Background: Increased basal activity of the hypothalamic–pituitary–adrenocortical (HPA) axis has been repeatedly demonstrated in Alzheimer’s disease (AD), and some studies suggest increased basal activity of the sympathetic nervous system (SNS) in this disorder; however, the effects of AD on HPA axis or SNS responses to a standardized aversive stressor have not been examined. The neuroendocrine response to aversive stress may be relevant to the pathophysiology of AD.

Methods: Plasma adrenocorticotropic hormone (ACTH), cortisol, norepinephrine (NE), and epinephrine responses to a 1-min cold pressor test (CPT) were measured in nine medically healthy AD outpatients (age 76 ± 2 years) and nine age- and gender-matched medically healthy cognitively normal older subjects (age 76 ± 1 year).

Results: The cortisol response to CPT was increased in the AD group but the ACTH response did not differ between groups. Basal NE concentrations were higher in the AD group. Although NE responses to CPT did not differ between groups, the blood pressure response to CPT was higher in the AD subjects.

Conclusions: These results suggest increased HPA axis responsiveness to CPT at the level of the adrenal cortex in AD. The results also suggest increased basal sympathoneural activity and increased cardiovascular responsiveness to sympathoneural stimulation in AD under the conditions of this experimental protocol. Increased SNS stimulatory modulation of the adrenal cortex is a possible mechanism contributing to the observed enhanced cortisol response to CPT in these AD subjects. Biol Psychiatry 2000;48:247–254 © 2000 Society of Biological Psychiatry

Key Words: Alzheimer’s disease, cortisol, ACTH, norepinephrine, epinephrine, stress

Introduction

The activity of the hypothalamic–pituitary–adrenocortical (HPA) axis and both the sympathoneural and sympathoadrenomedullary components of the sympathetic nervous system (SNS) may be increased in Alzheimer’s disease (AD). If increased activity of these stress responsive neuroendocrine systems does occur in AD, it could contribute to the pathophysiology of this disorder. Increased cortisol concentrations could impair memory (de Quervain et al 1998; Newcomer et al 1999) and even accelerate the neuropathology of AD by lowering the threshold for hippocampal neuronal damage (Sapolsky et al 1985). Increased SNS activity could contribute to sleep disturbance, cognitive impairment, and agitation in AD (Eisdorfer and Cohen 1978; Peskind et al 1995; Prinz et al 1979), and high concentrations of norepinephrine (NE) could exacerbate β-amyloid peptide neurotoxicity in AD (Fu et al 1998).

Evidence supporting increased activity of the HPA axis in AD is substantial and includes reports of increased basal concentrations of cortisol in plasma, urine, and cerebrospinal fluid (CSF; Davis et al 1986; Hartmann et al 1997; Maeda et al 1991; Martignoni et al 1990; Masugi et al 1989; Swaab et al 1994); decreased sensitivity of the HPA axis to feedback inhibition by dexamethasone (Hatzinger et al 1995; Jenike and Albert 1984; Molchan et al 1990; Raskind et al 1982); and increased cortisol (but not adrenocorticotropic hormone [ACTH]) responses to exogenous corticotropin releasing factor (CRF; Hatzinger et al 1995; Näslman et al 1996); physostigmine (Peskind et al 1996); a glucose load (de Leon et al 1988); and hypoglycemia (O’Brien et al 1994). Studies assessing effects of AD on SNS activity are few and results inconsistent. Some studies have reported increased basal plasma norepinephrine
(NE; Ahlskog et al 1996; Raskind et al 1984) and epinephrine (EPI; Peskind et al 1998) in AD, whereas others have found no effect of AD on basal plasma catecholamines (Vitiello et al 1993). Results of studies addressing AD effects on SNS responses to nonaversive pharmacologic or physical stimuli have also been mixed. The plasma NE response to upright posture was unaffected by AD (Vitiello et al 1993); the plasma NE and EPI responses to the α-2 adrenergic antagonist yohimbine are greater in AD than in young subjects but equivalent to those of normal older subjects (Peskind et al 1995, 1998); and plasma NE responses either to a mental performance task or thyrotropin releasing hormone infusion were blunted in AD (Borson et al 1989; Lampe et al 1989).

