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Relationships between Dehydroepiandrosterone Sulfate (DHEAS) and Cortisol (CRT) Plasma Levels and Everyday Memory in Alzheimer's Disease Patients Compared to Healthy Controls

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Fifty-two age-matched Alzheimer's disease (AD) patients (26 men, 26 women), mean age 76.2 years, were assessed with the Rivermead Behavioural Memory Test, a test of everyday memory, coincident with the measurement of plasma cortisol (CRT) and dehydroepiandrosterone sulfate (DHEAS) via radioimmunoassay. The AD patients were compared to a control group of age- and gender-matched healthy elderly men and women. No differences were found between the AD patients and the controls in DHEAS or CRT levels, or in the DHEAS/CRT ratio. There were no gender differences in DHEAS or CRT levels, or in the DHEAS/CRT ratio in subjects with AD. However, AD patients with higher levels of DHEAS scored better than those with lower levels on the subtests of Remembering a Name associated with a picture, Digit Span Total and Forward, and the Mini Mental Status Exam. AD patients with higher CRT levels performed worse on Delayed Route Recall than those with lower levels. These findings suggest that AD patients with higher endogenous levels of DHEAS may perform better on some memory tasks than those with lower levels, while AD patients with lower levels of CRT may perform better than those with higher CRT.

Increased levels of glucocorticoids, due either to environmental stress or to exogenous administration, have been associated with a number of adverse physiological and biochemical actions in the brains of rodents and monkeys, particularly in the hippocampus. These include damage to the hippocampal dendritic tree (Wooley, Gould, and McEwen, 1990), decreases in hippocampal long-term potentiation (LTP) (Foy, Stanton, Levine, and Thompson, 1987), and degeneration and depletion of hippocampal neurons and dendritic branching in the CA1 and CA3 layers (Uno, Tarara, Else, Suleman, and Sapolsky, 1989; Sapolsky, Uno, Rebert, and Finch, 1990; Uno, Lohmiller, Thieme, Kemnitz, Engle, Roecker, and Farrel, 1990). In humans, the elevated levels of cortisol (CRT) seen in individuals with Cushing's Syndrome were related to a decreased volume of the hippocampus as assessed by MRI (Starkman, Gebarski, Berent, and Shcteingart, 1992).

Reports of elevated CRT levels in Alzheimer's disease (AD) patients (Leblhuber, Neubauer, Peichl, Reisecker, Steimpartz, Windhager, and Dienstl, 1993; Svec and Lopez-S, 1989; Swaab, Raadsheer, Endert, Hofman, Kamphorst, and Ravid, 1994; Maeda, Tanimoto, Terada, Shintani, and Kakigi, 1990) led to speculation that some portion of the degenerative changes associated with this disease may be related to increased exposure to glucocorticoids. In a longitudinal investigation of 12 AD patients over a 1-year period, CRT levels at baseline correlated positively with cognitive deterioration over the next 12 months, as assessed by the Alzheimer's Disease Assessment Scale (Weiner, Vobach, Svetlik, and Risser, 1994). However, not all studies have found elevated CRT in AD patients compared to unaffected controls (Touitou *et al.,* 1982; Dodt *et al.,* 1991; Nasman *et al.,* 1996).

There is also reason to believe that dehydroepiandrosterone (DHEA), an adrenal androgen, and its sulfate, DHEAS, may influence cognition in people with AD. At low concentrations, DHEA and DHEAS function as allosteric antagonists of $GABA_A$ receptors. Noncompetitive binding with DHEA and DHEAS in-

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hibits GABA-induced neuronal activity, which is associated with cognitive impairment (Majewska, Demirgoren, Spivak, and London, 1990). When low doses of DHEA and DHEAS were added to 14-day-old embryonic mouse brain cultures, enhanced neuronal and glial survival occurred (Roberts, Bologna, Flood, and Smith, 1987). DHEAS administration increased the excitability of CA1 hippocampal neurons in hippocampal slices from rat brains, an effect that occurred within minutes and was reversible upon withdrawl of DHEAS (Meyer and Gruol, 1994). In intact rats, the application of DHEAS to the dentate gyrus resulted in increases in LTP at all doses compared to baseline (Yoo, Harris, and Dubrovsky, 1996), indicating that DHEAS can increase the electrical activity of this region. Some (Sunderland *et al.*, 1989; Yanase, Fukahori, Taniguchi, Nishi, Sakai, Takayanagi, Haji, and Nawata, 1996) but not all (Leblhuber, Windhager, Reisecker, Steinparz, and Dienstl, 1990; Leblhuber *et al.*, 1993; Cuckle, Stone, Smith, Wald, Brammer, Hajimohammedreza, Levy, Chard, and Perry, 1990; Spath-Schwalbe, Dodt, Dittmann, Schuttler, and Fehm, 1990; Birkenhager-Gillesse, Derksen, and Lagaay, 1994) studies have found that plasma DHEAS concentrations were lower in AD patients compared to healthy controls. Sunderland *et al.* (1989) failed to find correlations between levels of DHEAS and dementia severity or baseline cognitive scores in a sample of 10 AD patients. The possible significance of DHEAS levels in AD thus remains controversial.

In animal models, DHEAS has antiglucocorticoid actions in the liver by blocking the enzymatic effects of glucocorticoids. When administered to mice, DHEAS blocked dexamethasone (DEX)-induced production of tyrosine aminotransferase (Svec and Lopez-S, 1989) and antagonized the glucocorticoid effect on glucose-6-phosphate dehydrogenase (McIntosh and Berdanier, 1988). Based on these findings, Svec and Lopez-S (1989) suggested that the ratio of CRT to DHEAS could serve as an index of glucocorticoid agonist activity. If it is the case that AD patients have lower DHEAS than age-matched controls (Sunderland *et al.*, 1989), this would result in a ratio of agonist to antagonist much higher than that of the control population, which could lead to a mild but progressive degenerative effect of CRT on hippocampal cells. If, in turn, such degeneration caused dysregulation in feedback mechanisms to the adrenals, an ever-accelerating, forward-cascading degree of hippocampal damage, and presumably memory impairment, would follow (Sapolsky, Krey, and McEwen, 1986).

