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Research report

Serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (S) levels in medicated patients with major depressive disorder compared with controls

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ABSTRACT

Background: There is accumulating evidence regarding gender differences in clinical symptoms or response to antidepressants in patients with depression. However, less attention has been given to sex differences in the underlying biological mechanisms of depression. The adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S), play a critical role in controlling affect, mood, and anxiety. Changes in serum adrenal androgen levels have been reported in conditions pertaining to stress as well as in psychiatric disorders. The objective of the present study was to investigate differences in serum levels of adrenal androgens in male and female patients with major depressive disorder (MDD).

Methods: Participants included 90 inpatients with MDD at the psychiatric ward of Juntendo University Koshigaya Hospital who were receiving antidepressants. Serum levels of DHEA and DHEA-S were assessed at the time of admission. Matched controls (based on sex and age) included 128 healthy individuals. First, data from male and female MDD patients and controls were compared. Second, correlations between serum hormone levels and scores on the Hamilton Rating Scale for Depression (HAM-D) of patients with MDD were assessed by gender. In addition, effects of various factors on adrenal androgens were analyzed using multiple regression analysis.

Results: Serum DHEA levels were significantly increased in both male and female MDD patients compared with controls. Serum levels of DHEA-S in male patients were significantly decreased compared with male controls, whereas no significant differences were seen in female patients and controls. No significant correlations among adrenal androgens were observed in male patients with MDD, whereas significant positive correlations were found in both male and female controls. No significant correlations were seen between adrenal androgens and HAM-D scores in male or female patients. Multiple regression analysis showed that both hormones were affected by the age at onset of depression.

Limitations: All subjects in the present study were on antidepressant medications.

Conclusions: Elevated levels of serum DHEA may be associated with the biological pathophysiology of depression, as DHEA administration has been found to be effective for the treatment of depression. Findings of differential changes in DHEA-S levels in men compared with women may suggest distinct characteristics of these hormones between men and women with depression. However, DHEA/DHEA-S may be a poor indicator for evaluating severity of depression.

1. Introduction

Women are more than twice as likely as men to be diagnosed with depression. (Scheibe et al., 2003; Sloan and Kornstein, 2003). Accumulating evidence suggests the presence of gender differences in clinical symptoms, course of illness, personality traits, treatment-seeking behaviors, and response to antidepressants in depression (Scheibe et al., 2003; Sloan and Kornstein, 2003; Halbreich and Kahn, 2007; Keers and Aitchison, 2010). Women were found to experience more vegetative and atypical symptoms, anxiety, and anger than men (Scheibe et al., 2003; Halbreich and Kahn, 2007). Pharmacological studies have suggested that women show a superior response to selective serotonin reuptake inhibitors (SSRIs) and have fewer adverse drug reactions to SSRIs

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than men (Sloan and Kornstein, 2003; Keers and Aitchison, 2010), which is consistent with the close relationship between estrogen and serotonergic neural transmission, although this topic remains controversial. Estrogen not only affects the production of serotonin but also the expression and binding of serotonin to its receptors and transporters within the serotonin pathway. However, less attention has been given to gender differences in the endocrinologic features of depression, except for the role of estrogen in augmenting serotonergic transmission in the brain.

In addition to accumulating findings regarding the role of estrogen in depression, findings regarding the role of adrenal androgen levels in depression have been reported. These findings include data on dehydroepiandrosterone (DHEA) and its sulfoconjugated derivative (DHEA-S), which are secreted from the adrenal cortex and testis (Nieschlag et al., 1973). DHEA and DHEA-S are precursors to sex hormones and are converted to androgens and estrogens in peripheral tissues (Labrie et al., 1997). DHEA-S is the most abundant steroid hormone in the body with a concentration 250 and 500 times higher than that of DHEA in men and women, respectively (Nieschlag et al., 1973; Labrie et al., 1997). Under normal circumstances, DHEA is secreted synchronously with cortisol in response to corticotropin releasing hormone (CRH). Circulating endogenous DHEA and DHEA-S levels have been associated with diseases such as lupus, cancer, and diabetes, as well as other factors, including diet and exercise (Kroboth et al., 1999; Salek et al., 2002). They are also neuroactive in the brain (Corpechot et al., 1981; Majewska et al., 1990) and play an important role in controlling mood (Herbert, 1998). They have the potential to clinically influence the central nervous system and possibly affect stress levels, mental health, and psychiatric disorders. Changes in levels of DHEA or in the cortisol/DHEA ratio have been associated with the pathophysiology of depression with a hyperfunction of the hypothalamic–pituitary–adrenal (HPA) axis. To date, in terms of differences in levels of DHEA-S based on gender, concentrations of these steroids are much higher in men than in women (Sulcova et al., 1997; Yamaji and Ibayashi, 1969; Goldman and Glei, 2007). A recent longitudinal study also showed that basal plasma DHEA-S levels are higher and show a more pronounced decline with age for men than women (Tannenbaum et al., 2004).

