Neurosteroids and Cognitive Functions in Depressed Women

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ÖZET:

Depresyon tanısı almış kadınlarda nörosteroidler ve bilişsel işlevler

Amaç: Dehdroepiandrosteron (DHEA) ve onun sülfat esteri olan DHEAS GABA antagonistik özellikleri olan nörosteroidlerdir. Bu çalışmada amacımız depresif hastalarda DHEAS'nin serum düzeylerini ve onun salınışını kontrol eden sistemi deksametazon supresyon testi vasıtasıyla araştırmak suretiyle, onun depresyonun patofizyolojisinde rol oynayıp oynamadığını ve varsa bu hormondaki değişikliklerle depresyonda oluşan bilişsel değişiklikler arasındaki ilişkiyi incelemekti. Antidepresan tedavinin bu değişkenleri etkileyip etkilemediği de bu çalışmanın bir başka araştırma konusu idi.

Yöntem: Depresif epizod içinde bulunan 43 kadın hasta ve 22 kadın kontrol deneği çalışmaya alındı. Bilişsel işlevleri incelemek üzere hastalarda antidepresan tedavi öncesi ve sonrasında, kontrollerde ise bir kez Rey İşitsel-Sözel Öğrenme Testi, Wechsler Erişkin Zekâ Ölçeğinin sayı menzilleri alt testleri ve Stroop testi uygulandı. Kontrollerde bir kez, hastalarda ise tedavi öncesi ve sonrasında iki kez olmak üzere bazal kortizol ve DHEAS düzeyleri ile her iki hormonun deksametazona verdiği cevaplar ölçüldü.

Bulgular: Depresif kadınlar deksametazon supresyon testinde kontrollere göre deksametazona daha yüksek oranda kör cevap verdiler, bu bozukluk antidepresan tedaviden sonra düzeldi. Depresif kadınlarda bazal DHEAS düzeyi sağlıklı kadınlarınkinden yüksekti ve bu da antidepresan tedaviden sonra normale dönüyordu. Depresif kadınlar kontrollere kıyasla hafıza, öğrenme ve dikkat testlerinde yetersizlik gösterdiler ve bu bilişsel bozukluklar da tedavi ile düzelmekte idi.

Sonuçlar: DHEAS'nin depresif epizod sırasında yükselmesi ve antidepresan tedaviden sonra düşmesi bulgusu DHEAS'nin depresyon ile nedensel bir ilişkisinin olabileceğini telkin etmektedir. Bu hormonun depresyonda yükselen kortizolün depresif duygu durumu ve bilişsel bozukluklar gibi zararlı etkilerini telafi etmek amacıyla yükselmiş olabileceği düşünülebilir.

Anahtar sözcükler: bilişsel işlevler, dehidroepiandrosteron sülfat (DHEAS), deksametazon supresyon testi (DST), hipotalamik-pitüiter-adrenal (HPA) eksen, major depresyon, nörosteroidler.

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ABSTRACT:

Neurosteroids and cognitive functions in depressed women

Objective: Dehydroepiandrosterone (DHEA) and its sulfate ester dehydroepiandrosterone sulfate (DHEAS) are known to be neuroactive steroids and are proposed to have GABA antagonistic properties. The aim of this study was to investigate whether DHEAS is related to the pathophysiology of depression by examining alterations in serum DHEAS levels and its regulatory factors by the dexamethasone suppression test (DST), and whether there is any relationship between these alterations and cognitive functions in depression. We also investigated if any alteration takes place in these hormonal variables with antidepressant treatment.

Methods: Forty-three female inpatients suffering from a depressive episode and 22 healthy female controls were recruited. Rey Auditory-Verbal Learning Test (RAVLT), Wechsler Adult Intelligence Scale-Revised (WAIS-R), Digit Span Subtest (DSS) and Stroop Test were carried out to evaluate cognitive functions in the patient group before and after antidepressant treatment, and in the control subjects. In the patient and control groups, morning blood cortisol and DHEAS levels were measured followed by a DST. The same procedures were repeated after the response to treatment in the patients who responded to antidepressant treatment.