Indeed, a lower DHEAS/CRT (antagonist/agonist) ratio was found in elderly AD patients compared to age-matched controls, most particularly in women (Leblhuber *et al.*, 1993). However, neither the ratio of DHEAS/CRT nor the levels of CRT or DHEAS independently were correlated with memory function as assessed by the Mini Mental Status Exam (MMSE), or with the duration of AD symptoms. Lower DHEAS levels were associated with increased age, which resulted in a decrease in the DHEAS/CRT ratio in the more elderly controls. In the female AD patients, even lower ratios of DHEAS/CRT and higher levels of CRT were found compared to the control women.

Finally, the issue of the generalizability of performance on standard neuropsychological measures of function to everyday life is particularly important for AD patients. For this reason, we utilized an ecologically valid measurement of everyday memory that bridges laboratory-based measures of memory and assessments obtained by questionnaire and direct behavioral observation (The Rivermead Behavioural Memory Test (RBMT), Wilson, Cockburn, Baddeley, and Hiorns, 1989). In this study we investigated the relationships between CRT and DHEAS in AD patients and in healthy controls in an attempt to further elucidate the possible roles of these hormones on cognition in AD and in normal aging.

METHODS

Subjects

Subjects were recruited from the pool of patients with possible or probable Alzheimer's Disease who were being followed for annual clinical visits at the Jewish General Hospital/McGill University Memory Clinic, Montreal, Canada. Subjects were referred by the clinical staff of the Memory Clinic (neurologists and geriatricians), and screened for eligibility for the study. Exclusion criteria included diabetes, recent heart attack, stroke or recent head injury, use of any psychotropic medication, or lack of fluency in the English language. The diagnosis of possible or probable AD was made by the clinical staff based on the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the National Institute of Health and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann *et al.*, 1984), with the use of CT scans and routine blood work to rule out other possible causes of dementia. Charts were reviewed to determine the degree of dementia according to the Clinical Dementia Rating scale score (CDR; Hughes *et al.*, 1982), and only

those diagnosed as mildly to moderately demented (CDR 1 or 2) were included. Only patients assessed as capable of giving their own informed consent were recruited. Each eligible subject was approached by his/her physician and invited to participate in the study. If the patient was interested in participating, informed consent was obtained from the patient and their caregiver and witnessed by the physician and the research assistant who explained the study.

Another component of this study was an investigation of estrogen and memory (unpublished data), and for that reason, some AD patients and control women who were using estrogen replacement were specifically included in these samples. For those patients taking estrogen replacement therapy, the duration and dosage of the prescription was verified by the caregiver and by having the subject bring the pill container to the testing session whenever possible.

The healthy elderly control subjects were recruited through advertisements in local newspapers. The advertisements stated that McGill University was seeking men and women fluent in English over the age of 65 for a study of "thinking and mood". Those experiencing any major acute or chronic medical or psychiatric illness were excluded, including those with a history of stroke, recent heart disease, diabetes or vascular disorders, those recently diagnosed with depression, anxiety, dementia or psychotic disorders, and those currently taking any psychotropic medication. Other medications currently being taken were recorded. Others taking any medication known to affect cognition were excluded, except for those regulated on levothyroxine sodium (Synthroid, Knoll Pharma Inc., Ontario, Canada) to treat thyroid disease, which is common in elderly women. Past history of psychopathology was assessed by self-report but was not an exclusionary factor unless the person was currently taking a psychotropic medication. The final group of healthy elderly control subjects were matched on the basis of age, gender, and estrogen status to the AD patients. The healthy elderly control group consisted of 23 men, 23 estrogen nonusing women, and 6 estrogen users.

Materials

The RBMT (Wilson, Cockburn, and Baddeley, 1985) is an ecologically valid instrument that assesses everyday memory. The RBMT consists of the following subscales: Remembering a Name, Remembering a Belonging, Remembering an Appointment, Picture Recognition, Face Recognition, Story Recall (Immediate and Delayed), Route Recall (Immediate and Delayed), Remembering to Deliver a Message (Immediate and Delayed), Orientation, Date, and the Total Score (out of 24), which consists of the total of the scaled scores for each subtest. Additionally, results of more traditional neuropsychological tests, including the Wechsler Memory Scale (WMS) digit span (Weschler, 1945), object naming (The Boston Naming Test (BNT); Goodglass *et al.*, 1983), and the MMSE (Folstein *et al.*, 1975), were also obtained for the AD patients. The Geriatric Depression Scale (GDS; Yesavage, Brink, Rose, Lun, Huang, Adley *et al.*, 1983) was administered to both AD patients and Controls.

Procedure

AD patients. Once the patient agreed to participate in the study and signed the informed consent form, a 10-mL blood sample for hormonal assays was taken by the Memory Clinic nurse at the same time as blood was being collected for other studies, between 10 AM and 1 PM. Then, the patients and the caregiver answered a general information questionnaire that provided sociodemographic information as well as personal, medical, psychological, educational, and vocational history. This information was later verified with information in the patient's chart. Next, the RBMT, the WMS Digit Span, and the GDS were administed to the patient alone, which took approximately 30 min. The BNT and the MMSE were administered by a neuropsychologist at the annual clinic visit, which occurred within 2 weeks of the other test session and the drawing of the blood sample. When necessary, the patients and their family members were reimbursed for travel expenses to attend the testing session.

