NOTE

Serum Dehydroepiandrosterone (DHEA) and DHEA-Sulfate (DHEA-S) in Alzheimer’s Disease and in Cerebrovascular Dementia

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Abstract. A decreased concentration of dehydroepiandrosterone sulfate (DHEA-S) in patients with Alzheimer’s disease (AD) has been reported but is still controversial. In the present study, serum concentrations of DHEA and DHEA-S were determined in 19 patients with AD, 21 patients with cerebrovascular dementia (CVD) and 45 age- and gender matched elderly control individuals from the Japanese community at large. Serum concentrations of DHEA among controls, patients with AD and patients with CVD did not significantly differ from one another. However, patients with AD and patients with CVD were found to have lower concentrations of serum DHEA-S and a lower DHEA-S/DHEA ratio compared to normal control individuals. No significant difference was observed in the concentration of serum DHEA-S or the DHEA-S/DHEA ratio between patients with AD and those with CVD. These results suggest that reduced concentrations of serum DHEA-S may not be unique to AD, but instead reflect a common phenomenon in dementing diseases. However, since serum concentration of DHEA in these patients remained unchanged, the significance of DHEA in dementia remains unclear.

Key words: Dehydroepiandrosterone (DHEA), DHEA-sulfate, Alzheimer’s disease, Cerebrovascular dementia

DEHYDROEPIANDROSTERONE (DHEA) and its interconvertible sulfate ester, DHEA sulfate are abundant steroids that are produced primarily by the adrenal glands [1]. The plasma concentration of DHEA and DHEA-S increase during adrenarche, peak between the ages of 15 and 25, and then decrease steadily throughout life [1]. Although DHEA and DHEA-S have little, if any, intrinsic androgenic actions, it has been generally thought that these steroids exert their effect through metabolism to other steroids such as testosterone and estrogens. However, DHEA and DHEA-S have recently attracted wide-spread attention because several reports have clarified the beneficial effects of DHEA on obesity, lipid metabolism, atherosclerosis and diabetes mellitus [2].

Recently, administration of DHEA and DHEA-S to mice has been shown to enhance memory retention [3] and block the memory-impairing effects of scopolamine [4], thus suggesting another important effect of these steroids on the central nervous system, particularly in the prevention of dementia. Indeed, the serum concentration of DHEA-S in Alzheimer’s disease (AD) has been reported to be markedly reduced as compared with controls [5, 6]. A decreased concentration of DHEA may fail to protect partly degenerated or at-risk brain cells [5]. Since DHEA has been shown to have an anti-glucocorticoid effect [7], the mechanism may be partly explained by the excess effects of glucocor-
ticoid which is known to be neurotoxic to brain cells [7]. However, the exact concentrations of serum in DHEA-S must still be regarded as controversial, since five other studies found no difference in serum DHEA-S level between AD patients and controls [8–12]. All of the previous studies have focused only on circulating DHEA-S levels and have not yet examined another important index, namely serum DHEA levels in AD. In addition, circulating DHEA-S or the DHEA level has not been examined in other dementia-causing diseases.

In the present study, to reevaluate the significance of adrenal androgens in dementing diseases, we studied the concentrations of serum DHEA as well as DHEA-S in patients with AD and cerebrovascular dementia (CVD) in Japan.

### Materials and Methods

**Subjects**

Nineteen patients over the age of 60 with AD, and twenty-one with CVD, all of whom resided in the psychiatry department in Mitate Hospital (Fukuoka, Japan), and forty-five normal individuals participated in the study (Table 1). The diagnosis of AD and CVD in the patients were carried out by several psychiatrists in Mitate Hospital according to the American psychiatric Association's DSM-IV criteria [13]. The findings of computed tomography (CT) of the head were also taken into consideration for the differentiation of the two diseases. Namely, diffuse cerebral atrophy without cerebrovascular lesion was taken as suggestive of Alzheimer's disease, while cerebrovascular lesions such as multiple small infarctions in the cerebral cortex and/or small infarctions in basal ganglion favored the diagnosis of CVD. Serum chemistry examination failed to reveal liver or renal dysfunctions in any of the patients. Basic activities of daily life (such as walking and eating) were almost normal in the patients, although inability to perform up to the usual standard, reduced general comprehension and various abnormal behaviours were commonly observed. Control subjects (n=45) were healthy, elderly individuals with ages over 60 years who came to outclinics for taking annual check-ups (Table 1). They were examined physically and serologically.