Results: Depressive women had a more blunted cortisol responses in DST compared with the healthy women, and it was normalized with antidepressant treatment. Serum baseline DHEAS level was higher in the depressive women than that in the healthy women, and this was also normalized by antidepressant treatment. Depressive women had failure especially in memory, learning and attention tests compared to the controls, and these impairments in cognitive abilities recovered with antidepressant treatment.

Conclusions: These results suggest that DHEAS may have a causal relationship with depression since elevated DHEAS levels before treatment decreased to normal levels after a clinical response to treatment. DHEAS may be elevated in order to mitigate the depression-associated overactivity of cortisol and its harmful effects such as depressive mood and cognitive impairments in depression.

Key words: cognitive functions, dehydroepiandrosterone sulfate (DHEAS), dexamethasone suppression test (DST), hypothalamic-pituitary-adrenal (HPA) axis, major depression, neurosteroids.

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INTRODUCTION

Neurosteroids are the steroids synthesized de novo from cholesterol in the brain. It is also known that many neurosteroids are neuroactive (i.e. alter neuronal excitability by acting on specific neurotransmitter receptors such as gamma-amminobutyric acid (GABA) or glutamate receptors). Dehydroepiandrosterone (DHEA) and its sulfate ester dehydroepiandrosterone sulfate (DHEAS) are known to be neuroactive steroids and are proposed to have GABA antagonistic properties. These two hormones are the

components of the hypothalamic-pituitary-adrenal (HPA) axis since they are synthesized and secreted mainly by adrenal glands and are the hormones increased by stress. DHEAS is known to be more potent than DHEA in the brain cells (1).

In patients with major depression, it has been suggested that neuroactive steroids including allopregnanolone and DHEAS may play a role in the pathophysiology of the illness, and may be responsible for some of its symptoms (2). Furthermore, oral DHEAS has been reported to improve some symptoms in depressive patients (3). Although DHEAS is a hormone that is a part of HPA axis, it has been proposed to have antiglucocorticoid and cognition enhancing effects (2,4). Exogenous DHEAS has reported to have some beneficial effects on cognitive functions in animals (5). It has been suggested that DHEAS antagonizes the neurotoxic and memory impairing effects of high cortisol in the hippocampus (6,7).

Nonsuppression in dexamethasone suppression test (DST) is most frequently found in endogenous depression, highly state dependent, and usually interpreted as a reduced efficacy of the feedback loop mediated by pituitary glucocorticoid receptors (8,9). It has been reported that DST is positive (blunted response of cortisol to dexamethasone) in 40-50% of the melancoholic depressive patients (8). Since DHEAS is also one of the HPA axis hormones and synthesized by adrenal gland, at least partly, under the control of the ACTH, we thought that DHEAS might respond to dexamethasone challenge as well as to cortisol (10).

In order to investigate whether DHEAS is related to the pathophysiology of depression, we examined probable alterations in serum DHEAS levels and its regulatory factors by measuring baseline levels and response to the dexamethasone of DHEAS in depressed women. We also investigated whether there is any relationship between these alterations and cognitive functions and whether any alteration takes place with antidepressant treatment in these hormonal variables.

METHODS

Subjects:

This study was conducted in Erciyes University School of Medicine Psychiatry Department between January 2003 and January 2004. Forty-three inpatients in depressive episode (mean age±SD: 40.70±13.41 years, range: 18-65 years) were recruited in the study. Thirty-two of them had major depressive disorder (recurrent), and 11 had bipolar I disorder (the last episode depressive) according to DSM-IV criteria (11). All the patients were women so that we could obtain group homogeneity since some steroid hormones including DHEAS are produced by gonads as well as adrenal glands. The patients were diagnosed by two psychiatrists independently (SK, and EE). The control group was composed of 22 healthy women (mean age±SD: 41.73±9.01 years, range: 18-65 years) who did not have any psychiatric, neurological or endocrinologic disorder. The demographic and some clinical features of the patients and controls were shown in Table 1.