Control subjects. After being screened for eligibility, control subjects reported to the laboratory individually, females at 1000 h and males at 1230 h, and signed a consent form approved by the McGill University Ethics Committee. Female subjects had their blood samples taken by a registered nurse after their test session, whereas the male subjects had their samples taken before their neuropsychological test session. This was done in order to control for the time of day that the blood sample was taken and in view of the constraints on the availability of the blood technician. For all subjects, therefore, the blood sample was obtained between 1200 h and 1300 h on the day of testing. Test sessions for control subjects were carried out in the laboratory and each lasted 1.5 to 2 h. Subjects first completed a general information form that

TABLE 1
Sociodemographic Characteristics of AD Patients vs Controls

Group	Age (years)		Education (years)		Socioeconomic status	
	Mean	SEM	Mean	SEM	Mean	SEM
AD patients (n = 52)	75.85	1.05	10.55	0.48	49.61	2.00
Men (n = 27)	75.62	1.48	10.65	0.70	48.14	2.99
E nonusers (n = 22)	75.88	1.72	10.41	0.77	51.42	3.02
E-users (n = 3)	77.73	2.29	10.67	0.33	49.03	2.67
Controls (n = 52)	74.22	0.75	12.25[a]	0.44	54.80	1.96
Men (n = 23)	73.37	1.23	12.78[b]	0.75	48.14	2.66
E nonusers (n = 23)	74.83	1.07	11.30	0.55	51.42	3.21
E-users (n = 6)	75.11	2.03	13.83	1.14	49.03	4.59

[a] Controls had >Education than AD patients, $P = 0.01$.
[b] Male Controls had >Education than male AD patients, $P < 0.05$.

provided sociodemographic information as well as personal, medical, psychological, educational, and vocational history. Next, the test battery was administered. Each subject was paid $15 at the end of the session to compensate them for their transportation expenses.

Hormonal Assays

Ten milliliters of blood was collected via venipuncture into heparinized Vacutainer tubes. The blood was immediately centrifuged and the plasma stored at −50°C. All samples were analyzed by radioimmunoassay at the conclusion of the study. DHEAS was analyzed using the Radioimmunoassay Kit for the Quantitative measurement of DHEAS in Serum or Plasma (Diagnostic Systems Laboratories Inc., Webster, TX). The sensitivity of this assay is 0.46 μmol/L, with intra-assay precision of 4.1%, interassay precision of 10.0%, and 95% confidence. CRT was measured by the Clinical Assays GammaCoat CRT I-RIA Kit (Incstar Corp., Stillwater, MN), with a minimum sensitivity of 7 nmol/L, intra-assay reliability of 6.6%, interassay reliability of 9.8%, and 95% confidence. Both of these assay procedures report high specificity with very little nonspecific binding of the antiserum to other hormones.

RESULTS

Participants

Twenty-seven men, 22 estrogen nonusing women, and 3 estrogen-users participated in this study. All were diagnosed with either mild or moderate, possible or probable dementia, based on a full medical workup. The 3 estrogen-users were taking congugated equine estrogen (CEE) 0.625 mg daily (Premarin, Wyeth-Ayerst, Canada). The average CDR for the AD subjects was 1.24 (sd = 0.48), with 1 = mild dementia and 2 = moderate dementia. There were no differences between the three AD groups in the CDR scores. The 52 AD patients were matched with 52 control subjects recruited from the community. Twenty-three men, 23 estrogen nonusing women, and 6 estrogen-using women participated. Five of the estrogen-using women were taking CEE 0.625 mg daily, 2 of these were also taking medroxyprogesterone acetate (MPA) 2.5 mg daily (Provera, Upjohn Canada), and the sixth was taking CEE 0.30 mg daily. All subjects completed the RBMT. Sociodemographic characteristics of the two groups are presented in Table 1.

There was no gender difference in the age of the AD patients (mean 75.85 years, sd = 7.65). The average number of years of formal education was 10.55 years (sd = 3.4) and the socioeconomic status was 49.61, indicating that they were mostly middle class. Although AD patients and controls were matched on age and SES, t tests for independent samples indicated that the control men had more years of education than the AD men (t = 2.12, P = 0.39), whereas years of education did not differ between the women with AD and the control women.

Hormonal Assays

Group by gender ANOVA analyses of each of the hormone levels found no interactions between group

and gender and no main effects for group. Main effects for gender were found for the hormones DHEAS ($F(1, 85) = 6.15$, $P = 0.015$) and the DHEAS/CRT ratio ($F(1, 85) = 4.04$, $P < 0.05$) with higher levels occuring in the men. When probed with one-way ANOVA analyses using Bonferroni-corrected post hoc *t* tests, overall, the men had higher DHEAS ($F(2, 96) = 8.16$, $P < 0.001$) levels than both groups of women, and the men also had a higher ratio of DHEAS/CRT than the estrogen-users ($F(2, 93) = 6.23$, $P < 0.005$). The hormone levels for the AD patients and controls are presented in Table 2. Within the AD patients, there were no group differences in any of the hormone levels.

Memory Performance

There were significant group differences between the AD patients and controls on the scores of the memory tests, presented in Table 3. As expected, the control group performed significantly better than the AD patients overall after controlling for years of education with multivariate ANCOVA procedures ($P < 0.001$). The factoring out of educational level before conducting group comparisons resulted in adjustments in the means of only the Immediate ($P < 0.001$) and Delayed ($P < 0.05$) Route scores and the RBMT Total Score ($P < 0.05$).

