

Cerebrospinal Fluid Epinephrine in Alzheimer's Disease and Normal Aging

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Central nervous system (CNS) adrenergic systems are involved in regulation of behavior and blood pressure. The effects of Alzheimer's disease (AD) and normal aging on resting CNS adrenergic activity were estimated by measuring cerebrospinal fluid (CSF) epinephrine (EPI) concentrations in 74 persons with AD, 42 cognitively normal healthy older persons, and 54 healthy young persons. The responsiveness of CSF EPI to the alpha-2 adrenergic antagonist yohimbine and the alpha-2 adrenergic agonist clonidine was measured in smaller subject groups. Resting CSF EPI was higher in AD than in older or young subjects, and increased with dementia

severity in AD subjects. There was no relationship between resting CSF EPI and blood pressure. CSF EPI increased following yohimbine in AD and older subjects but not in young subjects. CSF EPI was unaffected by clonidine in all subject groups. The agitation increase following yohimbine was substantially greater in AD subjects than in older or young subjects. CNS adrenergic activity seems increased in AD, may further increase as AD progresses, and may be involved in the pathophysiology of agitation.

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Adrenergic nuclei have been identified in the central nervous system (CNS) (Kalia et al. 1985), and both neuroanatomic and animal behavioral studies suggest the involvement of their neurotransmitter epinephrine (EPI) in the central modulation of behavioral and cardiovascular function (Introvini-Collison et al. 1992; Lewis et al.

1988; Fuller 1982). CNS adrenergic systems potentially are relevant to the pathophysiology of the cognitive and behavioral features of Alzheimer's disease (AD), but the status of these systems in AD is unclear. The major source of adrenergic projections to the central nervous system (CNS) is the C1 area in the rostral ventral lateral medulla (Gianutsos and Moore 1978). Although the number of C1 adrenergic neurons is not reduced in AD, evidence of neurodegeneration is present in some of these neurons (Burke et al. 1994). Despite these neurodegenerative changes, increased concentrations of the rate-limiting EPI synthetic enzyme phenylethanolamine-N-methyltransferase (PNMT) have been demonstrated in the C1 area in a small number of subjects with advanced AD (Burke et al. 1990). This latter study raises the possibility that compensatory upregulation of EPI synthetic capacity occurs in surviving C1 neurons in AD.

Here we estimated the effects of AD and normal aging on resting CNS adrenergic activity by measuring EPI concentrations in cerebrospinal fluid (CSF) in large

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samples of subjects with AD and in normal older and young subjects. Because EPI does not cross from blood into brain or CSF (Weil-Malherbe et al. 1959), concentrations of EPI in CSF reflect EPI released from CNS adrenergic neurons and not from the peripheral sympathoadrenal system. In a second study, we estimated the effects of AD and aging on the responsiveness of CNS adrenergic systems by measuring changes in CSF EPI following administration of the alpha-2 adrenergic receptor antagonist yohimbine and the alpha-2 agonist clonidine. Effects of these pharmacologic agents on agitation and blood pressure also were measured. CSF norepinephrine concentrations determined in these studies have been reported previously (Peskind et al. 1995; Elrod et al. 1997).

These studies were approved by the University of Washington Human Subjects Review Committee, Seattle, and informed consent was obtained from all cognitively normal subjects and subjects in the earlier stages of AD. In addition, informed consent was obtained from the legal representatives of the patients with AD.

STUDY 1

Subjects

Subjects included 74 persons with AD (66 men and 18 women; age = 69 years \pm 6 [mean \pm SD]), 42 cognitively normal healthy older community volunteers (26 men and 16 women; age = 68 years \pm 7), and 54 healthy young male community volunteers (age = 26 years \pm 3). Subjects were nonsmokers in good general health and had been free of medications (except occasional nonprescription analgesics or laxatives) for at least 1 month prior to lumbar puncture. All were normotensive at screening examination ($<150/90$) and within 125% of ideal body weight (Metropolitan Life Insurance tables, 1983). All subjects were free of past or present major psychiatric or neurologic disorders (other than AD), renal or hepatic disease, diabetes mellitus, or symptomatic cardiovascular disease. All AD subjects met criteria for probable AD of the National Institute of Neurologic and Communicative Disorders and Stroke (McKhann et al. 1984) and the *DSM-III-R* criteria for dementia of the Alzheimer's type. All AD subjects were cooperative with the experimental procedure and free of disruptive agitation on the morning of study. Normal young and older subjects had a Mini Mental State Exam (MMSE) (Folstein et al. 1975) score of 29 or 30 (maximum score = 30) and no history or evidence of cognitive decline. The mean MMSE score of the AD patients was 13 ± 8). A cutoff score of 12 or higher was chosen prospectively to classify AD subjects as having mild/moderate disease ($n = 49$, mean MMSE score = 18 ± 4 , mean age = 69 \pm 6 years). Those with an MMSE score less than 12 were

considered to have advanced disease ($n = 25$, MMSE score = 4 ± 4 , mean age = 69 \pm 7 years).