Exclusion criteria for patients were having organic brain disorder, alcohol or other substance abuse or addiction, or any endocrinologic disorder currently or in the past. The patients who were on oral contraceptive therapy during the study, or who had anamnesis of head trauma or electroconvulsive therapy within the previous 6 months were also excluded from the study. None had a history of endocrine disorder and all were within 15% of their ideal body weight [height (cm)-100 according to Broca's index]. All were clinically and biochemically euthyroid, with normal screening of free thyroxine (fT_4), free triiodothyronine (fT_3) and basal TSH (within normal range according to standards of our biochemistry laboratory).

All subjects gave an informed consent before participating to the study and it was approved by the hospital ethics committee.

Procedures:

The patients had been drug-free for at least 2 weeks and washout was supervised in the hospital. They remained hospitalized during the whole treatment period. The severity of the clinical symptomatology was assessed by 17-item Hamilton Rating Scale for Depression (HRSD) (12) and Clinical Anxiety Scale (CAS) (13). All patients had 16 or more scores in HRSD before the treatment. After the

baseline neurocognitive evaluation and blood sampling for hormonal analysis, the patients were started various antidepressant drugs in standard antidepressant doses for 6 to 10 weeks (nine of them were treated with amitriptyline, 19 with venlafaxine, and 12 with SSRI). A decrease of more than 50% in HRSD scores was accepted as a positive response to the treatment.

At the end of the treatment, three patients who did not respond to the treatment were evaluated for only pretreatment hormonal and cognitive parameters, but not for post treatment investigations. Six of them withdrew from the study of their own accord. As a result, hormonal values of the remaining 34 patients were evaluated after the treatment. Furthermore, because nine patients were illiterate, they were exposed to cognitive tests neither before nor after the treatment. In sum, 34 patients before the treatment, and 27 patients after the treatment were able to be assessed concerning cognitive functions.

In the patient group, Rey Auditory-Verbal Learning Test (RAVLT), Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span Subtest (DSS) and Stroop Test were carried out in order to evaluate the cognitive functions before and after the antidepressant treatment. The same tests were fulfilled only once in the control group. These tests were done in a silent room and in the same period of time (09.00-11.00 a.m.) by one of the researchers (SK), who was not blind to the study protocol.

RAVLT gives information about immediate memory, attention, acquisition, retention, recall and recognition processes. It was adapted to Turkish and tested for reliability and validity by Oktem et al. (14,15,16). This test consists of reading a list of 15 words aloud to the subject. The subject is asked to repeat the words he can remember. The total number of the right words is recorded as instant memory score of the subject. Then, the same list is read to the subject nine times more, and the subject is asked to repeat the words he can remember each time. By this way, the learning ability of the subject is evaluated. After a 40-minute interval, the examiner asks the individual to remember the words without referring to the list.

WAIS-R DSS was reported to be mainly related to memory and attention sustaining (17). DSS includes forward and backward subtests. During both parts of the test, subjects are presented with a series of numbers and asked to repeat the digits either the same order (Digits Forward) for the first part or in the reverse order (Digits Backward) for the second part. DSS forward subtest is used to evaluate the immediate memory and attention, while DSS backward subtest is used to assess the mental control and working memory.

Stroop Test reflects mainly frontal functions of the brain and evaluates interference formation (18). It was adapted to Turkish and tested for reliability and validity by Karakas et al. (19). This test is composed of three 60-item trials using word, colour, and interference lists. The first trial involves the subject reading aloud a list of colour words as quickly as possible, and the second trial incorporates successive naming of the colour of the listed stimuli. The final trial uses the interference list, which consists of a series of colour names that differ from the colour of their print (e.g., the word 'red' printed in blue ink). The time, the number of corrections and the number of errors are recorded.

