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A Prospective Study on Cortisol, Dehydroepiandrosterone Sulfate, and Cognitive Function in the Elderly

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ABSTRACT

The objective of this study was to investigate the relation between the peripheral concentrations of the adrenal steroid hormones cortisol and dehydroepiandrosterone sulfate (DHEAS) and cognitive impairment and decline. A prospective study design was used. The setting was a suburb of Rotterdam, The Netherlands. The study population consisted of a sample of 189 healthy participants from the population-based Rotterdam Study, aged 55–80 yr, who were invited for an additional examination. Follow-up examinations took place 1.9 yr after baseline, on the average. We determined fasting blood levels of DHEAS before dexamethasone administration and of cortisol and corticosteroid-binding globulin before and after the administration of 1 mg dexamethasone overnight. The 30-point Mini-Mental State Examination (MMSE) was used to assess cognition. The associations with cognitive impairment (MMSE score of <26; 6% of the sample) and cognitive decline (drop in MMSE score of >1 point/yr; 24%) were estimated using logistic regression, with adjustment for age, sex, education, and depressive symptoms. An increase of 1 SD in the estimate of free cortisol (SD = 30.3) was associated with cognitive impairment, although not significantly [odds ratio (OR) = 1.5; 95% confidence interval (CI), 0.9–2.4]. A 1 SD increase in the natural logarithm of cortisol after the administration of 1 mg dexamethasone (SD = 0.68) was associated with an OR for cognitive decline of 1.5 (95% CI, 1.0–2.3). A 1 SD increase in DHEAS (SD = 2.10 μmol/L) was inversely, but nonsignificantly, related to cognitive impairment (OR = 0.5; 95% CI, 0.2–1.1) and cognitive decline (OR = 0.6; 95% CI, 0.4–1.1). The ratio of free cortisol over DHEAS was significantly related to cognitive impairment (OR = 1.8; 95% CI, 1.0–3.2). This prospective study among healthy elderly subjects suggested that basal free cortisol levels were positively related to cognitive impairment, and cortisol levels after dexamethasone treatment were related to cognitive decline. There was an inverse, but nonsignificant, association between DHEAS and cognitive impairment and decline. (*J Clin Endocrinol Metab* **83:** 3487–3492, 1998)

CORTISOL and dehydroepiandrosterone (DHEA) are adrenal steroid hormones. In animal studies, these hormones have been shown to have multiple effects on the function of the hippocampus, which is involved in learning and memory processes (1, 2). These adrenal steroids may thus be associated with cognitive impairment, which is a major symptom of dementia.

Hypothalamo-pituitary-adrenal (HPA) axis overactivity, which is related to stress and possibly also to aging, leads to increased cortisol levels (3). Sustained cortisol exposure in rodents and primates results in damage of the hippocampus (4). In human studies, increased cortisol levels and HPA axis overactivity have been associated with cognitive impairment and dementia (3, 5–11). Only a few studies have investigated the longitudinal association between cortisol and cognitive function. Lupien *et al.* (5) found a relationship between increases in cortisol levels over time and cognitive impairment in a small sample of healthy elderly. Among 194 healthy participants of the MacArthur Field Study, an association was observed between increasing cortisol levels and cognitive decline in women, but not in men (6).

DHEA and its sulfate, DHEAS, are regarded as markers of aging (12). In animal experiments DHEAS has been shown to enhance neuronal and glial survival and differentiation in culture (13, 14), and injection of DHEAS into the brains of mice improved long term memory (13). DHEAS may act directly on the hippocampus, as it has been shown to enhance the magnitude of hippocampal primed burst (2) and long term potentiation (15). There are a number of case-control studies on the association between DHEAS and Alzheimer's disease; however, these yielded conflicting results (16–18). In one prospective population-based study, there was no consistent association between DHEAS and subsequent cognitive function (19).

We examined the cross-sectional and longitudinal effects of peripheral levels of the steroid hormones cortisol and DHEAS on cognitive impairment and decline in a sample of participants from the prospective population-based Rotterdam Study.