Methods

Lumbar punctures were performed in the morning after subjects has fasted from the previous midnight. Subjects were prohibited from using caffeine or known stimulants of catecholamine release after midnight and until the end of the study. Subjects began bed rest at approximately 8:00 A.M. An hour later, a 19-gauge plastic catheter was inserted in an antecubital vein for blood sampling. Blood for determination of plasma EPI was obtained through the indwelling catheter immediately prior to lumbar puncture, which was performed 90 minutes after indwelling catheter placement. Lumbar puncture was performed atraumatically with a 25-gauge spinal needle while the patient was maintained in the lateral decubitus position. CSF EPI was measured in the 12th ml of CSF removed in all subjects. CSF samples were frozen immediately on dry ice and stored at -70°C until assay. Blood for EPI determination was collected in prechilled tubes containing EGTA and reduced glutathione, centrifuged within 1 hour of collection, and stored at -70° until assay. CSF and plasma EPI concentrations were determined within 1 month of sample collection by a sensitive single isotope radioenzymatic assay (Evans et al. 1978). The intra-assay coefficient of variation in this laboratory is less than 5%. The interassay coefficient is 12%. Approximately equal numbers of subjects from the AD group, the older normal group, and the young normal group were included in each individual assay. Systolic and diastolic blood pressure (BP) was obtained immediately following blood sample withdrawal and just prior to lumbar puncture by automatic blood pressure and heart rate monitor.

STUDY 2

Subjects

AD subjects, normal older subjects, and normal young subjects met the inclusion and exclusion criteria described above for Study 1. Subjects included 10 patients with AD (seven men and three women, mean age = 70 \pm 8 years); 10 older cognitively normal subjects (six men and four women, mean age = 71 \pm 4 years), and 11 normal young men (mean age = 27 \pm 5 years). MMSE score of the AD subjects was 14 ± 7 .

Methods

Each subject participated in three medication conditions administered in random order and separated by at least 1 week. The medication conditions included cloni-

dine hydrochloride, 5 µg/kg by mouth, yohimbine hydrochloride 0.65 mg/kg by mouth, and placebo. Medications were administered 90 minutes prior to lumbar puncture in each condition. Subjects were blind to the treatment conditions but clinical personnel performing the studies were aware of the treatment conditions for reasons of subject safety. Laboratory personnel performing the assays were blind to treatment condition. The timing and procedure of lumbar puncture, and blood and CSF acquisition and sample handling and BP and heart rate measurement were as described above for Study 1. The radioenzymatic assay for EPI also was the same as described in Study 1. CSF and plasma concentrations of yohimbine and its active metabolite, 11-hydroxy-yohimbine, and clonidine have been reported previously (Peskind et al. 1995; Le Corre et al. 1997). Agitation was quantified by summing scores on the Tension, Excitement, and Anxiety items of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). These BPRS items were rated by the same experienced psychiatric research nurse (SM) at the 90-minute time point just before lumbar puncture in all three conditions. These three BPRS items have been demonstrated to form an "agitation" factor in geropsychiatric patients (Overall and Beller 1983).

Statistical Analysis

Variables are expressed as mean \pm SD. Differences among groups were evaluated by one-way analysis of variance (ANOVA). Post hoc Newman-Keuls tests were used to evaluate differences between specific

groups following a significant ANOVA. In Study 2, differences between treatment conditions (comparison of yohimbine with placebo and comparison of clonidine with placebo) within groups were compared by paired *t*-test (two-tailed). Differences (Δ values) between active drug and placebo treatment conditions at the 90-minute time point were calculated for CSF and plasma EPI concentrations, systolic BP, diastolic BP, heart rate and agitation factor. The significance of differences in the Δ values of these variables among subject groups was evaluated by one-way ANOVA. Pearson product moment correlations were determined between selected variables for which rationale was available for a possible relationship (e.g., CSF EPI and resting BP).