The difference in the performance of the AD patients compared to the healthy elderly controls was most profound on the RBMT Total score ($F(1, 100) = 424.5$), Name Recall ($F(1, 100) = 144.5$), Remembering a Belonging ($F(1, 100) = 115.4$), Delayed ($F(1, 100) = 113.9$) and Immediate ($F(1, 100) = 111.5$) Story Recall, and Delayed Route ($F(1, 100) = 107.7$). In contrast, although their scores were significantly worse than the controls, the performance of the AD patients was least impaired on Forward ($F(1, 100) = 12.6$), Total ($F(1, 100) = 24.1$) and Backward ($F(1, 100) = 25.9$) Digit Span, Immediate Route recall ($F(1, 100) = 45.9$), and Picture ($F(1, 100) = 50.1$) and Face ($F(1, 100) = 52.5$) Recognition.

TABLE 2

Mean Hormone Levels of AD Patients vs Controls

	CRT (nmol/L)	DHEAS (umol/L)	DHEAS/CRT
AD patients overall	312.61	2.26	0.75
Men ($n = 26$)	325.31	2.53[a]	0.84[b]
E nonusers ($n = 21$)	303.05	2.12	0.71
E-users ($n = 3$)	266.33	0.70	0.28
Controls overall	345.79	2.42	0.73
Men ($n = 22$)	376.95	3.38[c]	0.98[d]
E nonusers ($n = 20$)	336.16	1.89	0.61
E-users ($n = 6$)	262.00	0.68	0.26

[a] AD men had >DHEAS levels than Control E-users ($P < 0.01$).
[b] AD men had >DHEAS/CRT ratio than Control E-users.
[c] Control men had >DHEAS levels than all female groups ($P < 0.01$).
[d] Control men had >DHEAS/CRT ratio than Control E nonusers, Control E-users, and AD E-users.

TABLE 3

Neuropsychological Test Scores—AD Patients vs Controls

Test Name	Max. possible score	AD Patients Mean	AD Patients SEM	Controls Mean	Controls SEM
Digit span	24	11.77	0.53	15.56*	0.50
Forward	12	6.90	0.30	8.67*	0.34
Backward	12	4.77	0.30	6.98*	0.24
Name recall	4	0.45	0.16	3.01*	0.11
Belonging	4	1.10	0.08	3.31*	0.17
Appointment/Results	2	0.23	0.10	1.44*	0.70
Picture recognition	10	6.45	0.14	9.58*	0.41
Story - Immediate	21	1.29	0.44	7.08*	0.19
Story - Delayed	21	0.30	0.43	5.68*	0.11
Face recognition	5	2.92	0.70	4.71*	0.22
Route - Immediate	5	2.72	0.12	4.21*	0.16
Route - Delayed	5	1.70	0.11	4.13*	0.19
Message	6	2.78	0.16	5.08*	0.19
Orientation	9	5.44	0.50	8.85*	0.34
Date	2	0.51	0.50	1.92*	0.12
RBMT Total	24	2.98	0.50	17.59*	0.42

* Control > AD, $P < 0.001$.

Pearson product-moment correlations between hormone levels and cognitive test scores were calculated in the men and estrogen nonusing women AD patients, but not in the estrogen users, as the number of *Ss* in this group was too small to permit such comparisons. Cutoff values of $P < 0.01$ were used for these correlations to control somewhat for the large number of correlations performed. Correlations between $P < 0.02$ and $P < 0.01$ will be discussed with caution. In the men with AD, CRT levels were positively associated with Face Recognition scores ($r = 0.474$, $P = 0.017$). In the women estrogen nonusers with AD, higher CRT levels were associated with better performance on the Boston Naming Test ($r = 0.589$, $P < 0.01$).

Low Vs High Hormone Groups

Since there were no significant group differences between levels of DHEAS, CRT, and the DHEAS/CRT ratio in the AD patients, the *Ss* were divided

TABLE 4
Cognitive Test Scores: Low Vs High Hormone Levels in AD Patients

Test name	Low DHEAS (n = 26)	High DHEAS (n = 24)	Low CRT (n = 25)	High CRT (n = 23)	Low DHEAS/ CRT	High DHEAS/ CRT
CDR	1.25	1.24	1.26	1.25	1.10	1.39
MMSE	18.67	21.52[a]	20.04	19.70	19.75	20.00
Boston naming	32.78	33.33	30.00	36.25	36.79	29.83
Digit span total	10.96	12.95[b]	11.71	11.95	11.57	12.10
Forward	6.24	7.74[c]	6.68	7.24	6.71	7.18
Backward	4.58	5.14	4.88	4.65	4.70	4.86
Name recall	0.19	0.75[d]	0.48	0.43	0.24	0.70
Belonging	1.00	1.29	1.20	1.00	1.24	0.96
Appointment/Results	0.19	0.33	0.16	0.35	0.24	0.26
Picture recognition	6.46	6.50	6.48	6.39	7.04	5.78
Story Recall - Immediate	1.15	1.60	1.28	1.50	1.26	1.52
Story Recall - Delayed	0.27	0.46	0.40	0.30	0.32	0.39
Face recognition	2.81	3.25	2.76	3.26	3.32	2.65
Route - Immediate	2.60	2.95	2.92	2.57	2.68	2.82
Route - Delayed	1.80	1.67	2.17	1.22[e]	1.76	1.64
Message	2.96	2.71	2.83	2.91	3.08	2.64
Orientation	5.08	6.04	5.40	5.60	5.40	5.61
Date	0.62	0.42	0.52	0.57	0.72	0.35
RBMT Total	3.15	3.04	3.24	2.91	3.48	2.65

[a,b,c,d] High DHEAS > Low DHEAS, $P < 0.05$.
[e] Low CRT > High CRT, $P < 0.05$.

into high and low groups for each of these hormones using a median split. The mean scores of the high vs low groups on each of the cognitive tests were then compared for each hormone measure with MANOVA analyses. The results of these comparisons can be seen in Table 4.