The effects of AD on either HPA axis or SNS responses to a standardized aversive stressor have not been examined. Cortisol elevation in response to aversive stress may be particularly relevant to the pathophysiology of hippocampal neurodegeneration in AD. In nonhuman primates, endogenous cortisol elevations in response to aversive stressors have been associated with hippocampal neurodegeneration (Magarinos et al 1996; Sapolsky et al 1990). In contrast, we were unable to demonstrate any neurodegenerative effects of chronic high dose exogenous cortisol in unstressed older macaques (Leverenz et al 1999).

Here we estimated the effects of AD on both HPA axis and SNS responses to the brief immersion of one hand in ice water (the “cold pressor test”). The cold pressor test (CPT) is a well-tolerated brief aversive stressor that increases SNS and HPA axis activity by activation of both thermal and nociceptor afferents (Bullinger et al 1984; Ebert et al 1992; Edelson and Robertson 1986; Kelly and Cooper 1998; Lindheim et al 1994). Because the sympathetic neural component of the SNS exerts stimulatory modulation of the adrenocortical response to ACTH (Bornstein and Chrousos 1999), elevated SNS activity may contribute to the reported increased cortisol but unaltered or reduced ACTH response in AD to pharmacologic and metabolic stimuli (de Leon et al 1988; Hatzinger et al 1995; Nasman et al 1996; O’Brien et al 1994; Peskind et al 1996). A stimulus like the CPT that simultaneously stimulates the SNS and HPA axis allows an assessment of the relationship between both basal and stimulated SNS activity and the cortisol response to stress.

In subjects with AD and age-comparable cognitively normal community volunteers, we measured plasma ACTH, cortisol, NE, and EPI responses to the CPT. We hypothesized plasma concentrations of these “stress hormones” (Selye 1973) in response to CPT would be increased in AD.

**Methods and Materials**

These studies were approved by the University of Washington Human Subjects Review Committee, Seattle, WA. Informed consent was obtained from all cognitively normal subjects and from the legal representatives of the subjects with AD (in each case, the AD subject’s spouse). The procedure and consent forms were reviewed with all AD subjects, and all verbally agreed to the procedure and signed the consent form. Given the inherent uncertainty of a cognitively impaired AD subject’s completely comprehending the study, the AD subject’s spouse and a neutral clinician observer not affiliated with the study were present during the study to help interpret the wishes of the AD subject.

**Subjects**

Subjects included 9 persons with AD (4 men and 5 women, mean age = 76 ± 2 years [mean ± SEM] and 9 older cognitively normal persons (4 men and 5 women, mean age = 76 ± 1 year). All subjects were nonsmokers in good general health and had been free of psychotic, antihypertensive, or other medications known to affect the SNS or HPA axis for at least 1 month prior to study. All were normotensive (blood pressure less than 150 mmHg systolic and 90 mmHg diastolic) and within 125% of ideal body weight (Metropolitan Life Insurance Company 1983). Body mass index (BMI) was significantly greater in cognitively normal older subjects (26 ± 1.3 SEM) than in AD subjects (23 ± 0.5). All subjects were free of past or present major psychiatric or neurologic disorders (other than AD), alcohol or drug abuse, renal or hepatic disease, diabetes mellitus, or symptomatic cardiovascular disease. AD subjects were outpatients who met criteria for probable AD of the National Institute of Neurologic and Communicative Disorders and Stroke (McKhann et al 1984). All AD subjects were cooperative with the experimental procedures and free of disruptive agitation on the mornings of the study. In addition, AD subjects were selected for participation only if a careful history from the caregiver and observation of the patient by clinical personnel revealed a pattern of cooperation with the caregiver and no history of disruptive agitation, delusions, hallucinations or major depressive episode. It was felt that selection of such AD subjects was necessary to increase the likelihood that AD subjects would be able to complete the protocol. Normal 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 at presudy screening evaluation was 17 ± 1 SEM, with a range of 8–23.

**Experimental Procedures**

Studies were conducted in a clinical research unit at the VA Puget Sound Health Care System. Subjects fasted from midnight prior to study and were maintained at bed rest from 8:00 AM throughout the study. At 8:30 AM, an intravenous catheter was placed in an antecubital vein for blood sampling and kept patent with a slow normal saline drip at 30 mL/hour. At 9:05 and 9:10 AM, blood samples were obtained for “baseline” measurements of ACTH and cortisol. Immediately after the second blood sample, the subject underwent the CPT. The subject immersed his/her right hand for 1 minute in slushy ice water (4°C) past the wrist and slowly rotated the hand to maintain maximal cold stimulus. All subjects in all groups initiated and completed the
Cold Pressor Test in Alzheimer’s Disease

Because some studies have suggested relationships between dementia severity and both SNS activity (Elrod et al 1997; Peskind et al 1998) and HPA axis activity (Gurevich et al 1989; Jenike and Albert 1984; Molchan et al 1990), the relationships between dementia severity and endocrine responses to CPT within AD subjects were evaluated by correlating MMSE scores with deltas for each endocrine parameter. Variables are expressed as mean ± SEM. Standard errors of the mean were used to facilitate graphic presentation of the data. Standard deviations can be calculated by multiplying SEMs by $\sqrt{n}$.