RESULTS

Study 1

CSF EPI concentrations in young, older, and AD subjects are presented in Figure 1. CSF EPI differed among groups ($F(2,164) = 4.45, p = .01$), with higher concentrations in AD subjects than in either older or young subjects. Higher CSF EPI in AD seemed to be caused in large part by higher CSF EPI in the advanced AD subgroup (MMSE < 12). An ANOVA comparing CSF EPI among the advanced AD subgroup (170 ± 100 pmol/l), the mild/moderate AD subgroup (130 ± 60 pmol/l) and the normal old group (110 ± 70 pmol/l) revealed a significant difference among groups ($F(2,110) = 4.17, p = .02$), with significantly higher CSF EPI in the severe AD subjects as compared to the normal older subjects.

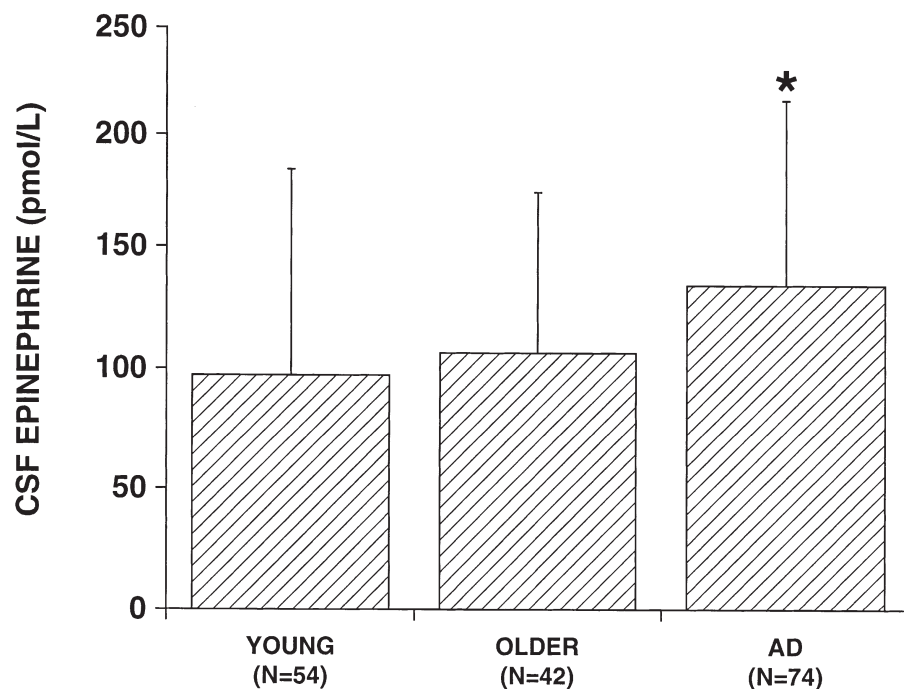


Figure 1. Resting cerebrospinal fluid epinephrine concentrations (pmol/l) in young and older normal subjects and Alzheimer's disease (AD) patients. (*Greater in AD patients than in young or older normal patients, $p < .05$, one-way analysis of variance followed by Newman-Keuls post hoc test.)

There was no effect of gender on CSF EPI in the AD or older groups. The significant negative correlation between dementia severity measured by the MMSE score (lower score denotes greater dementia severity) and CSF EPI in all AD subjects ($r = -0.33, p < .01$) also supported increased CSF EPI with increased AD severity.

Plasma EPI, systolic blood pressure, diastolic blood pressure, and heart rate were available for the majority of subjects (see Table 1). Plasma EPI significantly differed among groups ($F(2,122) = 3.19, p = .04$), with higher concentrations in AD than normal older or young subjects ($p < .05$). Blood pressure was affected by aging but not by AD. Both systolic BP and diastolic BP differed among groups ($F(2,133) = 8.27, p < .001$; $F(2,133) = 8.17, p < .001$). Each was significantly higher in both older normal subjects and AD subjects than in young subjects. Heart rate also differed among groups ($F(2, 133) = 6.35, p = .002$), with higher rates in AD than in normal older or young subjects ($p < .05$). In all subjects combined for whom simultaneous cardiovascular and CSF EPI values were available ($n = 133$), there were no significant correlations between CSF EPI and systolic BP ($r = 0.106$), diastolic BP ($r = 0.024$), or heart rate ($r = 0.128$). There were several significant, albeit modest, correlations between plasma EPI and cardiovascular parameters in all subjects combined for whom plasma EPI concentrations were available ($n = 109$). There were significant correlations between plasma EPI and systolic BP ($r = 0.258, p < .01$), and between plasma EPI and HR ($r = 0.329, p < .01$). The correlation between plasma EPI and diastolic BP was not significant ($r = 0.132$).

