, diabetes mellitus, and symptomatic cardiovascular disease. The patients with Alzheimer's disease met the same general health, psychiatric, and neurologic criteria with the exception of their Alzheimer's disease. The subjects with Alzheimer's disease met the criteria for probable Alzheimer's disease of the National Institute of Neurological and Communicative Disorders and Stroke (17) and the DSM-IV criteria for dementia of the Alzheimer's type. The subjects with Alzheimer's disease were free of disruptive agitation on the morning of study.

The mean Mini-Mental State (18) score of the 74 Alzheimer's disease patients was 13 (SD=4). A perfect score on this widely used dementia assessment instrument is 30. Each of the normal young and older normal subjects had a Mini-Mental State score of 29 or 30 and no history or evidence of cognitive decline. To estimate the effects of dementia severity on CSF norepinephrine levels in the subjects with Alzheimer's disease, they were classified as having mild/moderate disease severity if their Mini-Mental State score was 12 or higher and as having advanced disease if their Mini-Mental State score was less than 12. The arbitrary score of 12 was chosen prospectively because of its acceptance as a discriminator of subjects with mild/moderate Alzheimer's disease from those with advanced disease for inclusion in multicenter treatment outcome studies (19). This cutoff score produced 49 Alzheimer's disease patients with mild/moderate severity (35 men and 14 women); their mean Mini-Mental State score was 18 (SD=4), and their mean age was 69 years (SD=6). The resulting advanced-disease group contained 25 subjects with Alzheimer's disease (21 men and four women); their mean Mini-Mental State score was 4 (SD=4), and their mean age was 69 years (SD=7). Age at onset of symptomatic Alzheimer's disease was defined as the age at which the spouse or another person with regular contact with the patient first noted decline of cognitive function. Age at onset did not differ between the subjects with mild/moderate Alzheimer's disease (mean=64 years, SD=6) and those with advanced Alzheimer's disease (mean=63 years, SD=7) (t=0.53, df=72, p=0.60).

Procedures

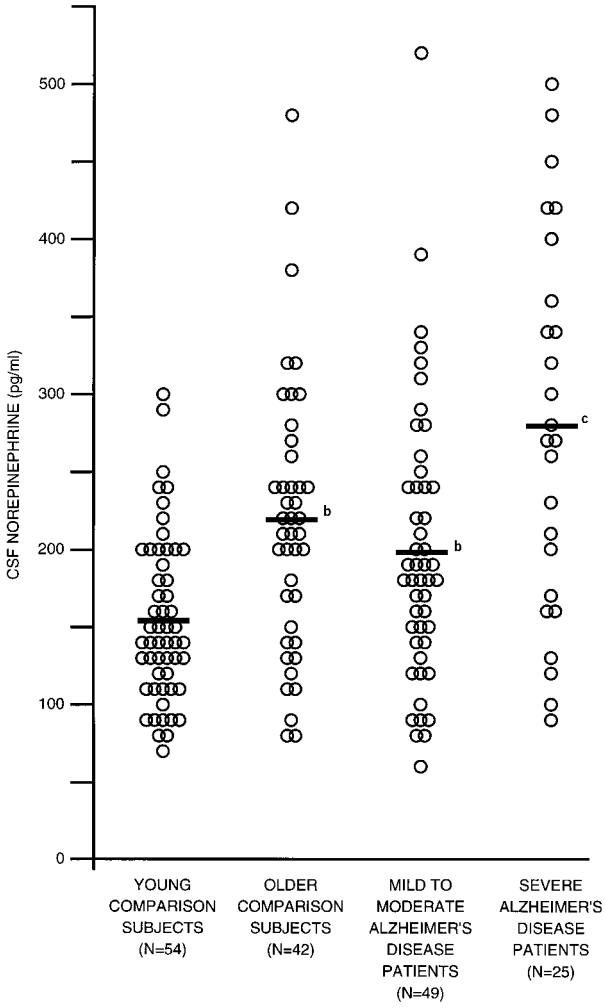
Lumbar punctures of the subjects who resided in the community were performed in the Special Studies Unit at the Seattle Division of the VA Puget Sound Health Care System. Lumbar punctures of the 10 subjects in long-term care were performed in the Alzheimer's disease unit of the American Lake Division of the VA Puget Sound Health Care System. The subjects were studied in the morning after fasting since midnight. They were prohibited from using caffeine or known stimulants of catecholamine release after midnight until the end of the study. An hour after the subject began bed rest, a 19-gauge plastic catheter was inserted into an antecubital vein. Blood for determination of plasma norepinephrine concentration was obtained through the indwelling catheter immediately before lumbar puncture, which was performed 90 minutes after catheter placement. Lumbar puncture was performed atraumatically with a 25-gauge spinal needle while the patient was maintained in the lateral decubitus position.