**Results**

**HPA Axis Parameters**

Corticotropin and cortisol concentrations are presented in Figure 1. Corticotropin concentrations and the ACTH response to CPT did not differ between groups. There was a significant overall effect for time $[F(11,176) = 3.24, p < .001]$ with equivalent ACTH increases by 5 min after CPT in both groups. The correlation between MMSE and delta ACTH for AD subjects was not significant ($r = -.34$). The cortisol response to CPT was greater in AD subjects than in normal older subjects. The cortisol AUC following CPT was greater in AD subjects than in normal older subjects ($p < .05$). Furthermore, only in AD subjects was there a significant cortisol increase at 15 min following CPT ($p < .01$). In addition, there was a significant correlation within AD subjects between basal plasma NE and cortisol AUC ($r = .69, p < .05$). The correlation between delta NE and cortisol AUC was not significant. Within AD subjects, there was a significant inverse correlation between MMSE score and delta cortisol ($r = -.74, p < .05$), suggesting a greater cortisol response in the more severely demented subjects.

**Catecholamines**

Norepinephrine and EPI concentrations are presented in Figure 2. Norepinephrine was significantly higher in AD subjects [group main effect, $F(1,176) = 8.41, p < .01$], but the acute NE response to CPT evident at 5 min did not differ between groups. Within the AD subjects, the correlation between MMSE score and delta NE was not significant ($r = -.14$). In contrast to NE, there was no acute EPI response to CPT, nor did EPI concentrations differ between groups [group main effect, $F(1,176) = 1.63, p = ns$].

**Cardiovascular Parameters: Mean Arterial Pressure and Heart Rate**

Mean arterial blood pressure responses to CPT are presented in Figure 3. There was a greater acute MAP increase following the CPT in AD subjects (group × time interaction, $F(1,176) = 4.75, p = .03$).

CPT without difficulty. Blood samples were obtained at 5, 10, and 15 min after the beginning of hand immersion and then every 15 min for a total sampling period of 135 min. Blood pressure and heart rate were measured automatically (Dinamap, Critikon, Tampa, FL) following the baseline samples, at the end of the 1-min CPT and then following each blood sample collection. Mean arterial blood pressure (MAP) was calculated as diastolic BP plus (systolic BP minus diastolic BP divided by 3).

**Chemical Assays**

Blood was collected into prechilled tubes containing ethylene-bis-$\beta$-aminoethyl ether N,N1 tetra-acetic acid (EGTA) and reduced glutathione for NE and EPI determination, and ethylene diamine-tetra-acetic acid (EDTA) for ACTH and cortisol determination. Blood samples were placed on ice and cold centrifuged at 4°C within 1 hour of collection. Plasma was stored at 4°C until assay. Plasma NE and EPI were determined within 1 month of sample collection by a sensitive single isotope radioimmunometric assay as previously described (Evans et al 1978). The intraassay coefficient of variation is less than 5% for both NE and EPI. The interassay coefficient is 6.5% in the greater than 300 pg/mL range and 12% in the 100 pg/mL range for NE and EPI. ACTH was measured by a double antibody sandwich radioimmunometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). The detection limit for ACTH was 2 pg/mL. Intra- and inter-assay coefficients of variation were 6.3% and 12.8%, respectively. Cortisol was measured in unextracted plasma as described previously (Wilkinson et al 1997). The detection limit for cortisol was 5 ng/mL. Intra- and inter-assay coefficients of variation were 4.6% and 10.2%, respectively. All samples from an individual subject and equal numbers of subjects from each group were assayed in a single assay.

**Subjective Discomfort Assessments**

Immediately following the CPT, subjects rated their subjective discomfort during the procedure using 100 mm Likert scales for pain and for anxiety.

