Psychopharmacology (1993) 111:23–26

Psychopharmacology
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Age and sex differences of dehydroepiandrosterone sulfate (DHEAS) and cortisol (CRT) plasma levels in normal controls and Alzheimer's disease (AD)

F. Leblhuber[1], C. Neubauer[1], Marianne Peichl[1], F. Reisecker[1], F. X. Steinparz[1], E. Windhager[1], and Elisabeth Dienstl[2]

[1]Department of Gerontology, Wagner-Jauregg-Krankenhaus, Wagner-Jauregg-Weg 15, A-4020 Linz, Austria
[2]Institute of Nuclear Medicine, Allgemeines Krankenhaus Linz, A-4020 Linz, Austria

Received February 18, 1992 / Final version October 20, 1992

Abstract. In 50 healthy subjects (23 female, 27 male, aged 18–81) and 24 patients with Alzheimer's disease (AD) (11 female, 13 male, aged 58–88) DHEAS and CRT plasma levels were studied. In normal subjects there was a clear negative correlation of DHEAS to age, while no significant age correlated decrease of CRT plasma levels was found. There was a significant decrease in the DHEAS/CRT ratio in elderly controls (aged > 60) as compared to young individuals (aged < 45). Overall there was a trend to lower DHEAS/CRT ratios in AD patients compared to age matched controls out of the total group of normals ($P < 0.1$), there was a significant decrease of this ratio in female AD patients ($P < 0.05$), compared to age matched female controls, but there was none in male Alzheimers; furthermore there was a significant difference in CRT plasma levels between female AD patients and age matched female controls ($P < 0.01$) and between female and male AD patients ($P < 0.05$). Considering the antiglucocorticoid effects of DHEAS, this ratio may account for its protective effect against hippocampal degeneration caused by glucocorticoids and possibly for the higher rate of AD in females.

Key words: DHEAS/CRT serum level – DHEAS/CRT ratio – Sex, age difference – Alzheimer's disease

In previous animal studies, hippocampal damage due to chronic glucocorticoid administration was reported and clinical relevance of these results in dementia was suggested (Sapolsky et al. 1986; Wolkowitz et al. 1990) with a possible role of dysfunction of the hypothalamic-pituitary-adrenal axis (HPAA) (Gurevich et al. 1990; Dodt et al. 1991).

In an earlier pilot study, Sunderland et al. (1989) demonstrated reduced plasma concentrations of DHEAS in Alzheimer's disease (AD) and discussed the possible importance of this hormone in the central nervous system. In a number of pilot studies (Cuckle et al. 1990; Späth-Schwalbe et al. 1990; Dodt et al. 1991) including our own results (Leblhuber et al. 1990, 1991a), no difference in mean serum levels between demented and mentally healthy aged controls was seen. On the other hand, DHEAS was shown to block enzymatic effects of glucocorticoids in animal models (McIntosh and Berdanier 1988; Svec and Lopez-S 1989), thus antiglucocorticoid actions of DHEAS may be postulated, though plasma levels of DHEAS may probably not reflect brain concentrations (Schneider et al. 1992).

In the present study, the plasma profiles of DHEAS and CRT were investigated in different age groups of normal individuals and in a number of drug-free patients with AD to study their specific role in primary degenerative dementia.

Material and methods

Fifty normal controls (23 females, aged 18–81; 27 males, aged 21–81) and 24 drug-free patients with AD (11 females, aged 58–86; 13 males, aged 62–88), randomly selected from our Department of Gerontology, were studied. All control subjects had normal mental status (examined independently by two of the investigators) with no clinical signs of depression or dementia, there were no clinical signs or routine laboratory parameters of infection. From the total of 50 normals, a subgroup of 20 age-matched normal subjects were compared to 24 AD subjects. Informed consent was obtained from all individuals, or in case of the AD patients from one of their relatives. The study was approved by the hospital ethics committee.