In the patient and control groups, 1 day after the cognitive tests and at 8.00 in the morning blood samples for cortisol and DHEAS were taken via an antecubital venous catheter. The dexamethasone suppression test was started on the same day at 11.00 p.m., by giving 1 mg of dexamethasone orally followed by assays of serum cortisol and DHEAS of 08.00 a.m., 04.00 p.m., and 11.00 p.m. on the following day. All blood samples were immediately centrifuged at 4°C and at 3000 r.p.m. for 5 min. within 2 hours of collection, and stored at -70°C until the analysis. Throughout the tests, subjects remained in bed and did not smoke. The same procedures were repeated after the response to the treatment in the patients who responded to antidepressant treatment.

Nonsuppression on DST was defined as a serum cortisol level greater than 5 μg/dl in any measurement on the day following dexamethasone according to the criteria of Caroll et al. (1981)(20). Moreover, the degree of response of the hormones (cortisol and DHEAS) to dexamethasone (Δcortisol and ΔDHEAS) was calculated as basal value – minimum

post-dexamethasone value. Alterations in the basal hormonal values with antidepressant treatment (Δ^2 cortisol and Δ^2 DHEAS) were calculated as post-treatment basal value – pre-treatment basal value. Lastly, the alterations with treatment in the Δhormonal values (ΔΔcortisol and ΔΔDHEAS) were calculated as post-treatment Δ value – pre-treatment Δ value.

Serum cortisol and DHEAS levels were assayed by RIA (radioimmunoassay) kits (for cortisol DSL-2100, for DHEAS DSL-3500, USA). For cortisol, the sensitivity was 0.3 μg/dl, the intra- and inter-assay coefficients were 5.3% for cortisol pools of 19.21 μg/dl and 8.9% for cortisol pools of 19.18 μg/dl, respectively. For DHEAS, the sensitivity was 17 ng/ml, and the intra- and inter-assay coefficients were 7.8% for 1870 ng/ml, and 10.0% for DHEAS pools of 1734 ng/ml, respectively.

Data analysis:

Student's t test for independent groups was used to compare the patient and control groups with regard to demographic data such as age, body mass index (BMI) and the duration of education. To compare basal cortisol and DHEAS levels between the two groups two-way ANOVA test was carried out, by taking the status of being ill and menopause as between-subject factors, and the age and BMI as covariates. Student's t test for the paired samples was performed for the comparison of basal hormonal values of the patients before and after the treatment. The responses of the hormones to dexamethasone were assessed with repeated measures ANOVA test followed by Greenhouse-Geisser correction, taking sampling time (basal, 8th, 16th and 24th hours after dexamethasone) and treatment (before and after the treatment) as within-subjects factors, and age and BMI as covariates. For the comparison of the calculated values such as cortisol/DHEAS ratio and Dhormone values between the patients and controls, nonparametric Mann-Whitney U test was used. The comparisons of these parameters before and after the treatment in the patients were performed by Wilcoxon test. Neurocognitive test scores of the patients and controls were compared by ANCOVA test taking age and education level as covariates.

Chi-square ($\chi 2$) test was used to investigate the differences in the DST abnormality between the patient and control groups, and before and after the treatment in the patients. When the patients were divided into two subgroups as DST (+) and (-) ones, all comparisons of the hormonal and neurocognitive parameters between the two subgroups were repeated by the same tests. Pearson's correlation test was used to investigate the relationships between demographic, hormonal and cognitive parameters of the patients.

RESULTS

There was no significant difference in age, education level, BMI, smoking, and menopause status between the patient and control groups (Table 1).

Table 1: Demographic features of the patient and control groups.

Demographic data	Patients (n=43) Mean±SD	Controls (n=22) Mean±SD	Comparison	
Age (years)	40.70±13.41	41.73±9.01	t=0.37	p>0.05
Education level (years)	6.28±4.09	6.91±3.66	t=0.63	p>0.05
BMI	27.23±5.32	27.06±3.69	t=0.15	p>0.05
Menopause (%)	30.2	18.2	$\chi 2$=1.09	p>0.05
Smoking (%)	39.5	30.1	$\chi 2$=0.37	p>0.05
Illness duration (month)	78.91±98.85	-------		

BMI: Body mass index

As for having DST abnormality, while 19 out of 43 patients (44.2%) had positive DST response of cortisol before the antidepressant treatment, 1 out of 34 patients (2.3%) had abnormal DST ($\chi 2$=18.00, p<0.001) after the treatment. However, 1 out of 22 control subjects (4.5%) had positive DST response. There was a significant difference between the pre-treatment patients and controls in terms of DST abnormality ($\chi 2$=10.74, p<0.001).