### Table 1. Subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>AD</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>n=27</td>
<td>n=7</td>
<td>n=12</td>
</tr>
<tr>
<td>(73.2 ± 9.3 yo)</td>
<td>(73.7 ± 3.8 yo)</td>
<td>(78.2 ± 6.1 yo)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>n=18</td>
<td>n=12</td>
<td>n=9</td>
</tr>
<tr>
<td>(73.1 ± 8.5 yo)</td>
<td>(75.3 ± 8.0 yo)</td>
<td>(74.1 ± 9.4 yo)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>n=45</td>
<td>n=19</td>
<td>n=21</td>
</tr>
<tr>
<td>(75.3 ± 8.9 yo)</td>
<td>(74.7 ± 6.7 yo)</td>
<td>(76.4 ± 7.7 yo)</td>
<td></td>
</tr>
</tbody>
</table>

The number in the parenthesis indicates the age of subjects (mean ± SD). AD, Alzheimer's disease; CVD, cerebrovascular dementia.

None of these controls had central nervous diseases, liver or renal dysfunctions. Blood samples were obtained after an overnight fast. All serum samples were stored at −20 °C and tested in the same assay.

**Radioimmunoassay (RIA)**

The concentration of serum in DHEA was measured using the Coat-A-Count DHEA RIA kit (Diagnostic Products Corporation, Los Angels, USA) after extraction of serum by dichloromethane (Wako, Osaka, Japan). DHEA-S concentration in the serum was directly measured using the Coat-A-Count DHEA-SO4 kit (Diagnostic Products Corporation, Los Angels, USA). Interassay coefficient variation (CV) of RIAs for DHEA and DHEA-S were 4.9% and 8.7%, respectively [14, 15]. Intraassay CV of RIAs for DHEA and DHEA-S were 5.4% and 8.4%, respectively [14, 15].

**Statistics**

A one-factor analysis of variance (ANOVA) was performed to test the significance of the differences among the three groups. When the one-factor ANOVA was significant (P<0.05), statistical significance between two groups was examined using Fisher's Protected Least Significant Difference (Fisher’s PLSD) test. A P value of <0.05 was also considered to indicate statistical significance in Fisher’s PLSD test.

**Results**

A comparison of the serum concentrations of DHEA and DHEA-S as well as the DHEA-S/DHEA...
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ratio among the three groups are graphed in Figs. 1, 2, and 3. The serum concentrations of DHEA among controls (n=45), patients with Alzheimer’s disease (AD), and patients with cerebrovascular dementia (CVD). One-factor analysis of variance (ANOVA) to test mean differences in the levels of DHEA among these three groups was not significant in either gender-matched and total comparison. The actual values in male subjects were 1.44 ± 0.78 (mean ± SD) ng/ml in N, 1.34 ± 0.37 ng/ml in AD, and 1.38 ± 0.78 ng/ml in CVD, respectively. The actual values in female subjects were 1.29 ± 0.92 ng/ml in N, 1.22 ± 0.96 ng/ml in AD, and 1.51 ± 0.61 ng/ml in CVD, respectively. The actual values in total (male plus female) subjects were 1.38 ± 0.83 ng/ml in N, 1.26 ± 0.78 ng/ml in AD, 1.44 ± 0.70 ng/ml in CVD, respectively.

Fig. 1. Comparison of serum concentrations in DHEA among normal controls (N), patients with Alzheimer’s disease (AD), and patients with cerebrovascular dementia (CVD). One-factor analysis of variance (ANOVA) to test mean differences in the levels of DHEA among these three groups was not significant in either gender-matched and total comparison. The actual values in male subjects were 1.44 ± 0.78 (mean ± SD) ng/ml in N, 1.34 ± 0.37 ng/ml in AD, and 1.38 ± 0.78 ng/ml in CVD, respectively. The actual values in female subjects were 1.29 ± 0.92 ng/ml in N, 1.22 ± 0.96 ng/ml in AD, and 1.51 ± 0.61 ng/ml in CVD, respectively. The actual values in total (male plus female) subjects were 1.38 ± 0.83 ng/ml in N, 1.26 ± 0.78 ng/ml in AD, 1.44 ± 0.70 ng/ml in CVD, respectively.

Fig. 2. Comparison of serum concentrations of DHEA-S among normal controls (N), patients with Alzheimer’s disease (AD) and patients with cerebrovascular dementia (CVD). NS stands for “not significant”. One-factor analysis of variance (ANOVA) to test mean differences in the levels of DHEA-S among these three groups was significant in both gender-matched and total comparisons. Statistical significance between groups were examined using Fisher’s PLSD test. The actual values in male subjects were 58.9 ± 38.5 µg/dl (mean ± SD) in N, 35.1 ± 15.9 µg/dl in AD, and 34.6 ± 18.9 µg/dl in CVD, respectively. The actual values in female subjects are 60.3 ± 36.1 µg/dl in N, 30.4 ± 25.2 µg/dl in AD, and 31.8 ± 17.1 µg/dl in CVD, respectively. The actual values in total (male plus female) subjects were 59.4 ± 37.2 µg/dl in N, 32.1 ± 21.9 µg/dl in AD, 33.4 ± 17.8 µg/dl in CVD, respectively.