Mini mental status (MMS) was performed in all AD patients. None of the females studied was pregnant or took contraceptives. For characteristics of AD patients and controls see Table 1. Diagnosis of AD was established by DSM-III-R; X-ray CT and SPECT was performed in all AD patients to confirm the diagnosis, but detailed SPECT measurements calculating different regions of interest were not performed. Routine laboratory tests, folic acid, vitamine B_{12}, T_3, T_4 and TSH were also performed in all patients. Blood samples for DHEAS and CRT plasma measurements were obtained at 8 a.m. after an overnight fast, stored at −20 °C and tested in duplicate in the same assay, using commercial kits (DHEAS – Diagnostic Products Corporation, CRT – Abbot, method tdx); the coefficient of variation between assays was 10.5% (DHEAS) and 4.8% (CRT), the intraassay coefficient of variation ranged from

Correspondence to: F. Leblhuber

Table 1. Patient's characteristics, DHEAS and CRT measures and DHEAS/CRT ratios

		N	AGE		CRT μg/ml		DHEAS ng/dl					Ratio	
			mv	sd	mv	sd	mv	sd	med	lqu	uqu	mv	sd
AD	Male	13	76.3	7.1	18.6	4.1	847	711	611	528	1170	4.4	3.4
	Female	11	78.8	5.0	24.4	6.0	430	272	360	217	716	2.1	1.9
CO	Male	10	75.3	8.6	16.5	4.5	796	583	546	343	827	5.0	3.9
	Female	10	75.3	7.0	17.1	4.6	735	634	536	371	1128	4.8	4.5
CY	Male	17	32.5	7.9	18.1	4.0	3468	1486	3081	2133	4034	19.5	7.8
	Female	13	35.0	5.6	19.7	4.8	2114	946	2431	1501	2634	10.7	4.4

N = number of patients and age and sex matched controls out of the total of 50 normals
AD = Alzheimer's disease
CO = controls, old (> 60)
CY = controls, young (< 45)
mv = mean value
sd = standard deviation
med = median
lqu = lower quartile
uqu = upper quartile

4.8% at 306 ng/ml to 5.5% at 5823 ng/ml for DHEAS and from 3.5% at 4.3 μg/dl to 2.0% at 39.9 μg/dl for CRT. The DHEAS/CRT ratio was calculated in all subjects studied. Data were analized by Student's *t*-test and by nonparametric Mann-Whitney *U* test. In a supplementary pilot study, repeated morning CRT levels were performed in an additional ten drug-free AD patients (five female, five male, aged 70.5 ± 7.0) and ten age and sex matched normals to find out the variability of the 8 a.m. CRT level. Data were analyzed by Student's *t*-test for paired data.

Results

All AD patients showed diffuse cortical and subcortical atrophy without any focal lesion on CT, while SPECT images showed bilateral temporoparietal hypoperfusion in all of them. MMS was 5.2 ± 6.5, and there was no statistical difference in MMS between female and male AD subjects. No correlation was found between the MMS and the DHEAS ($r = -0.23$), the CRT level ($r = -0.04$) and the DHEAS/CRT ratio ($r = -0.21$); the DHEAS ($r = 0.01$), CRT ($r = 0.03$) levels and the DHEAS/CRT ratio ($r = 0.02$) did not correlate with the duration of symptoms. In all AD patients, routine laboratory tests including electrolytes, blood cell count, hemoglobin, hematocrit, platelet estimate, serum enzyme parameters, urine parameters, blood glucose, bilirubin, bicarbonate, creatinine, BUN, total protein, vitamin B_{12}, folic acid and T_3, T_4 and TSH were within normal limits. A strong negative correlation was found between age and DHEAS ($r = -0.8$ for females and $r = -0.7$ for males) in normals, as already reported previously (Leblhuber et al. 1990, 1991a), but no significant correlation was found between CRT plasma levels and age ($r = 0.01$ for females, $r = 0.2$ for males), as shown before (Leblhuber et al. 1991b): therefore, the DHEAS/CRT ratio dropped significantly in older subjects (aged > 60 years), as compared to young individuals (aged < 45 years), see Fig. 1. Repeated determinations of CRT morning levels in ten AD patients and ten age and sex matched controls showed low intraindividual variability (Pearson coefficient of variation 12% and 10%, respectively).