**Statistical Analysis**

Differences in catecholamine, ACTH, and cortisol concentrations and cardiovascular parameters among groups and over time were evaluated for statistical significance by analysis of variance (ANOVA) with repeated measures. ACTH, NE, and cortisol differences from baseline to 5 min (maximum response times for ACTH and NE) or 15 min (maximum response time for cortisol) were calculated, and differences in these “deltas” between groups were analyzed by $t$ test. MAP and heart rate differences from baseline to the 1-min sample point were calculated and analyzed in a similar manner. In addition, area under the curve (AUC) following CPT was calculated for each endocrine parameter by the trapezoidal method and compared between groups by Student’s $t$ test. Because of a possible noradrenergic facilitatory effect on cortisol release directly at the adrenal cortex (Bornstein and Chrousos 1999), correlations were performed between both basal plasma NE and plasma NE delta and cortisol AUC.
interaction \([F(12,192) = 2.20, p = 0.01]\). Heart rate increased significantly from baseline to 1 min in AD subjects (61 ± 2 bpm to 66 ± 2 bpm; \(t = 4.19, p < .01\)). Although heart rate increased in control subjects (63 ± 3 bpm to 65 ± 4 bpm), this increase was not significant; the changes in heart rate from baseline to 1 min did not differ between AD and control groups.

**Subjective Discomfort Ratings**

There were no significant differences between AD and healthy older control subjects for ratings of pain (59 ± 12 vs. 42 ± 10) or anxiety (18 ± 8 vs. 20 ± 6). Within AD subjects there were no significant correlations between delta cortisol and either pain or anxiety ratings or between MMSE score and either pain or anxiety ratings.

**Discussion**

This is the first report of the effects of AD on neuroendocrine responses to a standardized aversive stressor. The effects of AD on basal hormone concentrations and hormonal responses to CPT varied among the HPA axis, the sympathoneural component of the SNS, and the sympathoadrenomedullary component of the SNS. The results provide support for increased adrenocortical but not pituitary corticotroph responsiveness in AD to this
aversive stressor. The elevated plasma NE concentrations in AD suggested increased basal sympathoneural activity during the experimental procedure, but these NE elevations appeared independent of the acute CPT stimulus.

**HPA Axis**

The enhanced adrenocortical but not pituitary corticotroph response to CPT in AD is consistent with results of several recent studies. Näsman et al (1996) and Hatzinger et al (1995) reported enhanced cortisol but unaltered or even reduced ACTH response to direct stimulation of the pituitary corticotroph by exogenous CRF in AD subjects. They also are consistent with our report of enhanced cortisol but unaltered ACTH responses to physostigmine infusion in AD subjects (Peskind et al 1996), and an enhanced cortisol but blunted ACTH response in AD to hypoglycemia (O’Brien et al 1994). The increased stress responsiveness of cortisol but not ACTH in the current study may have been a function of increased tonic sympathoneural activity (as suggested by increased basal plasma NE concentrations) in the AD subjects. In addition to the primary stimulatory regulation by ACTH of cortisol synthesis and release from the adrenal cortex, these processes are under stimulatory modulation by sympathoneural innervation of the adrenal cortex (Bornstein and Chrousos 1999). The observed positive correlation between basal NE and cortisol AUC following CPT in AD subjects is consistent with this possibility. Studying HPA axis responses to supraptuitary, pituitary, and adrenocortical stimuli in the same subject with concurrent evaluations of sympathoneural activity would clarify further the effects of AD on HPA axis regulation.

The significant inverse correlation between the cortisol response to CPT and MMSE score (lower MMSE indicates more severe dementia) suggests greater HPA axis response to CPT in the more advanced stages of AD, and is consistent with several studies noting greater resistance of the HPA axis to dexamethasone suppression in more advanced AD subjects (Gurevich et al 1989; Jenike and Albert 1984; Molchan et al 1990). This relationship also is consistent with the possibility that elevated cortisol responsiveness may contribute to the pathophysiology of the hippocampal neurodegenerative processes that contribute to the clinical expression of AD. This latter possibility is further supported by Lupien et al’s report of greater hippocampal atrophy and declarative memory deterioration in AD patients whose plasma cortisol increased over time (Lupien et al 1998), and de Leon and colleagues’ report of greater cortisol responses to oral glucose in AD patients with more severe hippocampal atrophy (de Leon et al 1988).

It is possible that the greater cortisol response to CPT in AD subjects could have been a result of their cognitive impairment, making the discomfort of the CPT a more novel or otherwise more distressing experience. Previous investigators have reported significant relationships between subjective pain appraisal and the cortisol response to CPT in normal volunteers (Bullinger et al 1984); however, the equivalent pain and anxiety ratings between AD and control subjects in the current study argue against a differential psychological appraisal of the CPT accounting for the observed differences in cortisol responses between groups.