Subjects and Methods

Study population

The Rotterdam Study is a single center prospective population-based study (20) designed to investigate determinants of chronic disabling

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diseases in the elderly. The conduct of the study was approved by the medical ethics committee of Erasmus University, and written consent was obtained from all participants. All residents of Ommoord, a suburb in Rotterdam, aged 55 yr or over, including those living in homes for the elderly, were invited to participate. The baseline examinations started in May 1990 and continued until June 1993. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate. During a home visit, trained interviewers administered a questionnaire, covering, among other areas, socio-demographic background, medical history, and medication use. This was followed by 2 clinical examinations at the research center, including neuropsychological testing. The follow-up examination started in September 1993 and lasted until December 1994. Of the 7,215 subjects who were still alive, 6,315 (88%) agreed to participate.

For the present additional examination, a random sample (n = 219) was taken of participants from the Rotterdam Study, who had completed the baseline examination in the preceding 6 months, were between 55–80 yr old, and had no history of psychiatric or endocrine diseases, including diabetes mellitus treated with medication. There were no differences in age, sex, or education between our sample and the other participants of the Rotterdam Study in the same age range and without dementia or known diabetes mellitus. The mean baseline Mini-Mental State Examination (MMSE) score was higher in our sample [28.1 (SD = 1.6) *vs.* 27.6 (SD = 1.9); $P = 0.002$].

Blood measurements

Blood was obtained after an overnight fast at the research center between 0800–0900 h and was allowed to coagulate for 30 min. Serum was separated by centrifugation and quickly frozen in liquid nitrogen. In addition, an overnight dexamethasone suppression test was performed (21). Participants were given a tablet of 1 mg dexamethasone and were instructed to take this at 2300 h. The next morning, at the same time as on the previous day, a fasting blood sample was obtained in the same manner. Measurements included cortisol and corticosteroid-binding globulin (CBG) before and after dexamethasone, and DHEAS before dexamethasone. CBG levels were estimated using a double antibody RIA with murine monoclonal antibodies against human CBG and radioiodinated CBG as the tracer (Medgenix Diagnostics, Brussels, Belgium). Variation coefficients for this assay were below 12%. Cortisol and DHEAS were estimated using Coat-A-Count kits provided by Diagnostic Products (Los Angeles, CA). These kits use immobilized antibodies against the respective steroids and radioiodinated tracers. The specificity of the antibodies was high. Of the endogenous steroids, 11-deoxycortisol showed the highest cross-reaction in the cortisol assay (11.4%); for the DHEAS assay, estrone sulfate had the highest cross-reactivity (0.56%). Variation coefficients for these assays were less than 12.5% for cortisol and less than 6.0% for DHEAS. Two measures of cortisol were examined, *i.e.* total cortisol and an estimation of free circulating cortisol, using a formula that included cortisol, CBG, and albumin concentrations, according to the method of Södergard *et al.* (22) The correlation coefficient of free cortisol with total cortisol was 0.61. Suppression of total cortisol after dexamethasone treatment can be regarded as a measure of negative feedback sensitivity of the HPA axis to glucocorticoids. Because the cortisol level after dexamethasone administration was not normally distributed, we used the natural logarithm for further calculations. We also investigated the ratio of free cortisol over DHEAS, because DHEAS may antagonize the actions of cortisol (23–25).

MMSE

Global cognitive function was tested with the Dutch version of the 30-point MMSE during the (first) visit to the research center (26). It was administered by specially trained research assistants. The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction. This screening test was originally created for a clinical setting (26) and is extensively used in epidemiological studies (27). Although it tests mainly cortical functions, these are important to daily functioning and are severely affected in dementia. If less than 4 individual items (of 20) were not answered by the subject, these were rated as errors (28). If a subject did not answer 4 or more individual items, the total MMSE score was considered missing. Cognitive impairment was defined as a score below 26 (29), and cognitive decline as a drop in the MMSE score of more than 1 point/yr (approximately >1 SD). The mean follow-up time between the first and second MMSEs was 1.9 yr (SD = 0.23).