Accumulating evidence has reported alterations of serum levels of adrenal androgens in patients with MDD. To our knowledge, however, there has been little evidence linking sex-specific alterations in DHEA and DHEA-S. The aims of the present study were (1) to explore differences in serum levels of DHEA and DHEA-S between MDD patients and controls separately for men and women and (2) to assess the correlation between two adrenal androgens and clinical symptoms of MDD, and the influence of clinical factors on serum levels of adrenal androgens in patients with MDD separately for men and women.

2. Methods

2.1. Participants

A total of 90 inpatients with MDD (44 men, mean age, 50.7 years, range, 32–70 years; 46 women, mean age, 51.3 years, range, 34–68 years) were recruited from Juntendo Koshigaya Hospital between May 2006 and May 2012. All patients were hospitalized for mixed anxiety-depressive symptoms and met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV-TR) criteria for MDD. Patients had either suffered a single episode or recurrent depressive episodes. Patients were excluded if they had a history of other psychiatric disorders including delusions, severe or acute medical illnesses, neurological disorders, or the use of drugs that may cause depression. Patients showing clinical evidence of dementia or with Mini-Mental State Examination (MMSE) scores <24 were also excluded. Depressive symptoms were assessed using the Hamilton Rating Scale for Depression (HAM-D) on admission. All patients were on antidepressant medication, but were still considered to be in a depressive state at the time of the study. Patients were receiving antidepressant therapy, including SSRIs, serotonin and noradrenaline re-uptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), at the required dose to obtain an optimal clinical response with minimal side effects. The following antidepressive agents were prescribed alone or in combination: TCAs in 34 cases, SSRIs in 21 cases, SNRI in 14 cases, and other antidepressants in 11 cases. The daily dosage of antidepressants administered on admission was converted to the equivalent dose of imipramine (e.g., the imipramine 25 mg equivalent was set at 5 mg of paroxetine, 10 mg of mianserine, 25 mg of amitriptyline, 25 mg of amoxapine, 25 mg of fluvoxamine, and 50 mg of trazodone; Inagaki and Inaba, 2006). The age at onset of a first depressive episode, number of depressive episodes, and duration of last depressive episode were confirmed via medical records. Depressive symptoms were assessed using HAM-D on admission, and symptoms were categorized into four groups: "anxiety somatization" (total score for psychic anxiety, somatic anxiety, somatic symptoms, general somatic symptoms, hypochondriasis and insight), "cognitive disturbance" (total score for feelings of guilt, suicide, agitation, derealization, paranoid symptoms, and obsessional and compulsive symptoms), "retardation" (total score for depressed mood, work and activities, retardation, and genital symptoms), and "sleep disturbance" (total score for early insomnia, middle insomnia, and late insomnia; Feighner et al., 1993).

A total of 128 healthy participants (50 men, mean age, 45.9 years, range, 32–72 years; 78 women, mean age, 49.2 years, range 33–71 years) were recruited as a control group. All controls were working at least part-time or were students and did not have any history of depression, dementia, or other neuropsychiatric diseases. All control subjects underwent an annual medical examination including a complete laboratory examination. Results revealed no signs of physical or mental illness. Controls with MMSE scores <24 were excluded.

The present study was approved by the Medical Ethics Committee of Juntendo University and was performed in accordance with the regulations outlined by Juntendo University. All participants provided written informed consent after the study had been fully explained.

2.2. Procedures

We compared serum DHEA and DHEA-S levels between patients with MDD and matched controls in men and women, respectively. Blood samples were taken at 07:00–08:00, before breakfast, and collected during both the follicular and luteal phases of the menstrual cycle in female patients and controls. Blood was centrifuged immediately after it was drawn and stored at $-80\,^{\circ}C$ until use. We performed single point measurements. Serum levels of DHEA and DHEA-S were all measured at the SRL Laboratory (Tokyo, Japan). For DHEA, a radioimmunoassay (RIA) was used (DPC DHEA, Diagnostic Products Corporation, Los Angeles, CA, USA). For DHEA-S, a chemiluminescent immunoassay (CLEIA) was used (Access DHEA-S, Beckman Coulter KK, Tokyo, Japan). The detection limits for DHEA and DHEA-S were 0.064 ng/ml and 11 ng/ml, respectively. Inter- and intra-assay coefficients of variation were 10.2 and 9.1% for DHEA, and 10.6% and 7.2% for DHEA-S, respectively.