Baseline DHEAS level was significantly higher in the patients before the treatment than in the controls (F=3.22, df=1,65, p<0.05) (Table 2). It was observed that menopause and BMI had no effect on the DHEAS levels (F=0.25, df=1,65, p>0.05; F=0.24, df=1,65, p>0.05, respectively), whereas age had a significant negative effect on this hormone (F=7.89, df=1,65, p<0.05). ΔDHEAS values were higher in the patient group compared to the control group (F=4.73, df=1,65, p<0.05). Other hormonal values did not differ between the patient and control groups (Table 2).

When the cortisol and DHEAS responses to dexamethasone were evaluated as whole responses by repeated measures ANOVA test, cortisol level was suppressed by dexamethasone both before and after the antidepressant treatment in the patients (F=11.60, p<0.001), while DHEAS response was not significantly different before or after the treatment (F=1.18, p>0.05) (figure 1,2). Furthermore, treatment had a significant effect on the cortisol response to dexamethasone in the patients, independently from age and BMI effects

Table 2: Hormonal values of the patients and controls

	Before treatment (n=43) Mean±SD	After treatment (n=34) Mean±SD	Controls (n=22) Mean±SD
Basal cortisol (µg/dl)	15.51±5.59	15.55±5.60	17.13±6.11
Basal DHEA-S (ng/ml)	2864.65±2246.97*	2403.79±2702.62	2018.50±1135.51
Cortisol/DHEA-S	0.014±0.021	0.015±0.016	0.012±0.081
Δ Cortisol	12.98±5.31	12.25±7.98	14.60±5.60
ΔDHEA-S	1632.70±1706.96**	1010.85±1874.83	834.64±792.31

*: Higher than that of controls (F=3.22, p<0.05), **: Higher than that of controls (F=4.73, p<0.05)

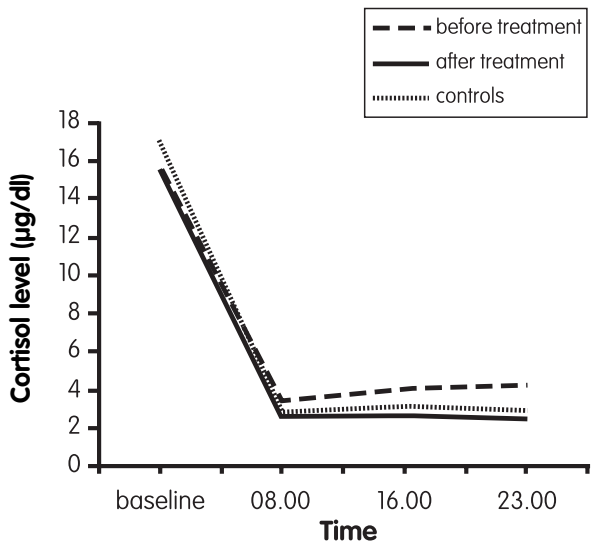

Figure 1. Cortisol responses to dexamethasone in the patients before and after the treatment and in the control group.