CSF norepinephrine was measured in the 12th ml of CSF removed. Although there is a slight gradient of norepinephrine concentrations in the first 12 ml of CSF removed after lumbar puncture, norepinephrine levels do not further increase after the 12th ml has been removed (20). The CSF samples were frozen immediately on dry ice and stored at –70 °C until assay. Blood for norepinephrine determination was collected into prechilled tubes containing ethylene glycol bis(beta-aminoethyl ether)- N,N'-tetraacetic acid (EGTA) and reduced glutathione. The blood samples were placed on ice and cold centrifuged within 1 hour of collection; the plasma was stored at –70 °C until assay. CSF and plasma norepinephrine were determined within 1 month of sample collection by a sensitive single-isotope radioenzymatic assay, as previously described (21). The intra-assay coefficient of variation is less than 5.0%. The interassay coefficient is 6.5% above 300 pg/ml and 12.0% at about 100 pg/ml. Systolic and diastolic blood pressure were obtained by using an automatic blood pressure and heart rate monitor after blood sampling. Mean arterial blood pressure was calculated as the sum of the diastolic pressure plus one-third of the difference between the systolic and diastolic pressures.

Statistical Analyses

The results are expressed as means and standard deviations. Differences among groups were evaluated by one-way analysis of variance followed by Newman-Keuls post hoc tests. It was predicted that the CSF norepinephrine concentration would be higher in the subjects with advanced Alzheimer's disease than in the other groups. The relationship between dementia severity (as reflected in Mini-Mental State score) and CSF norepinephrine level among all of the subjects with Alzheimer's disease was estimated by Pearson product-moment correlations. We used t tests to evaluate the significance of age differences between groups and the effects of gender within the normal older and Alzheimer's disease groups. A probability of $p<0.05$ (two-tailed) was accepted as statistically significant.

FIGURE 1. CSF Norepinephrine Concentration in Young Normal Subjects, Older Normal Subjects, Patients With Mild/Moderate Alzheimer's Disease, and Patients With Advanced Alzheimer's Disease[a]



[a]Horizontal lines indicate mean values. Significant difference among groups (F=13.05, df=3, 166, p<0.001).
[b]Significantly higher than the value for the young normal subjects (p<0.05, Newman-Keuls post hoc test).
[c]Significantly higher than the value for each of the other groups (p< 0.01, Newman-Keuls post hoc tests).

TABLE 1. Plasma Norepinephrine Concentration and Mean Arterial Pressure in Young Normal Subjects, Older Normal Subjects, Patients With Mild/Moderate Alzheimer's Disease, and Patients With Advanced Alzheimer's Disease

	Plasma Norepinephrine[a]			Mean Arterial Pressure[b]		
		Level (pg/ml)			Pressure (mm Hg)	
Group	N	Mean	SD	N	Mean	SD
Normal subjects						
Young	44	199[c]	61	51	88[c]	7
Older	32	327	149	32	95	9
Alzheimer's disease						
Mild or moderate	33	332	222	33	95	10
Advanced	18	405	206	20	96	8

[a]Significant difference among groups (F=9.16, df=3, 123, p<0.001).
[b]Significant difference among groups (F=8.23, df=3, 132, p<0.001).
[c]Significantly lower than the value for each of the other groups (p< 0.01, Newman-Keuls post host tests).

RESULTS

The CSF norepinephrine levels differed significantly among groups (figure 1). Consistent with our hypothesis, CSF norepinephrine was highest in the subjects with advanced Alzheimer's disease. Post hoc comparisons demonstrated that the CSF norepinephrine level was significantly higher in the subjects with advanced Alzheimer's disease (mean=279 pg/ml, SD=122) than in the subjects with mild/moderate Alzheimer's disease (mean=198 pg/ml, SD=89), the normal older subjects (mean=219 pg/ml, SD=88), and the normal young subjects (mean=154 pg/ml, SD=53). Among the subjects with Alzheimer's disease, there was a significant negative correlation between Mini-Mental State score (a lower score indicates greater impairment) and CSF norepinephrine concentration (r=–0.43, N=74, p<0.001). Because some of the subjects with advanced Alzheimer's disease were institutionalized, we compared the CSF norepinephrine levels of the 10 institutionalized patients (mean Mini-Mental State score=0, SD=1) and the 15 community-dwelling subjects (mean Mini-Mental State score=6, SD=4) who had advanced Alzheimer's disease. CSF norepinephrine level did not differ significantly between the institutionalized patients (mean= 319 pg/ml, SD=100) and the community-dwelling patients (mean=253 pg/ml, SD=131) with advanced disease (t=1.35, df=23, p=0.19).