Other measurements

A number of factors were considered as possible confounding variables: age, sex, and education, classified into four levels: completed primary education; lower vocational or general education; intermediate vocational or general education; and higher vocational training, college, or university (Unesco, Paris, France). For all analyses on cortisol we adjusted for symptoms of depression. Symptoms of depression were assessed at the follow-up examination with translated versions of the Center for Epidemiologic Studies Depression Scale (CES-D) (30) in the first 99 participants and the Hospital Anxiety and Depression Scale (HADS) (31) in the last 46 participants. In 44 participants, there was no (complete) depression scale available; these subjects were significantly older and had a lower baseline MMSE score, but the measures of cortisol and DHEAS were not different from those in subjects with data on the depression scale. We used the standard cut-off of 16 or above for the CES-D (30) and a cut-off of 8 or above for the HADS (after exclusion of the anxiety items) (31) to identify subjects with depressive symptoms. Body mass index (weight/height^2) was considered a possible confounding factor, because low food intake and low body weight might induce relative resistance to the dexamethasone suppression test, and a low body mass index has been related to dementia (32). In the analyses of cognitive decline, we also adjusted for the baseline MMSE score.

Statistical analysis

One subject who was using hydrocortisone and one subject who had a greatly elevated DHEAS level (15.1 μmol/L) were excluded from the analyses. Complete information on cognitive function at baseline was available for 189 subjects. Follow-up data on cognitive decline were available for 169 subjects. For the analyses of cortisol, estrogen users (n = 2) and users of antiepileptics (n = 4) were excluded, as these medications can influence cortisol and/or CBG levels and sensitivity to dexamethasone.

Differences in baseline characteristics according to cognitive impairment and according to steroid hormone levels above and below the median were tested with the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables. Logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the risk of cognitive impairment and decline. The independent variables of interest were total cortisol, free cortisol, the natural logarithm of cortisol after dexamethasone administration, DHEAS, and the free cortisol/DHEAS ratio. We included confounding variables in the model. A missing indicator variable was created for the missing values for the depressive symptoms. We also investigated whether there was effect modification by gender (33) by including the product term as a covariate in the model. All tests were two sided, and $P < 0.05$ was considered statistically significant. Data analyses were performed using BMDP statistical software (BMDP Statistical Software, Inc., Los Angeles, CA).

Results

The mean age of the participants at baseline was 67.3 yr (SD = 5.7). Fifty percent of the sample was female. The median baseline MMSE score was 28 (range, 20–30), and 6.3% of the subjects were cognitively impaired. The mean drop in the MMSE per yr was 0.22 (SD = 0.95); 24% showed a drop in the MMSE score of more than one point per yr. There were no differences in age, sex, or cortisol and DHEAS levels between subjects with and subjects without complete information on cognitive function. Compared with subjects who attended the follow-up examination (n = 169), those who did not (n = 20) were older (71.1 *vs.* 66.9 yr; $P = 0.002$) and had a lower median MMSE score (27 *vs.* 28; $P = 0.001$). There were no differences in cortisol, CBG, or DHEAS levels between these groups.

Subjects with cognitive impairment were older, more often

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had symptoms of depression at follow-up, and had lower DHEAS concentrations and higher ratios of cortisol to DHEAS (Table 1). Subjects with a total cortisol level above the median (506.5 nmol/L) had a lower body mass index than those with a total cortisol level below the median [25.8 (SD = 3.8) *vs.* 27.1 (SD = 3.4); $P = 0.01$]. Subjects with a free cortisol concentration above the median were older and less often female (Table 2). Participants with DHEAS levels below the median were more often female (66% *vs.* 34%; $P < 0.001$).