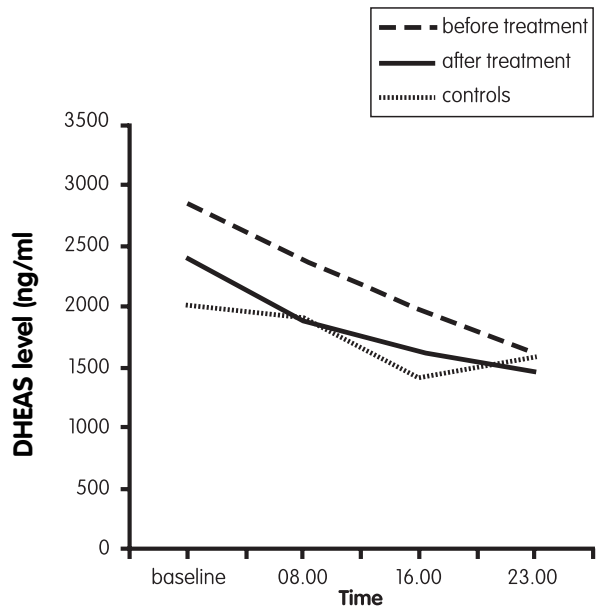

Figure 2. DHEAS responses to dexamethasone in the patients before and after the treatment and in the control group.

No differences were found in any hormonal values of post-treatment patient and control groups. There was no any difference in the hormonal values of the patients before and after the treatment (Table 2).

When the patients were divided into DST (+) and (-) subgroups, it was found that basal cortisol level was higher in the DST (+) ones than that of in the (-) ones (t=2.79, p<0.05). Other hormonal parameters did not differ between these two subgroups.

(F=3.96, p<0.05).

Similar to the patients, in the control group cortisol was suppressed significantly by dexamethasone while DHEAS suppression was not significantly different (F=14.83, p<0.001; and F=0.96, p>0.05, respectively) (Figure 1,2).

Table 3: Neuropsychological test results of the patients before and after treatment

Neuropsychological Tests	Before treatment n=35 Mean±SD	After treatment n=27 Mean±SD	Controls n=22 Mean±SD	Comparison of the pretreatment values of patients and controls	Comparison of the pre- and post-treatment values of the patients
RAVLT					
First trial	5.43±2.21	6.70±1.84	6.76±1.76	F=7.58, p<0.05	Z=-2.86, p<0.05
Total learning	114.80±19.04	124.70±17.18	128.62±9.74	F=16.12, p<0.001	Z=-3.37, p=0.001
Delayed total recall	14.66±0.91	15.00±0.00	15.00±0.00	F=3.86, p<0.05	Z=-2.03, p<0.05
DSS					
Forward digit span	6.09±1.57	7.23±1.56	7.29±1.19	F=13.43, p=0.001	Z=-3.23, p=0.001
Backward digit span	4.75±1.46	6.31±1.41	6.62±1.07	F=31.35, p<0.001	Z=-4.07, p<0.001
Stroop					
Duration difference	70.73±39.28	59.48±26.77	58.40±20.18	F=2.24, p>0.05	Z=-3.63, p<0.001
Number of corrections	4.83±2.63	4.26±1.81	4.20±2.31	F=0.91, p>0.05	Z=-0.95, p>0.05
Number of errors	2.40±3.11	2.17±2.06	1.95±1.73	F=0.64, p>0.05	Z=-0.12, p>0.05

RAVLT: Rey Auditory-Verbal Learning Test

DSS: Digit Span Subtest (DSS) of Wechsler Adult Intelligence Scale-Revised (WAIS-R)

Concerning RAVLT and DSS scores, all subtest scores of the patients before the treatment were worse than both post-treatment scores of the patients and those of controls (Table 3). There was no statistically significant difference in Stroop test scores between the patients and the controls. Post-treatment neurocognitive test scores of the patients were not different companed to those of the controls, when age and education level were controlled.

In the patients, basal DHEAS and ΔDHEAS levels were found negatively correlated with age (r=-0.65, p<0.001; r=-0.51, p<0.001, respectively). There was a negative correlation between the duration of the illness and the basal DHEAS level (r=-0.34, p<0.05). Positive correlations were found between basal cortisol levels and DSS forward and backward scores (r=0.38, p<0.05; r=0.49, p<0.05, respectively), between basal DHEAS and total learning and DSS forward scores (r=0.38, p<0.05; and r=0.45, p<0.05, respectively).