Advanced age per se affected CSF norepinephrine concentration. Although CSF norepinephrine level did not differ significantly between the normal older subjects and the subjects with mild/moderate Alzheimer's disease, both groups had significantly higher CSF norepinephrine concentrations than the normal young subjects (figure 1). There were no effects of gender on CSF norepinephrine level within subject groups.

Plasma norepinephrine concentration and mean arterial blood pressure sampled systematically just before lumbar puncture were available for the majority of subjects (table 1). Plasma norepinephrine level significantly differed among groups. This difference was accounted for by higher plasma norepinephrine levels in both the normal older subjects and the subjects with Alzheimer's disease than in the young subjects. In contrast to CSF norepinephrine, plasma norepinephrine did not differ significantly among the patients with advanced Alzheimer's disease, those with mild/moderate Alzheimer's disease, and the normal older subjects. Mean arterial blood pressure also significantly differed among groups (table 1). As for plasma norepinephrine level, mean arterial blood pressure was higher in the normal older subjects and the subjects with Alzheimer's disease than in the young subjects, but it did not differ between the normal older subjects and the subjects with Alzheimer's

disease regardless of disease severity. There were no effects of gender on plasma norepinephrine level or mean arterial blood pressure within subject groups.

DISCUSSION

These results confirm and extend reports of increased CSF norepinephrine concentrations in the advanced stages of Alzheimer's disease (4, 9). These results also are consistent with a recent report of a positive correlation between Alzheimer's disease severity and plasma level of MHPG (10), a norepinephrine metabolite partially derived from CNS noradrenergic activity (22). The large numbers of subjects in the current study increase the generalizability of these findings to the population of individuals with Alzheimer's disease.

These results also confirm our previous report of an association between higher CSF norepinephrine levels and advanced age (23). Hence, CSF norepinephrine concentrations increase despite reports of decreased numbers of norepinephrine-producing locus ceruleus neurons with normal aging (24, 25). These locus ceruleus neurons are the major source of noradrenergic innervation of the neuraxis (5, 26). The relationship between Alzheimer's disease and CSF norepinephrine level is even more surprising. Postmortem studies of subjects with Alzheimer's disease consistently show massive loss of locus ceruleus noradrenergic neurons (5–8). Despite the clear degeneration of the locus ceruleus in Alzheimer's disease, the age-associated elevation of CSF norepinephrine persists in the earlier stages of Alzheimer's disease and becomes even more pronounced in advanced Alzheimer's disease.

A higher CSF norepinephrine concentration in advanced Alzheimer's disease is consistent with results of neurochemical studies of postmortem brain tissue in which both norepinephrine and its metabolite MHPG were measured concurrently (27, 28). Brain tissue norepinephrine turnover (estimated by the ratio of MHPG to norepinephrine) in these studies was higher in Alzheimer's disease patients than in older comparison subjects. Furthermore, in a study notable for both brief postmortem delay before tissue preservation and for the subjects' lack of antemortem psychotropic medication use, cortical norepinephrine concentrations tended to be higher in the subjects with Alzheimer's disease (29).

Increased CSF norepinephrine as Alzheimer's disease progresses is consistent with postmortem neurochemical studies of Alzheimer's disease patients with complicating behavioral disorders. Brain tissue norepinephrine concentrations were higher in subcortical areas in Alzheimer's disease patients with psychosis (30), a behavioral complication that becomes more prevalent as Alzheimer's disease worsens (1). In contrast, norepinephrine concentrations were lower in cerebral cortex in Alzheimer's disease patients with depression (31), a behavioral complication most prevalent in the early stages of Alzheimer's disease (32).