Multiple logistic regression analyses showed that there was no association between total cortisol and cognitive impairment or decline after adjustment for age, sex, educational level, and depressive symptoms at follow-up (Table 3). The OR for the association with cognitive impairment according to a 1 SD increase in the free cortisol level (SD = 30.3) was 1.5 (95% CI, 0.9–2.4). CBG levels were not associated with cognitive function (data not shown). The natural logarithm of cortisol after dexamethasone treatment was associated with a significantly increased risk of cognitive decline (adjusted OR per SD increase = 1.5; 95% CI, 1.0–2.3). The DHEAS level was inversely, but not significantly, related to cognitive impairment (OR = 0.5; 95% CI, 0.2–1.1) and decline (OR = 0.6; 95% CI, 0.4–1.1). As expected, the ratio of cortisol over DHEAS was significantly associated with cognitive impairment (OR = 1.8; 95% CI, 1.0–3.2). Adjustment for body mass index did not change these estimates. Exclusion of subjects with depressive symptoms (n = 14) essentially yielded the same estimates, but CIs were wider because of the smaller sample size (results not shown). There were no significant interactions between the variables of interest and sex.

Additionally, we investigated the association with the memory item of the MMSE (34), as cortisol and DHEAS are believed to influence the function of the hippocampus, which is involved in memory processes. Fifty-three percent of the subjects scored less than three points on the recall of three words. There was no significant association of free cortisol or DHEAS with memory impairment (OR = 1.0; 95% CI, 0.7–1.4 and OR = 1.2; 95% CI, 0.9–1.7, respectively).

Discussion

In this prospective study of healthy older subjects, we investigated the association between the peripheral concentrations of two adrenal steroid hormones and cognitive function. The results suggest that a high free cortisol level was related to cognitive impairment. The cortisol level after dexamethasone administration, as a measure of negative feedback sensitivity of the HPA axis, was associated with an increased risk of cognitive decline. DHEAS, which may antagonize the actions of glucocorticoids, appeared to be inversely related to cognitive impairment and decline, although this was not significant. The ratio of cortisol to DHEAS was significantly related to cognitive impairment. These associations could not be explained by differences in age, sex, education, depressive symptoms at follow-up, or body mass index. There was no relationship between the adrenal hormones and the specific memory item of the MMSE.

Methodological issues

It could be argued that selection bias may have affected the validity of our results. Participants were healthy and rela-

TABLE 2. Characteristics according to free cortisol above and below the median (The Rotterdam Study)

	Free cortisol[a]		*P* value[b]
	<23.0 nmol/L (n = 91)[c]	≥23.0 nmol/L (n = 92)[c]	
Mean age (yr)	66.2 (5.8)[d]	68.4 (5.5)	0.04
Sex (% female)	59	40	0.01
Only primary education (%)	34	29	0.30
Body mass index (kg/m^2)	26.2 (3.5)	26.7 (3.9)	0.75
Depressive symptoms at follow-up (%)	6	15	0.16

[a] Calculated, based on total cortisol, CBG, and albumin levels, as described by Södergard (22).
[b] By Mann-Whitney or χ^2 test.
[c] In total, six subjects were excluded because they were using estrogens or antiepileptics.
[d] The SD is in *parentheses*.

TABLE 1. Baseline characteristics according to cognitive impairment (The Rotterdam Study)

	Cognitive impairment[a]		*P* value[b]
	Absent (n = 177)	Present (n = 12)	
Mean age (yr)	67.1 (5.7)[c]	71.3 (4.0)	0.01
Sex (% female)	50	58	0.56
Only primary education (%)	32	42	0.72
Body mass index (kg/m^2)	26.4 (3.7)	26.2 (3.7)	0.86
Depressive symptoms at follow-up (%)	9	29	0.08
Mean cortisol (nmol/L)[d]	512 (134)	544 (142)	0.45
Mean free cortisol (nmol/L)[d,e]	31.7 (29.2)	48.1 (42.3)	0.16
Mean logarithm of cortisol after dexamethasone (nmol/L)[d]	3.12 (0.68)	3.32 (0.61)	0.29
Mean dehydroepiandrosterone sulfate (μmol/L)	3.36 (2.09)	2.25 (2.00)	0.03
Mean free cortisol/dehydroepiandrosterone sulfate ratio (nmol/μmol)[d]	13.6 (17.8)	53.1 (98.8)	0.01

CBG, Corticosteroid-binding globulin.
[a] Defined as a Mini-Mental State Examination score of less than 26 at baseline.
[b] By Mann-Whitney or χ^2 test.
[c] The SD is in *parentheses*.
[d] Six subjects were excluded because they were using estrogens or antiepileptics.
[e] Calculated, based on total cortisol, CBG, and albumin levels, as described by Södergard (22).