AD subjects in the high DHEAS group performed better than those with lower DHEAS levels on the tests of Name Recall ($F(1, 47) = 7.19$, $P < 0.01$), Total ($F(1, 44) = 4.12$, $P < 0.05$) and Forward ($F(1, 44) = 4.64$, $P < 0.05$) Digits, and they also had higher MMSE scores ($F(1, 44) = 4.92$, $P < 0.05$). Those with lower CRT levels performed better on the Delayed Route Recall task ($F(1, 47) = 6.01$, $P < 0.05$) than the *Ss* in the upper range of CRT values.

Mood Scores

The AD patients scored an average of 8.67 on the GDS, out of a possible total score of 30, where higher scores indicate more depressive symptoms. This was significantly higher than the mean score of the control group (3.98, $t = 5.41$, $P < 0.001$). When hormone and gender groups were examined using one-way ANOVA analyses with Bonferroni-corrected post hoc t tests, group differences were found ($F(5, 88) = 7.22$, $P < 0.0001$) such that the AD female estrogen nonusers scored higher than all three control groups on the GDS (10.00 vs 3.38, 4.80, and 3.20), and the AD men scored higher than the control men (7.75 vs 3.38). There were no significant differences between the AD estrogen users (mean 7.00) and the control estrogen users (mean 3.20) on this measure, which might possibly have been due to small sample size of the estrogen users.

DISCUSSION

The comparison of healthy elderly control *Ss* and AD patients provided some information on possible differences in endocrine status between these two groups. Contrary to our hypothesis, there were no overall group differences between AD patients and controls in levels of either of the hormones that we measured. The AD patients had the same CRT levels as healthy controls in this study. Others have previously reported higher CRT levels (Leblhuber *et al.*, 1993; Swaab *et al.*, 1994; Maeda *et al.*, 1990; Davis *et al.*, 1986) and dysregulation of the HPA axis (O'Brien, Ames, Schweitzer, Colman *et al.*, 1996; Hatzinger *et al.*, 1995; Nasman *et al.*, 1995, 1996; O'Brien, Ames,

Schweitzer, Mastwyk *et al.*, 1996) in AD patients compared to controls. However, in those studies, AD patients with elevated CRT levels differed from ours in several ways. They were younger (aged 64.1) and had a presenile form of AD (Davis *et al.*, 1986), were much more severely demented (MMSE = 1.6, Maeda *et al.*, 1991; MMSE = 5.2, Leblhuber *et al.*, 1993), were inpatients (Maeda *et al.*, 1991), and were suffering from various forms of dementia (Maeda *et al.*, 1991). Additionally, all those studies had small sample sizes. Our findings are consistent with others who failed to find differences in CRT levels between AD patients and age-matched controls (Touitou *et al.*, 1982; Dodt *et al.*, 1991; Nasman *et al.*, 1991).

Because no challenge of the HPA axis was performed in this study, HPA dysregulation may have been present but not observed, although severe dysregulation of the HPA axis would likely have been reflected in elevated CRT levels. However, no comment can be made regarding the presence of more subtle forms of HPA dysregulation. It is possible that the elevated CRT levels found in more severely demented AD patients by others are a result of prolonged HPA dysregulation, and might not be evident earlier in the disease process.

One limitation of the experimental design was that only one measure of CRT was taken from each of the AD patients and controls. Since CRT levels are known to fluctuate diurnally and in response to stressful stimuli (Bohnen *et al.*, 1990; Kirschenbaum *et al.*, 1996), one sample may not provide an accurate baseline. On the other hand, the blood sample was taken at approximately the same time of day for both the AD patients and the healthy elderly subjects, which controlled for diurnal fluctuations. However, it is possible that had CRT levels been taken at a different time of the day, or had several samples been taken and averaged, the relationship of CRT plasma levels to aspects of cognitive performance may have been different.

Another methodological issue relating to the timing of the test battery is due to the fact that women control subjects were administered the test battery before the blood sample was taken, whereas the male controls and the AD patients were tested after the blood sample was obtained. Thus, it is possible that CRT may have been elevated in the female controls following testing, had they perceived the test session as stressful. On the other hand, it is possible that the men and AD patients may have been anticipating stressful activity when their blood sample was drawn before the test session, which may have similarly caused their CRT levels to be elevated. Although we cannot rule out any influence of our methodology on CRT production, there were, in fact, no gender differences in CRT levels of the healthy elderly, and the mean levels of all participants were well within the normal range of CRT values based on the norms of the laboratory that performed the assays.

In the present study, AD patients did not have lower DHEAS levels compared with our healthy elderly controls. Although lower levels of DHEAS have been reported in AD patients (Sunderland *et al.*, 1989; Nasman *et al.*, 1991; Yanase *et al.*, 1996), more often than not, investigators have failed to find such differences in DHEAS levels between AD patients and controls (Leblhuber *et al.*, 1990, 1993; Cuckle *et al.*, 1990; Spath-Schwalbe *et al.*, 1990; Birkenhager-Gillesse *et al.*, 1994). Of the studies that found group differences, the AD patients were much younger than those in our sample (61 years, Sunderland *et al.*, 1989) and may have had a familial subtype of AD or more severe dementia (Nasman *et al.*, 1990). The inconsistency in these findings suggests that age and severity of the disease might modify DHEAS levels in AD patients.