Study 2

CSF EPI, plasma EPI, BP, and agitation measurements 90 minutes after yohimbine and placebo administration are presented in Table 2. CSF EPI was significantly higher in the yohimbine condition than in the placebo condition in AD subjects ($t = 3.27, p = .01$) and normal older subjects ($t = 3.35, p < .01$) but not in young sub-

jects ($t = 0.77, p = .46$). Plasma EPI was significantly higher in the yohimbine than the placebo condition in normal older ($t = 3.66, p < .01$) and normal young subjects ($t = -3.92, p < .01$) and tended to be higher in the yohimbine condition in AD subjects ($t = 2.18, p = .06$).

The responses of these parameters 90 minutes after clonidine and placebo are presented in Table 3. CSF EPI did not differ between clonidine and placebo conditions in any subject group. Plasma EPI was significantly lower in the clonidine than placebo condition only in the young subjects ($t = 3.75, p < .01$). Systolic and diastolic blood pressure measurements were significantly higher in yohimbine than placebo conditions in older and AD subjects but not in young subjects. Systolic and diastolic BP measurements were significantly lower in clonidine than placebo conditions in all subject groups.

Agitation factor scores increased following yohimbine as compared to placebo in each subject group ($p < .01$). This yohimbine effect differed among groups ($F(2,26) = 13.23, p < .0001$) with a greater increase of agitation in AD subjects than in normal older or young subjects ($p < .01$). In all subjects combined, there was a significant correlation between CSF EPI increases following yohimbine and agitation factor increases following yohimbine ($r = 0.46, p = .05$), but not between increases in plasma EPI concentration and agitation factor scores ($r = 0.27, p = \text{ns}$).

Concentrations of yohimbine and its active metabolite 11-hydroxy-yohimbine in CSF and plasma in these subjects have been reported previously (Peskind et al. 1995). In summary, neither the total concentrations of yohimbine plus its active metabolite 11-hydroxy yohimbine nor the concentrations of clonidine differed among groups in either CSF or plasma.

DISCUSSION

The results of Study 1 do not support decreased CNS adrenergic activity in AD and suggest that CNS adrenergic activity may increase as the disease progresses.

Table 1. Plasma Epinephrine (EPI), Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate in Normal Young and Older Subjects and Patients with Alzheimer's Disease (AD)

	Young Subjects	<i>n</i>	Older Subjects	<i>n</i>	Patients with AD	<i>n</i>
Plasma EPI (pmol/l)	270 ± 130	45	240 ± 160	35	340 ± 200*	67
Systolic blood pressure (mmHg)	119 ± 11	56	130 ± 16**	38	129 ± 16**	64
Diastolic blood pressure (mmHg)	72 ± 9	56	77 ± 8**	38	78 ± 7**	64
Heart rate (beats/min)	62 ± 10	56	64 ± 9	38	68 ± 10*	64

*Greater than in young or older normal subjects, $p < .05$.

**Greater than in young subjects, $p < .001$.

Table 2. Cerebrospinal Fluid (CSF) and Plasma Epinephrine (EPI) Concentrations, Agitation Ratings, Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) at 90 Minutes after Administration of Placebo and Yohimbine Hydrochloride in Normal Young and Older Subjects and Patients with Alzheimer's Disease (AD)

	Young Subjects		Older Subjects		Patients with AD	
	Placebo	Yohimbine	Placebo	Yohimbine	Placebo	Yohimbine
	(n = 11)	(n = 11)	(n = 10)	(n = 10)	(n = 10)	(n = 9)
CSF EPI (pmol/l)	120 ± 90	130 ± 50	110 ± 70	160 ± 60*	120 ± 60	190 ± 90*
Plasma EPI (pmol/l)	270 ± 170	540 ± 360*	280 ± 200	530 ± 260*	300 ± 130	410 ± 180
Agitation	3 ± 0	6 ± 1*	4 ± 1	8 ± 2*	6 ± 4	14 ± 4**
SBP	125 ± 5	122 ± 38	135 ± 17	151 ± 31*	129 ± 10	154 ± 15*
DBP	70 ± 9	75 ± 9	75 ± 3	87 ± 14*	76 ± 8	87 ± 14

Data are given as mean ± SD. Significance of differences between yohimbine and placebo conditions within groups analyzed by paired *t*-test (two-tailed). Significance of these differences among groups determined by one-way analysis of variance followed by Newman-Keuls post hoc tests.