Fig. 3. Comparison of serum concentrations of DHEA-S among normal controls (N), patients with Alzheimer’s disease (AD) and patients with cerebrovascular dementia (CVD). NS stands for “not significant”. One-factor analysis of variance (ANOVA) to test mean differences in the levels of DHEA-S among these three groups was significant in both gender-matched and total comparisons. Statistical significance between groups were examined using Fisher’s PLSD test. The actual values in male subjects were 58.9 ± 38.5 µg/dl (mean ± SD) in N, 35.1 ± 15.9 µg/dl in AD, and 34.6 ± 18.9 µg/dl in CVD, respectively. The actual values in female subjects are 60.3 ± 36.1 µg/dl in N, 30.4 ± 25.2 µg/dl in AD, and 31.8 ± 17.1 µg/dl in CVD, respectively. The actual values in total (male plus female) subjects were 59.4 ± 37.2 µg/dl in N, 32.1 ± 21.9 µg/dl in AD, 33.4 ± 17.8 µg/dl in CVD, respectively.

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Discussion

Many investigators have recently attempted to identify a specific marker in either serum or the cerebrospinal fluid (CSP) to differentiate AD from
other forms of dementia. Imbalanced concentrations of some neuropeptides such as somatostatin [16] and neuropeptide Y [17] in CSF in patients with AD have been reported, although they are not yet well established.

DHEA-S has also been proposed as a possible marker for AD since a marked reduction in the plasma concentration of DHEA-S in patients with AD compared with normal controls was first reported by Sunderland et al. [5]. Five subsequent reports [8–12] have not supported these findings, while one report by Näsmann et al. [6] studying 45 AD patients, the largest sample size so far, has demonstrated a lower concentration of serum DHEA-S not only in patients with AD but also in patients with multi-infarct dementia (MID). Such a discrepancy may be attributed to slight differences in the sample size, age and gender distribution. The present study supports the previous findings of lower DHEA-S concentrations in patients with AD than normal individuals. However, a reduced concentration of serum DHEA-S was also observed in patients with CVD to a similar extent to that observed in patients with AD. These results, along with the findings of Näsmann et al. [6] suggest that a reduced concentration of serum DHEA-S may be a general phenomenon observed in dementia rather than a specific phenomenon observed only in patients with AD.

Despite the fact that DHEA is no less important than DHEA-S in biological activity [2–4], no previous report has examined serum concentrations of DHEA in patients with dementia. This is probably because of the assumption that the serum concentration of DHEA-S exemplifies that of DHEA. Although the changes in the serum concentration of DHEA roughly mimic those of DHEA-S throughout life [1, 14, 15], the values do not always appear to be correlated. Indeed, the correlation of both concentrations in the serum over 60 years of age in the present study was very weak even in normal individuals (R=0.37, P<0.05, n=45), suggesting that individual variation in the rate of mutual conversion between DHEA and DHEA-S in elderly persons was larger than expected. After all, unlike the serum concentration of DHEA-S, the serum concentration of DHEA among patients with Alzheimer’s disease, patients with CVD and normal controls did not significantly differ from one another. These results, together with the decreased ratio of serum DHEA-S/DHEA in both disease suggests either a relative decrease in the conversion of DHEA to DHEA-S or a relative increase in the conversion of DHEA-S to DHEA in the patients with dementia. The mechanism for the different rate of interconversion between these two adrenal androgens in dementia remains unclear at present.

Even if serum concentration of DHEA-S or the DHEA-S/DHEA ratio decreases in dementia, the physiological significance of DHEA in dementia remains unclear since the serum concentration of DHEA itself was unchanged in these patients. Although the origin of brain DHEA is unknown, the de novo synthesis of DHEA in the brain has been suggested since brain DHEA is not affected by dexamethasone-induced adrenal inhibition or even by castration or adrenalectomy [18]. Therefore, the evaluation of DHEA or DHEA-S by serum concentration, which mainly originates from the adrenal and gonadal tissues, may not be adequate to esti-
mate the role of DHEA in the central nervous system. In order to reach a better understanding of the significance of DHEA in dementia including Alzheimer’s disease, an evaluation of the DHEA concentration in the brains of the patients may be essential.

References