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TABLE 3. Adjusted odds ratios (95% confidence intervals) for the risk of cognitive impairment and decline according to a 1 SD increase in cortisol and dehydroepiandrosterone sulfate

	SD	Risk of	
		Cognitive impairment[a] (n = 12/189)	Cognitive decline[a] (n = 40/169)
Total cortisol (nmol/l)[b]	140.1	1.2 (0.6–2.3)	0.9 (0.6–1.4)
Free cortisol (nmol/l)[b,c]	30.3	1.5 (0.9–2.4)	0.9 (0.6–1.4)
Cortisol after dexamethasone (nmol/L)[b,d]	0.68	1.1 (0.6–1.9)	1.5 (1.0–2.3)
Dehydroepiandrosterone sulfate (μmol/L)	2.10	0.5 (0.2–1.1)	0.6 (0.4–1.1)
Free cortisol/dehydroepiandrosterone sulfate ratio (nmol/μmol)[b]	31.5	1.8 (1.0–3.2)	0.9 (0.5–1.6)

Odds ratio was adjusted for age, sex, education, and symptoms of depression (and baseline Mini-Mental State Examination score in the analyses of cognitive decline).

[a] Cognitive impairment: Mini-Mental State Examination score of less than 26 at baseline; cognitive decline: drop in the Mini-Mental State Examination score of more than one point per yr.

[b] Six subjects were excluded because they were using estrogens or antiepileptics.

[c] Calculated, based on total cortisol, CBG, and albumin levels, as described by Södergard (22).

[d] After logarithmic transformation.

tively young, and follow-up duration was short, leading, on the average, to only a small drop in the MMSE score. Combined with the small sample size, this would only impede the detection of a significant modest association. Furthermore, the 20 subjects in our sample without a MMSE score at follow-up (due to death or nonresponse) had a significantly lower baseline MMSE score and were older than subjects who were not lost to follow-up, but there were no differences in cortisol or DHEAS levels, making selective loss to follow-up less likely.

The MMSE was used to assess cognitive function. Although the MMSE is developed as a global clinical screening test, it is a valid and reliable indicator of cognitive impairment, with a test-retest reliability generally between 0.80–0.95 (35). The MMSE was not originally created to measure cognitive decline and may be less sensitive to small changes in cognitive function. However, the reliability of the change in the MMSE after 1 yr or more in patients with dementia was 0.74, which is reasonable (36).

Another methodological issue is that we may not have adequately adjusted for depression. Depression is strongly associated with cognitive impairment (37) and also with increased cortisol levels and diminished suppression of cortisol after dexamethasone treatment (38). Thus, depression is potentially an important confounder or intermediate. The use of two different questionnaires might not have been optimal. The CES-D was designed for epidemiologic research, whereas the HADS was designed for a clinical setting. Both have been validated, but the CES-D is probably more reliable, especially in this setting (30). Furthermore, we adjusted for symptoms of depression at follow-up and not at baseline. Thus, there may be residual confounding in our results for cognitive impairment, but less in our results for cognitive decline.

Cortisol and HPA axis overactivity

Our results confirm the findings of the few prospective studies that have investigated the association between cortisol and cognition (5, 6). A prospective study among 19 healthy elderly subjects showed a relationship between increases in basal cortisol levels over time and 2 out of 17 cognitive measures, *i.e.* explicit memory and selective attention (5). Although the researchers used a conservative test for significance, they did not adjust for age or other possible confounders. Among 194 healthy elderly participants from the MacArthur Field Study, an association was observed between a rise in cortisol levels and a decline in memory performance, but only in women (6). No associations were found with abstraction and spatial ability.