The reason for the absence of a significant cortisol increase in the healthy older subjects following CPT is not clear. Because this study was performed in the morning, a modest cortisol response to CPT may have been obscured by the decline in cortisol concentrations that occurs in the morning as part of the normal plasma cortisol diurnal rhythm (Wilkinson 1989). Cortisol measurements during a resting morning condition without CPT would have been necessary to evaluate this possibility.

**Sympathetic Nervous System**

Plasma NE concentrations were higher in AD subjects throughout the experimental protocol, but the NE responses to CPT did not differ between groups. These findings are consistent with increased basal sympathoneural activity but unaltered responsiveness to CPT. We previously reported increased resting plasma NE concentrations in AD subjects with advanced dementia (Elrod et
al 1997; Raskind et al 1984) and others have reported increased resting plasma NE in AD subjects with mild to moderate dementia (Ahlskog et al 1996).

Body mass index, a measure of overall adiposity, was greater in the normal older subjects than in the AD subjects. In healthy persons, BMI is positively correlated with both sympathetic nerve discharge and urinary NE excretion (Scherrer et al 1994; Troisi et al 1991; Ward et al 1996). The effect of AD on plasma NE might have been even greater if BMI had been equal between groups.

In a separate sample of AD outpatient subjects studied in our laboratory, basal and yohimbine-stimulated plasma dihydroxyphenylacetic acid (DOPA) concentrations tended to be higher in AD than nondemented older comparison subjects (Raskind et al 1999). Because plasma DOPA provides an estimate of NE biosynthesis (Goldstein et al 1987; Kvetnansky et al 1992) these plasma DOPA data suggest a tendency toward increased NE biosynthesis in AD subjects during the conditions of that study. Using another approach to assess SNS activity, Aharon-Peretz et al (1992) demonstrated that power spectrum analysis of electrocardiographic recordings suggested increased cardiac sympathetic stimulation in AD. The higher MAP response to CPT in these AD subjects leaves open the possibility of a subtly enhanced sympathoneural response to CPT that was not detectable using plasma NE measurements or a greater end organ responsiveness to sympathoneural stimulation. NE kinetic studies as well as concurrent measurements of plasma NE together with its precursor DOPA and its intraneuronal metabolite dihydroxyphenylglycol (which provides an estimate of NE turnover [Li et al 1983; Eisenhofer et al 1992]) would provide a more comprehensive assessment of AD effects on basal and stress responsive sympathoneural activity (Esler et al 1988).

Other studies are not consistent with increased basal sympathoneural activity in AD. Vitiello et al (1993) found no difference in plasma NE or EPI concentrations between a large sample of AD subjects and age-comparable nondemented comparison subjects, and reduced systolic blood pressure responses to upright posture in AD subjects, particularly those manifesting depressive symptoms. The discrepancies between the current data and the findings of Vitiello et al (1993) possibly reflect differences in experimental settings. Their AD subjects (but not their older healthy comparison subjects) were residents of the experimental unit in which the study was conducted, and perhaps had become acclimated to this environment. In contrast, the subjects in the current study came to an unfamiliar research setting directly from home. Furthermore, they were informed as part of the consent process that the CPT was likely to be uncomfortable, albeit for a brief period of time. The higher plasma NE concentrations in the AD subjects participating in the current study may have reflected their greater SNS responsiveness to a novel setting or greater arousal in anticipation of an aversive stimulus.

These results suggest increased responsiveness in AD of several classic stress-sensitive neuroendocrine systems to at least some types of stressors. Aversive physical stimuli and/or encountering an unfamiliar environment may be types of stressors to which persons with AD are particularly responsive. If these results can be confirmed in larger numbers of AD subjects, they could have implications for the management of AD (Brady et al 1991). For example, several antidepressant drugs have been demonstrated in preclinical studies to reduce the HPA axis response to stress (Barden 1999; Dellbende et al 1991) and the associated aversive stress-induced hippocampal pyramidal cell dendritic atrophy (Magarinos et al 1999). If the hypothesized involvement of enhanced neuroendocrine responses to stress in the pathophysiology of AD (Sapolsky 1992) can be confirmed, clinical trials to assess the effects of drugs that reduce these responses on AD symptomatology and progression would be warranted.

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