DISCUSSION

The results of the present study are mainly: i) although basal cortisol levels of depressive women were normal, they had more blunted cortisol responses in DST compared to the healthy women, which was normalized with the antidepressant treatment, ii) serum baseline DHEAS level was higher in the depressive women than that in the healthy women, and this was also normalized by antidepressant treatment, iii) it seems that dexamethasone suppressed the DHEAS levels more markedly in the patients before the treatment in comparison with the controls, while this difference disappeared after the treatment, iv) depressive women had failure especially in memory, learning and attention tests compared to the controls, and these impairments in cognitive abilities recovered with the antidepressant treatment.

Evaluation of hormonal data:

Baseline cortisol and DHEAS levels:

HPA axis abnormalities are among the most reported neuroendocrinological findings in depressive patients (21,22). DHEA and DHEAS are also adrenal steroids, and are proposed to have causal relationship with major depression. However, there is a remarkable inconsistency about DHEAS level in depression and its etiological relationship with the illness in literature. Additionally, whether blood levels of DHEAS reflect adequately the brain levels of the hormone may be a problem since the amount of DHEAS in the cerebrospinal fluid (CSF) is 0.1% of the blood level. Nevertheless, serum DHEAS levels may be used as an indicator of brain hormone levels because CSF and blood levels of DHEAS are proportional in a high degree (5).

In the present study, it was found that baseline serum DHEAS values of the depressive women were significantly higher than those of the healthy women. In previous studies, decreased (23-26), normal (27,28), or increased (29-34) DHEAS levels have been reported.

DHEAS level has a great variability between the individuals although nearly stable over the day in the same person (35). It is also known that it decreases with age (30). Therefore, these inconsistent findings in baseline DHEAS levels may be due to differences in age, gender, time of blood sampling, drugs, and concomitant physical or psychiatric disorders in the above-mentioned studies.

Our findings are in line with the studies that report increased DHEAS in depression (29-34). This increase may be a component of hyperactive HPA axis, and parallel to increased cortisol in the depressive patients (34). Nonetheless, the effects of these two hormones, which are parts of the HPA axis, may be contrast to each other, since DHEAS has been reported to have antiglucocorticoid effects. Increased CRH and ACTH in depression may stimulate also DHEAS secretion simultaneously with cortisol from adrenal glands. In depression, increased CRH has been proposed to result from the resistance of glucocorticoid receptors (GR) to glucocorticoids. For DHEAS, this resistance of GR seems to present from the birth on, since DHEAS does not have a negative feedback effect on the hypothalamus or pituitary gland (5). Therefore, even if blood or brain DHEAS escalates in depression, it cannot inhibit CRH or ACTH, thus cannot suppress the levels of the cortisol or of itself.

It may also be thought that DHEAS, as a stress hormone, might enhance compensatory to harmful effect of increased cortisol in depression. Indeed, exogenous DHEA has been shown to be effective in the treatment of major depression, and therefore endogenous DHEAS may play a role as an antidepressant (3,24).

Another explanation of the increased DHEAS in depressive women may be that: Allopregnanolone and DHEAS are neuroactive steroids that are both synthesized from pregnenolone through two different ways of synthesis. In depression, it can be considered that the balance between the two ways of synthesis impairs, and in turn, because of the shift from allopregnanolone to DHEAS synthesis, DHEAS increases while allopregnanolone decreases. Indeed, plasma and CSF allopregnanolone have been reported to decrease in major depression, and to normalize with antidepressant treatment (37-39). Therefore, increase in DHEAS may be an epiphenomenona of the decreased allopregnanolone in depression. If this hypothesis holds true, the critical enzymes in shifting from allopregnanolone to DHEAS in the neurosteroid synthesis may be 3ß HSD or P450c17. Taking into account the findings of the previous studies that GABA inhibits 3ß HSD and P450c17 enzymes via GABA-A receptors (40), it can be suggested that altered neurotransmitter activities in depression may change the activities of these enzymes. Despite all these speculations, because we did not measure the levels of serum allopregnanolone in the study, we cannot exactly infer such a conclusion from the available data.