The similar ages of the groups with mild/moderate Alzheimer's disease and advanced Alzheimer's disease eliminates the possibility that the higher CSF norepinephrine level in the subjects with advanced Alzheimer's disease can be attributed to aging. However, it was surprising that reported age at onset and thus calculated duration of clinical illness also did not differ between the mild/moderate and advanced groups. This finding raises the possibility of faster disease progression in the group with advanced Alzheimer's disease. Another possible explanation is that the apparent disease severity of some of the patients with advanced Alzheimer's disease, as defined by Mini-Mental State score, may have been exaggerated by the presence of aphasia or poor cooperation with the cognitive testing procedure.

A mechanism that might explain these findings is locus ceruleus neuronal plasticity. In the rat, locus ceruleus noradrenergic axons regenerate in response to damage in brain areas innervated by the locus ceruleus (33). Damage to the locus ceruleus itself leads to increased norepinephrine synthetic capacity (34, 35) and regeneration of ascending noradrenergic projections (36) by surviving locus ceruleus neurons. Forebrain regions can become markedly hyperinnervated by these regenerating locus ceruleus neurons, whereas brainstem, cerebellum, and spinal cord are unaffected (36). Similar compensatory responses could occur in human aging and Alzheimer's disease.

Another possible mechanism for increased CSF norepinephrine in the face of locus ceruleus neuronal loss is reinnervation of cholinergically denervated brain regions (such as hippocampus) by noradrenergic processes derived from locus ceruleus neurons or from sympathetic nervous system neurons accompanying the cerebral vasculature. This phenomenon has been well characterized in rats after surgical cholinergic denervation (37). Such noradrenergic "sprouting" could occur in Alzheimer's disease given the substantial cholinergic denervation that occurs in this disease (38).

It also is possible that decreased clearance of norepinephrine from CSF contributes to increased CSF norepinephrine concentrations in aging and Alzheimer's disease. To date, norepinephrine kinetics have been studied only in plasma. Although an increase in plasma norepinephrine with normal aging is predominantly a function of increased norepinephrine appearance, some decrease in plasma norepinephrine clearance also occurs in older subjects (39). A substantial portion of norepinephrine released into the synapse is metabolized intraneuronally after neuronal reuptake (40). The extensive neuronal loss in Alzheimer's disease could potentially reduce clearance of norepinephrine from the synapse and increase norepinephrine appearance in the CSF compartment.

Decreased α_2-adrenergic inhibition of CNS noradrenergic activity could contribute to the observed increase in CSF norepinephrine in aging and Alzheimer's disease. Decreased α_2 receptor binding has been reported in cerebral cortical tissue from Alzheimer's disease patients (41), and we previously reported an aging-

related decrease in responsiveness of CSF norepinephrine to the α_2 agonist clonidine (23). However, in a more recent study we demonstrated no effects of advanced age or Alzheimer's disease on the ability of clonidine to suppress CSF norepinephrine (42). The demonstration of higher plasma norepinephrine concentration and mean arterial blood pressure in the older subjects is consistent with previous reports of increased sympathetic nervous system activity with normal human aging (23, 40, 43). The lack of an effect of Alzheimer's disease on plasma norepinephrine level or mean arterial blood pressure regardless of disease severity failed to confirm our earlier findings in a small group of subjects with Alzheimer's disease (4) but agrees with other reported data (44).

If an increased CSF norepinephrine concentration in advanced Alzheimer's disease does reflect increased synaptic norepinephrine concentrations at CNS sites, such increased CNS noradrenergic activity could contribute to patients' cognitive deficits (10) or to the disruptive agitated behaviors that are highly prevalent in the advanced stages of Alzheimer's disease (1). In Alzheimer's disease patients with mild to moderate disease, robust increases of CSF norepinephrine following administration of the α_2-adrenergic antagonist yohimbine were accompanied by substantial agitation (42). Although normal older persons achieved similar CSF norepinephrine increases after yohimbine administration, they did not manifest agitation (42). Thus, persons with Alzheimer's disease may have increased sensitivity to the arousing and anxiogenic effects of CNS noradrenergic stimulation (45). Increased β-adrenergic receptors in Alzheimer's disease (46) could contribute to such increased sensitivity. This possibility suggests that drugs that reduce CNS noradrenergic outflow or block CNS adrenergic receptors could reduce disruptive agitated behaviors in persons with Alzheimer's disease. Anecdotal reports suggest that the β-adrenergic antagonist propranolol may prove useful in the management of that important clinical problem (47–49).

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