*Greater than in placebo condition, *p* < .01.

**Difference between placebo and yohimbine conditions greater in AD than in young or older normal subjects, *p* < .01.

These results are compatible with the observation of increased PNMT protein and enzymatic activity in the C1 adrenergic nucleus in a small sample of advanced AD subjects (Burke et al. 1990). Although these investigators interpreted increased PNMT activity in C1 in advanced AD as evidence of decreased axonal transport to adrenergic projection areas, the present CSF EPI findings suggest that increased C1 PNMT in advanced AD, indeed, reflects upregulation of CNS adrenergic neuronal activity. The results of Study 2 suggest that, at least in the sample of predominantly mild/moderate AD subjects participating in the three lumbar puncture protocol, the response of CNS adrenergic systems to stimulation by an alpha-2 antagonist is unimpaired.

These results provide the first evidence in humans for regulation of CNS adrenergic systems by alpha-2 adrenergic inhibitory receptors. They are consistent with neurophysiologic studies in the rat demonstrating regulation of brainstem C1 adrenergic neurons by yohimbine and clonidine (Li et al. 1995). That yohimbine significantly increased CSF EPI only in the old subjects

whether or not they had AD suggests that aging may affect sensitivity of CNS adrenergic systems to alpha-2 antagonists. Studying the CSF EPI response to yohimbine in larger numbers of older and young subjects is necessary to confirm this possibility. In contrast to the stimulatory affect of yohimbine on CSF EPI, clonidine did not decrease CSF EPI overall or in any subject group. The absence of an inhibitory alpha-2 agonist effect on CSF EPI suggests endogenous tonic inhibition of CNS adrenergic neurons that cannot substantially be enhanced by administration of an exogenous alpha-2 agonist such as clonidine. These results also demonstrated alpha-2 adrenergic regulation of plasma EPI in humans, confirming a previous report from our laboratory (Murburg et al. 1991) and consistent with a recent report of increased plasma EPI following administration of an alpha-2 antagonist (Schmidt et al. 1997). Advanced age did not seem to affect responsiveness of plasma EPI to stimulation by yohimbine.

Resting CSF and plasma EPI were higher in AD subjects than in cognitively normal subjects in the large

Table 3. Cerebrospinal Fluid (CSF) and Plasma Epinephrine (EPI) Concentrations, Agitation Ratings, Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) at 90 Minutes after Administration of Placebo and Clonidine Hydrochloride in Normal Young and Older Subjects and Patients with Alzheimer's Disease (AD)*

	Young Subjects		Older Subjects		Patients with AD	
	Placebo	Clonidine	Placebo	Clonidine	Placebo	Clonidine
	(n = 11)	(n = 11)	(n = 10)	(n = 10)	(n = 10)	(n = 9)
CSF EPI, pmol/l	120 ± 90	100 ± 60	110 ± 70	110 ± 50	120 ± 60	120 ± 70
Plasma EPI, pmol/l	270 ± 170	190 ± 170*	280 ± 200	230 ± 130	300 ± 130	270 ± 190
Agitation	3 ± 0	3 ± 0	4 ± 1	3 ± 0	6 ± 4	3 ± 0
SBP	125 ± 5	106 ± 10**	135 ± 17	100 ± 13**	129 ± 10	100 ± 3**
DBP	70 ± 9	59 ± 8**	75 ± 3	59 ± 4**	76 ± 8	63 ± 7**

Data are given as mean ± SD. Significance of differences between clonidine hydrochloride and placebo treatment conditions within groups analyzed by paired *t*-tests.

*Less than in placebo condition, *p* < .01.

**Less than in placebo condition, *p* < .001.

samples in Study 1, but did not differ among the smaller samples in Study 2. This discrepancy may reflect the absence of AD subjects with very advanced disease or persistent agitation from Study 2. Very advanced dementia or persistent agitation would have made AD subjects unsuitable candidates for the more rigorous protocol of Study 2.