The antagonistic effects of DHEAS on GABA in the brain (Majewska, 1995) coupled with its antiglucocorticoid effects (Svec and Lopez-S, 1989), suggest a possible role for DHEAS in the dementia process. When AD *Ss* were subdivided by a median split into low and high DHEAS groups, the group with high DHEAS levels performed better than the group with low levels on four tasks, Digits Total and Forward, Name Recall, and the MMSE, even though the low DHEAS group was not more demented as assessed by the CDR. This association of DHEAS with better memory is consistent with findings that DHEAS administration caused neuronal sprouting in the rat hippocampus (Roberts *et al.*, 1987). An inverse relationship between DHEAS levels and the presence of dementia occurred in male nursing home residents (Rudman *et al.*, 1990), but the sample in that study consisted of mixed etiology dementia syndromes. In a study of three men and three women with major depression, DHEAS administration resulted in improvements of mood and of "automatic" memory processing, but performance on explicit verbal recall tasks remained unaffected (Wolkowitz *et al.*, 1997). In that study, DHEAS levels were correlated with decreases on the Hamilton Depression Rating Scale subscale items assessing "cognitive disturbance". The finding in the present study that higher DHEAS levels in AD patients were associated with better cognitive performance is interesting, but its possible etiological or clinical significance is uncertain due to the fact that,

overall, DHEAS levels of AD patients did not differ from those of our age-matched controls.

Since the MMSE was not administered on the same day that blood was drawn for the DHEAS assay, the relationship between DHEAS levels and MMSE scores may be less reliable than the findings for Digit Span and Name Recall, which were administered on the same day that blood was drawn. However, although there is considerable variation of DHEAS levels between individuals, there tends to be modest intraindividual fluctuation, with the highest diurnal levels occurring during the daytime hours, and longitudinal changes occurring very slowly over the course of many years (Majewska, 1995). Thus, although it is methodologically desirable to concomitantly administer tests and draw blood, in the case of DHEAS, blood drawn within 2 weeks, and at the same time of day, as the administration of the MMSE would likely reflect current fluctuating levels reliably enough to classify subjects into high or low DHEAS groups.

It is important to note that plasma RIAs of DHEAS may not accurately reflect levels of this steroid in the brain, where they may be many times higher (Majewska, 1995). Indeed, it is questionable whether correspondence exists between DHEAS levels in plasma and in the brain, since higher plasma concentrations of DHEAS have been reported in males compared to females (Vermeulen, 1995), but post mortem studies have found higher levels in female rather than male brains (Lanthier and Patwardhan, 1986). The exact nature of the relationship between peripheral plasma levels and brain levels of DHEAS awaits further comparative research.

If a higher ratio of DHEAS/CRT was beneficial to cognitive performance as others have suggested (Svec and Lopez-S, 1989), the men and estrogen nonusers would have shown superior performance compared to the estrogen users in this study, concomitant with their higher DHEAS/CRT ratios. However, this did not occur in any instance. If any group appeared to have an advantage over the others with respect to their performance on the cognitive tests, it was the healthy elderly estrogen users, who actually had the lowest DHEAS/CRT ratio of any group. Therefore, our results provide no support for the idea that a higher DHEAS/CRT ratio is a protective factor against cognitive decline in healthy elderly people or in those with mild to moderate AD.

Predictably, AD patients performed worse on every aspect of the RBMT and on the Digit Span tests compared to controls. The RBMT was developed to assess rehabilitation in head-injured patients and accurately reflects everyday memory functioning by its high correlations with objective ratings by a caregiver (Wilson *et al.*, 1989). Three RBMT subtests (Story Recall, Route Recall, and Name Recall) were very sensitive to gradations of dementia in AD patients and could distinguish "minimal dementia" from "low-scoring normal" groups (Beardsall and Huppert, 1991). In our study, these same subtests easily discriminated AD patients with mild to moderate dementia from healthy elderly controls.

The most difficult RBMT subtests for the AD patients, as assessed by the magnitude of the group differences between the AD patients and the controls, were those that involved recall without a recognition component, such as having to remember a belonging at the end of the test session or recall a story or a route. These types of tasks are also typically the most impaired with normal aging (Craik, 1991, 1994) and most dependent on hippocampal structures (Squire, 1992). On the other hand, Digit Span, which registers the least impairment, is not primarily dependent on the medial temporal lobe memory system (Moscovitch and Winocur, 1992; Kolb and Wishaw, 1985), the area most damaged in AD (West *et al.*, 1994). Digit Span measures attention/concentration and short-term memory, which are relatively unaffected by increasing age in the normal population (Craik and Jennings, 1992). Neither were the AD patients as impaired on Picture and Face Recognition as they were on the explicit recall tasks. These recognition tasks are also generally easier (Wilson, 1989) and show less impairment with normal aging (Craik, 1991) than explicit recall tasks. Thus, the AD patients in this sample showed the greatest impairments on tasks that depend upon the hippocampal memory system and on which performance declines somewhat with normal aging (e.g., explicit verbal memory). It seems, then, that the pattern of cognitive decline differs quantitatively but not qualitatively in AD patients and in normal elderly subjects.

Recently, an MRI study of normal elderly and predemented individuals found a constant rate of hippocampal and parahippocampal volume loss with aging, regardless of whether dementia develops in the future (Kaye *et al.*, 1997). Such a decrease in hippocampal volume with aging could also explain the declines in hippocampally dependent cognitive abilities associated with aging (Craik, 1994).

In summary, although the AD patients in this study had plasma levels of steroid hormones that did not differ from those of the healthy elderly controls, they were in the early stages of the disease, and it may be

that decreases in levels of DHEAS and elevated levels of CRT do not appear until dementia is more severe. The pattern of everyday memory functioning in AD patients was qualitatively similar to that of our healthy elderly but profoundly different quantitatively. The AD patients were most impaired on explicit recall tasks, followed by recognition tasks and then short-term memory and attention tasks. Higher DHEAS levels were related to better cognitive performance in these AD patients, whereas lower CRT levels were associated with better performance on one task. Studies of individuals in a more advanced stage of AD may help to further elucidated any relationships between steroid hormones and memory performance in AD patients.

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REFERENCES

Beardsall, L., and Huppert, F. A. (1991). A comparison of clinical, psychometric and behavioural memory tests: Findings from a community study of the early detection of dementia. *Int. J. Geriatric Psychiatry* **6,** 295–306.