It has been shown that HPA axis overactivity is more frequent among patients with Alzheimer's disease (10). Also, in early dementia, a decreased sensitivity to glucocorticoid feedback, using low doses of dexamethasone, has been shown. (11) In addition, cortisol has been associated with severity of dementia and cognitive decline in demented patients (8, 9). Furthermore, patients with Cushing's syndrome more often present with cognitive impairment (39). Finally, one of the side-effects of treatment with synthetic corticosteroids is cognitive deterioration (40).

The relation between cortisol and cognitive function may be due to different effects of cortisol on the hippocampus. In experimental animal studies, administration of corticosterone led to a decrease in the number of pyramidal cells in the hippocampus (4), soma shrinkage (41), and a reduction in the number and length of dendritic branches (42). In patients with Alzheimer's disease and Cushing's syndrome, higher cortisol levels were associated with lower hippocampal volumes (43, 44). Therefore, stress-induced HPA axis overactivity and increased cortisol levels may cause hippocampal damage and, subsequently, cognitive decline. On the other hand, hippocampal damage, *i.e.* as a result of Alzheimer pathology, may lead to HPA axis overactivity and increased cortisol levels, because hippocampal neurons are involved in the negative feedback of glucocorticoid secretion. This is described as the glucocorticoid cascade of aging (45). Of course, both sequences of events may also proceed at the same time.

DHEAS

There has been one previous prospective population-based study that investigated the relationship between DHEAS and subsequent cognitive impairment, in which no consistent association was found (19). The follow-up duration was quite long (16 yr), and subjects with lower DHEAS levels at baseline had a higher mortality, suggesting that there may have been selective survival bias. There have been

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a number of case-control studies on DHEAS levels and Alzheimer's disease. Some found that Alzheimer's disease patients had lower DHEAS levels than controls (16, 46), but this could not be confirmed by others (17, 18). These studies were mostly based on small numbers of patients and controls, thereby increasing the possibility of false negative results. A small pilot study among patients with major depression showed improvement of selective memory functions after DHEA administration (47).

Serum levels of DHEAS are the highest of all steroids in humans. Cerebrospinal fluid levels of DHEA and DHEAS correlated significantly with peripheral concentrations (48). There are a number of plausible mechanisms for an association between DHEAS and cognitive function. Animal experiments showed that DHEAS can enhance neuronal and glial survival and differentiation in culture (13, 14), perhaps because DHEAS acts as a γ-aminobutyric acid antagonist (49). Furthermore, DHEAS can improve memory in mice (13), which may be due to a direct effect of DHEAS on hippocampal neurons, through enhancement of the magnitude of the hippocampal primed burst (2) and long term potentiation (15) in rats. Another explanation for the association with cognition may be that DHEA can be transformed into estrogens in peripheral tissues. (50) The risk of Alzheimer's disease has been shown to be reduced in women using estrogen compared with those who did not (51). Furthermore, DHEA may act as a glucocorticoid antagonist, as described for a number of systems (23–25). Therefore, a high ratio of cortisol over DHEAS may especially lead to hippocampal damage (15) and thus to cognitive impairment. Indeed, the present study showed a significant association between the cortisol/DHEAS ratio and cognitive impairment. Finally, DHEAS may be regarded as a marker of general health status and could therefore be related to cognitive function.

Conclusion

In conclusion, this small prospective study in healthy older subjects indicates that there may be an association between adrenal steroid hormones and cognitive function. Free cortisol appeared to be associated with cognitive impairment, and cortisol after dexamethasone treatment increased the risk of cognitive decline. DHEAS was inversely, but not significantly, associated with cognitive impairment and decline. However, these results are preliminary, and larger follow-up studies of longer duration are needed to verify these findings. It remains unclear whether the observed cognitive impairment and decline are the direct result of the altered levels of the peripheral steroids or *vice versa*, or if another factor influences both adrenal steroid biosynthesis and the processes leading to reduced cognitive function.

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