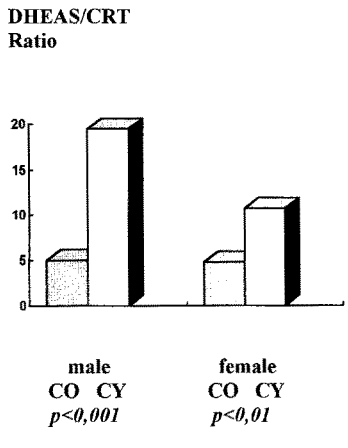

Fig. 1. Mean values of controls: young (*CY*), old (*CO*)

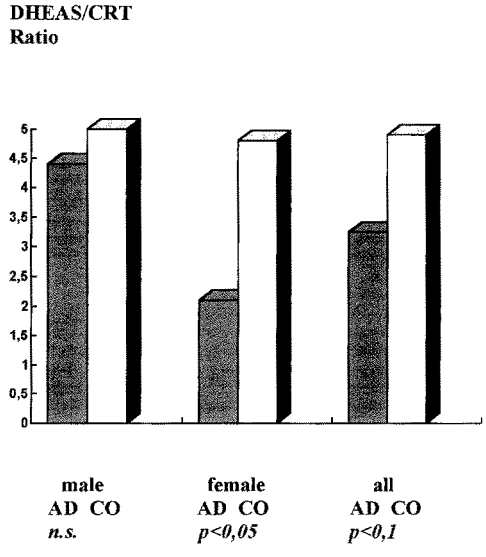

Fig. 2. Mean values of 20 age and sex matched controls (*CO*) and 24 Alzheimer patients (*AD*)

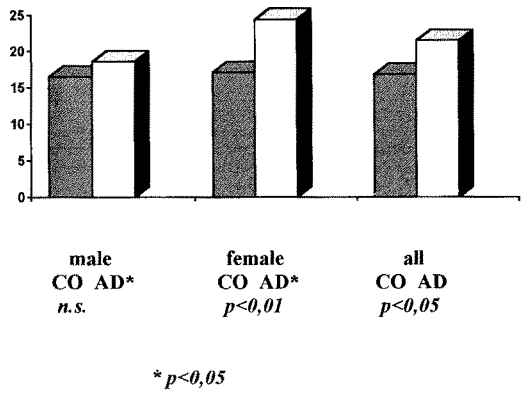

Fig. 3. Mean values of patients (*AD*) and age sex matched controls (*CO*)

A trend to a lower DHEAS/CRT ratio was found in AD patients as compared to age matched controls ($P < 0.1$); by calculating both sexes separately, a significant difference was found in the DHEAS/CRT ratio between female AD patients and age matched female controls ($P < 0.05$). No significant difference was seen between male AD subjects and an age matched cohort of male normals, see Fig. 2. Furthermore, a significant difference was found between the CRT levels of female AD subjects and age matched normal females ($P < 0.01$). However, no such difference could be traced between the respective male categories (see Fig. 3), and there was no difference in CRT plasma levels between female and male normals aged < 60 years. A significant difference of CRT was seen between female and male AD patients ($P < 0.05$), see Fig. 3.