Birkenhager-Gilesse, E. C., Derksen, J., and Lagaay, A. M. (1994). Dehydroepiandrosterone sulfate (DHEAS) in the oldest old, age 85 and over. *Ann. N.Y. Acad. Sci.* **719,** 543–552.

Blishen, B. R. (1967). A socio-economic index for occupations in Canada. *Canadian Rev. Sociol. Anthropol.* **4,** 41–53.

Bohnen, R., Houx, P., Nicolson, N., and Jokkes, J. (1990). Cortisol reactivity and cognitive performance in a continuous mental task paradigm. *Biol. Psychiatry* **31,** 107–116.

Craik, F. I. M. (1991). Memory functions in normal aging. *In* T. Yanagihara and R. C. Petersen (Eds.), *Memory Disorders,* pp. 347–367. Dekker, New York.

Craik, F. I. M. (1994). Memory changes in normal aging. *Curr. Directions Psychol. Sci.* **3,** 155–158.

Craik, F. I. M., and Jennings, J. M. (1992). Human Memory. *In* F. I. M. Craik and T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition,* pp. 51–110. Earlbaum, Hillsdale, NJ.

Cuckle, H., Storn, R., Smith, D., Wald, N., Brammer, M., Hajimohammedreza, I., Levy, R., Chard, T., and Perry, L. (1990). Dehydroepiandrosterone sulphate in Alzheimer's Disease. *Lancet* **336,** 449–450.

Davis, K. L., Davis, B. M., Greenwald, B. S., Mohs, R. C., Mathe, A. A., Johns, C. A., and Horvath, T. B. (1986). Cortisol and Alzheimer's disease, I: Basal studies. *Am. J. Psychiatry* **143,** 300–305.

Dodt, C., Dittmann, J., Hruby, J., Spath-Schwalbe, E., Born, J., Schuttler, R., and Fehm, H. L. (1991). Different regulation of adrenocortocotropin and cortisol secretion in young, mentally healthy elderly and patients with senile dementia of Alzheimer's type. *J. Clin. Endocrinol. Metabol.* **72,** 272–276.

Folstein, M., Folstein, S., and McHugh, P. (1975). "Mini-Mental State"—A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatic Res.* **12,** 189–198.

Foy, M. R., Stanton, M. E., Levine, S., and Thompson, R. F. (1987). Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behav. Neural Biol.* **48,** 138–149.

Hatzinger, M., Z'Brun, A., Hemmeter, U., Seifritz, E., Baumann, R., Holsboer-Trachsler, E., and Heuser, I. J. (1995). Hypothalamic-pituitary-adrenal system function in patients with Alzheimer's Disease. *Neurobiol. Aging* **16,** 205–209.

Kaye, J. A., Swihart, T., Howieson, D., Dame, A., Moore, M. M., Karnos, T., Camicioli, R., Ball, M., Oken, B., and Sexton, G. (1997). Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. *Neurology* **48,** 1297–1304.

Kirschbaum, C., Wolf, O. T., May, M., Wippich, W., and Hellhammer, D. H. (1996). Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci.* **58,** 1475–1483.

Kolb, B., and Wishaw, I. Q. (1985). *Fundamentals of Human Neuropsychology,* 2nd ed. Freeman, New York.

Lanthier, A., and Patwardhan, V. V. (1986). Sex steroids and 5-en-3-hydroxysteroids in specific regions of the human brain and cranial nerves. *J. Steroid Biochem.* **25,** 445–449.

Leblhuber, F., Neubauer, C., Peichl, M., Reisecker, F., Steinpartz, F. X., Windhager, E., and Dienstl, E. (1993). Age and sex differences in dehydroepiandrosterone sulfate (DHEAS) and Cortisol (CRT) plasma levels in normal controls and Alzheimer's disease (AD). *Psychopharmacology* **111,** 23–26.

Leblhuber, F., Windhager, E., Reisecker, R., Steinparz, F. X., and Dienstl, E. (1990). Dehydroepiandrosterone sulphate in Alzheimer's Disease. *Lancet* **336,** 449.

Maeda, K., Tanimoto, K., Terada, T., Shintani, T., and Kakigi, T. (1990). Elevated urinary free cortisol in patients with dementia. *Neurobiol. Aging* **12,** 161–163.

Majewska, M. D. (1995). Neuronal action of dehydroepiandrosterone: Possible roles in brain development, aging, memory and affect. *In* F. L. Bellino, R. A. Daynes, P. J. Horsby, D. H. Lavrin, and J. E. Nestler (Eds.), *Annals of the New York Academy of Sciences, 774: Dehydroeipandrosterone (DHEA) and Aging.* (pp. 111–120).

Majewska, M. D., Demirgoren, S., Spivak, C. E., and London, E. D. (1990). The neurosteroid dehydroepiandrosterone sulfate is an antagonist of the $GABA_A$ receptor. *Brain Res.* **526,** 143–146.

McIntosh, M. K., and Berdanier, C. D. (1988). Differential effects of adrenalectomy and starvation refeeding on hepatic lipogenic responses to dehydroepiandrosterone and glucocorticoid in BHE and Sprague-Dawley rats. *J. Nutrit.* **118,** 1011–1017.

McKhann, G., Drachmann, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34,** 939–944.

Meyer, J. H., and Gruol, D. L. (1994). Dehydroepiandosterone sul-

fate alters synaptic potentials in area CA1 of the hippocampal slice. *Brain Res.* **633,** 253–261.

Moscovitch, M., and Winocur, G. (1992). The neuropsychology of memory and aging. *In* F. I. M. Craik and T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition*, pp. 315–371. Earlbaum, Hillsdale, NJ.

Nasman, B., Olsson, T., Fagerlund, M., Eriksson, S., Viitanen, M., and Carlstrom, K. (1996). Blunted adrenocorticotropin and increased adrenal steroid response to human corticotropin-releasing hormone in Alzheimer's Disease. *Biol. Psychiatry* **39,** 311–318.