CSF and plasma measurements of yohimbine, 11-hydroxy yohimbine and clonidine did not reveal differences in drug levels among groups. These results make it unlikely that pharmacokinetic factors, such as differential drug absorption, metabolism or blood-brain barrier integrity among groups, were underlying mechanisms for the observations of Study 2.

Higher resting plasma EPI in the large (Study 1) sample of AD subjects than in either normal older or young subjects may suggest increased adrenomedullary activity in AD under the conditions of this study. The higher heart rate in AD subjects may reflect the higher plasma EPI concentrations in this subject group. In a previous report, plasma EPI was not found to differ between AD and healthy older subjects (Vitiello et al. 1993). Preparation for lumbar puncture in the current study may have elicited greater adrenomedullary response in AD subjects than in the cognitively intact older or young subjects. The interpretation of plasma EPI concentrations without kinetic measurements of EPI appearance rate into or clearance from plasma must be made cautiously. Similar caution also applies to interpretation of CSF EPI concentrations. In human aging, slightly increased, slightly decreased, and unchanged clearance of EPI from plasma have been reported (Esler et al. 1995a; Esler et al. 1995b; Wilkie et al. 1985; Morrow et al. 1987). If decreased EPI clearance accompanied aging in the subjects in the current study, it could have contributed to the higher EPI concentrations in AD than in young subjects in Study 1.

A possible mechanism for the observed increased CSF EPI concentrations despite reported degenerative changes in some C1 adrenergic neurons (Burke et al. 1994) is provided by animal studies of the response of central noradrenergic systems to partial injury. Damage to the locus ceruleus or noradrenergic terminals in locus ceruleus projection areas produces a compensatory increase in norepinephrine synthetic capacity and neuronal firing rate in surviving noradrenergic neurons (Acheson et al. 1980; Nakamura and Sakaguchi 1990). Catecholamine synthetic capacity in LC lesioned animals can increase to levels higher than in control animals (Acheson and Zigmond 1981). If a similar compensatory response to injury exists for human C1 adrenergic neurons, it could explain the retention of CNS adrenergic responsiveness in AD.

Animal studies suggest an important role for CNS adrenergic system in the regulation of resting blood pressure (Lewis et al. 1988), and reduced blood pressure in a

small sample of AD patients has been linked with C1 adrenergic degeneration on postmortem examination (Burke et al. 1990). The current CSF EPI and blood pressure results provide no support for reduced blood pressure in AD or CNS adrenergic regulation of blood pressure. Resting blood pressure and blood pressure responses to clonidine and yohimbine did not differ between these samples of AD and cognitively normal older subjects. Furthermore, correlations between CSF EPI and blood pressure were not significant or even suggestive of a relationship between CNS adrenergic activity and blood pressure regulation. That such a relationship exists is not ruled out by the current study. CSF EPI concentrations may not be a sensitive indicator of activity of the subpopulation of C1 adrenergic efferents projecting to CNS nuclei regulating cardiovascular function.

These results suggest the possibility that CNS adrenergic systems contribute to the pathophysiology of the clinically troublesome agitated behaviors common in the advanced stages of AD (Reisberg et al. 1987). That CSF EPI concentrations were highest in advanced AD subjects supports this possibility. The significant correlation between CSF EPI and agitation responses to yohimbine also suggests a relationship between CNS adrenergic activity and agitation. In a previous report, we demonstrated increased CSF norepinephrine in these advanced AD subjects (Peskind et al. 1995). Increased responsiveness of both CNS noradrenergic and adrenergic systems could potentiate agitation in advanced AD. A recent report relating agitation to adrenergic receptor density in AD postmortem brain tissue provides further support for involvement of CNS catecholamine systems in the expression of agitation in this disease (Russo-Neustadt and Cotman 1997). These investigators found increased concentrations of alpha adrenergic and beta adrenergic receptors in postmortem brain tissue from patients with an antemortem history of disruptive agitation compared to either AD patients without antemortem agitation or age-matched cognitively normal subjects. Clinical reports suggest that pharmacologic blockade of beta adrenergic receptors decreases aggression and agitation in AD (Weiler et al. 1988; Yudofsky et al. 1981; Shankle et al. 1995). Further studies are necessary to explore the possible role of CNS adrenergic and noradrenergic systems in the pathophysiology of disruptive agitation in AD and to examine the therapeutic efficacy of pharmacologic reduction of adrenergic activity in the behaviorally disturbed patient with AD.

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