Discussion

Gender and age differences in hormone parameters have already been described (Touitou et al. 1982, 1983; Lucey et al. 1991). DHEA is one of these, and is involved in maturing and aging processes. Its sulfonated form, DHEAS (water soluble), is the most abundant circulating steroid. Its age dependent decrease and its significant sexual dimorphism have already been described (Orentreich et al. 1984; Sunderland et al. 1989; Dodt et al. 1991). While a very similar age correlated regression of DHEAS in normals was seen in our own measurements (Leblhuber et al. 1990, 1991a), there was no significant decrease in DHEAS serum levels between demented and mentally healthy elderly in the study of Dodt and colleagues (1991) as well as our own series. The discrepancy between these results and those of Sunderland et al. (1989) could be explained in part by the fact that patients were on average 13 and 14 years older (Leblhuber et al. 1990; Dodt et al. 1991) than patients in the above mentioned paper (Sunderland et al. 1989), probably indicating different subtypes of AD (Greenwald et al. 1986). In addition, recent DHEAS measurements in AD in larger sample sizes still give conflicting results: while Näsman and coworkers (1991) found lower serum levels of DHEAS in their AD subjects, Schneider et al. (1992) could not delineate any difference between patients and controls.

Nevertheless, there are intriguing lines of evidence that DHEAS has effects on the central nervous system (Mohan 1989; Sunderland et al. 1989) and that some metabolic effects of glucocorticoids are antagonized by DHEAS (McIntosh and Berdanier 1988; Svec and Lopez-S 1989). There is evident CRT-related impairment of cognitive functions (Carpenter and Gruen 1982; Wolkowitz et al. 1990) and DHEAS can ameliorate cognitive deficits in animals (Flood et al. 1988). Therefore, provided that DHEA is an antiglucocorticoid also in man, the DHEAS/CRT ratio, first mentioned by Svec and Lopez-S (1989), may be a measure of the neurotoxic effects of endogenous glucocorticoids. Our results demonstrate a clear age correlated decrease of this ratio in normal female individuals ($P < 0.01$), which is even more pronounced in male individuals ($P < 0.001$), see Fig. 1.

Further gender differences were seen in AD subjects: a significant difference in CRT as well as in the DHEAS/CRT ratio was found in female ADs compared to age matched female controls ($P < 0.01$ and $P < 0.05$, respectively), while no such differences in these parameters were seen in males. These significant differences in females contribute to an overall trend towards a lower DHEAS/CRT ratio ($P < 0.1$) and higher CRT plasma levels ($P < 0.05$) in AD subjects, if both sexes are calculated together (see Figs 2 and 3); higher CRT levels in AD subjects were also described by Davis et al. (1986). Contrary to these results, other authors (Touitou et al. 1982, 1983; Dodt et al. 1991; Näsman et al. 1991) did not find major changes in plasma CRT between elderly demented and healthy individuals. A possible explanation for the discrepancy between our results in a cohort of drug-free AD subjects and the latter studies may be different subpopulations and age groups of patients with dementia with different diagnostic criteria: CT studies were performed in only half of the cases and different medication with possible diverse effects on the HPAA was given in the series of Näsman et al. (1991). In the series of Schneider and coworkers (1992) patients were described as mildly affected and mean age of patients was lower compared to our AD patients. The sample size of female and male cohorts was even smaller than ours in the studies of Touitou et al. (1982, 1983) and Dodt et al. (1991), probably causing these discrepancies.

In earlier epidemiological studies (Mölsä et al. 1982) rates of dementia were higher in females than in males, which could be only partly explained by demographic and social factors (Kay 1986). Thus, the sex difference in hormonal parameters (CRT and DHEAS/CRT ratio) could at least to some extent account for the phenomenon of female preponderance of dementias (Mölsä et al. 1982). Further studies in larger cohorts of different age and sex groups and a more detailed analysis of the HPAA in dementia including stimulation and suppression tests (Davis et al. 1986; Dodt et al. 1991; Lawlor et al. 1992) are needed to find out whether changes in the CRT plasma

levels and the DHEAS/CRT ratio are consistent endocrine abnormalities found in AD (Hermann et al. 1991).

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