Nasman, B., Olsson, T., Viitanen, M., and Carlstrom, K. (1995). A subtle disturbance in the feedback regulation of the hypothalamic-pituitary-adrenal axis in the early phase of Alzheimer's Disease. *Psychoneuroendocrinology* **20,** 211–220.

O'Brien, J. T., Ames, D., Schweitzer, I., Colman, P., Desmond, P., and Tress, B. (1996). Clinical and magnetic resonance imaging correlates of hypothalamic-pituitary-adrenal axis function in depression and Alzheimer's Disease. *Br. J. Psychiatry* **168,** 579–587.

O'Brien, J. T., Ames, D., Schweitzer, I., Mastwyk, M., and Colman, P. (1996). Enhanced adrenal sensitivity to adrenocorticotrophic hormone (ACTH) is evidence of HPA axis hyperactivity in Alzheimer's Disease. *Psychol. Med.* **26,** 7–14.

Roberts, E., Bologna, L., Flood, J. F., and Smith, G. E. (1987). Effects of dehydroepiandrosterone and its sulfate on brain tissues in culture and on memory in mice. *Brain Res.* **406,** 357–362.

Rudman, D., Shetty, K. R., and Mattson, D. E. (1990). Plasma DHEAS in nursing home men. *J. Am. Geriatrics Soc.* **38,** 421–427.

Sapolsky, R. M., Krey, L. C., and McEwen, B. S. (1986). The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocrine Rev.* **7,** 284–301.

Sapolsky, R. M., Uno, H., Rebert, C. S., and Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J. Neurosci.* **10,** 2897–2902.

Spath-Schwalbe, E., Dodt, C., Dittmann, J., Schuttler, R., and Fehm, H. L. (1990). Dehydroepiandrosterone sulphate in Alzheimer's Disease. *Lancet* **i,** 14112.

Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99,** 195–231.

Starkman, M. N., Gebarski, S. S., Berent, S., and Schteingart, D. E. (1992). Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol. Psychiatry* **32,** 756–765.

Sunderland, T., Merril, C. R., Harrington, M. G., Lawlor, B. A., Molochan, S. E., Martinez, R., and Murphy, D. L. (1989). Reduced plasma DHEA concentrations in Alzheimer's Disease. *Lancet* **Sept. 2,** 570.

Svec, S., and Lopez-S, A. (1989). Antiglucocorticoid actions of dehydroepiandrosterone and low concentrations in Alzheimer's disease. *Lancet* **ii,** 1335–1336.

Swabb, D. F., Raadsheer, F. C., Endert, E., Hofman, M. A., Kamphorst, W., and Ravid, R. (1994). Increased cortisol levels in aging and Alzheimer's Disease in postmortem cerebrospinal fluid. *J. Neuroendocrinol.* **6,** 681–687.

Touitou, Y., Sulon, J., Bogdan, A., Touitou, C., Reinbergy, A., Beck, H., Sodoyex, J. C., Demey-Ponsart, E., and Van Cauwenberge, H. (1982). Adrenal circadian system in young and elderly human subjects: A comparative study. *J. Endocrinol.* **93,** 201–210.

Uno, H., Lohmiller, L., Thieme, C., Kemnitz, J. W., Engle, M. J., Roecker, E. B., and Farrell, P. M. (1990). Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. *Dev. Brain Res.* **53,** 157–167.

Uno, H., Tarara, R., Else, J. G., Suleman, M. A., and Sapolsky, R. M. (1989). Hippocampal damage associated with prolonged and fatal stress in primates. *J. Neurosci.* **9,** 1705–1711.

Vermeulin, A. (1995). Dehydroepiandrosterone sulfate and aging. *Ann. N.Y. Acad. Sci.* **774,** 121–127.

Weiner, M. F., Vobach, S., Svetlik, D., and Risser, R. C. (1993). Cortisol secretion and Alzheimer's Disease progression: A preliminary report. *Biol. Psychiatry* **34,** 158–161.

Wechsler, D. (1945). A standardized memory scale for clinical use. *J. Psychol.* **19,** 87–95.

West, M. J., Coleman, P. D., Flood, D. G., and Troncoso, J. C. (1994). Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet* **344,** 769–772.

Wilson, B. A., Cockburn, J., and Baddeley, A. D. (1985). *The Rivermead Behavioural Memory Test.* Thames Valley Test Company, Titchfield.

Wilson, B. A., Cockburn, J., Baddeley, A. D., and Hiorns, R. (1989). The development and validation of a test battery for detecting and monitoring everyday memory problems. *J. Clin. Exp. Neuropsychol.* **11,** 855–870.

Wolkowitz, O. M., Reus, V. I., Roberts, E., Manfredi, F., Chan, T., Raum, W. J., Ormiston, S., Johnson, R., Canick, J., Brizendine, L., and Weingartner, H. (1997). DHEA treatment of depression. *Biol. Psychiatry* **41,** 311–318.

Wooley, C. S., Gould, C., and McEwen, B. S. (1990). Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res.* **531,** 225–231.

Yanase, T., Fukahori, M., Taniguchi, S., Nishi, Y., Sakai, Y., Takayanagi, R., Haji, M., and Nawate, H., (1996). Serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) in Alzheimer's Disease and in cerebrovascualr dementia. *Endocrine J.* **43,** 119–123.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lun, O., Huang, V., Adey, M., and Leirer, V. (1983). Development and validation of a geriatric depression screening scale. *J. Psychiatric Res.* **17,** 37–49.

Yoo, A., Harris, J., and Dubrovsky, B. (1996). Dose-response study of dehydroepiandrosterone sulfate on dentate gyrus long-term potentiation. *Exp. Neurol.* **137,** 151–156.