Responses of cortisol and DHEAS to dexamethasone:

In the present study, we investigated the response of DHEAS besides cortisol to dexamethasone in order to understand more accurately the factors mediating the secretion of adrenal neurosteroids, and thus impairments of HPA axis in general. It has been reported that approximately 50% of the patients with major depression have blunted cortisol response to dexamethasone, which points to impairment in the normal inhibitory feedback mechanisms in the HPA axis. DHEAS is also secreted mainly by adrenal glands; however the factors that mediate its secretion are not so clear. It is thought by and large that pituitary ACTH stimulate adrenal DHEAS secretion, nevertheless, the modulations of cortisol and DHEAS secretions by ACTH do not seem the same (5,41). For example, adrenarche, puberty and normal process of aging have great effects on DHEAS levels although they do not affect cortisol levels so consciously (42). Hence, ACTH may not be the only regulatory factor on adrenal steroids such as DHEAS. The fact that despite the higher levels of ACTH, there are normal DHEAS concentrations in Cushing disease also supports this suggestion (43). It is also unclear how DHEAS secretion is controlled, how it responses to dexamethasone, and whether it alters during major depressive disorder.

In the present study, depressive women had abnormal DST in a proportion of 44.2%, though only 4.5% of healthy controls had abnormal DST. This result is very consistent with the well-known finding that in nearly half of the depressive patients endogenous

cortisol cannot be suppressed enough (9,44). Moreover, the finding that after the clinical improvement the ratio of DST abnormality reduced to 2.3% in the patients suggests that this abnormal response is a state marker constrained to the depressive episode. The cause of this nonsuppression has been claimed to be primarily the hyposensitivity of the hypothalamic GRs to cortisol (45). Some authors claim that all other findings that imply hyperactivity of HPA axis (CRH hypersecretion, hypercortisolemia etc.) may be secondary to this receptor abnormality. The finding that the number of GRs in mononuclear blood cells is reduced which recovers with antidepressant treatment also supports this hypothesis (46).

We found that the level of suppression of DHEAS after dexamethasone (ΔDHEAS) in the depressive patients before treatment was higher than that of controls, which is contrary to suppression of cortisol. This finding also supports the notion that there must be different mechanisms of modulation of cortisol and DHEAS, affected by depression in different manners. ACTH may be a partial regulator of DHEAS, and dexamethasone may suppress DHEAS levels via an independent mechanism from ACTH (27). There may be an inducing factor of DHEAS secretion from adrenal gland other than ACTH. Actually, some authors put forward the presence of such a factor, which is secreted from pituitary and named "androgen releasing hormone" (42). Therefore, it is possible that the release of this hypothetic stimulator is not disturbed, in contrast to ACTH, in depression.

Another suggestion related with this finding may be that zona reticularis cells secreting DHEAS in the adrenal gland may be hypersensitive to ACTH or, if there is, other DHEAS stimulators. For this reason we might have found increased basal DHEAS in depressive patients. In depressive patients, ACTH response to CRH is blunted while cortisol response is normal, which means that cortisol-releasing cells are also hypersensitive to ACTH in depression (45,47). However, if both DHEAS and cortisol responses of the adrenal cortex to ACTH become hypersensitive in depression, why DHEAS response is suppressed more severely by dexamethasone while cortisol response is not in our patients? The solution of this issue may be that increase in the sensitivity of DHEAS-secreting zona reticularis cells to ACTH may be far higher than that of cortisol-secreting cells. The cause (or the result) of this hypersensitivity may be alteration in the activity of the enzymes that discriminating the two different ways of the steroid biosynthesis, i.e. allopregnanolone or DHEAS ways.

The effects of antidepressant treatment on the hormonal values:

In this study increased DHEAS levels in the depressed patients were normalized after the clinical response to antidepressant treatment. As far as we know, there are a few studies having investigated the effects of treatment on DHEAS levels in depressed patients, which have inconsistent results. Some studies reported a reduction in DHEAS levels after the antidepressant treatment (28,32,33), while some reported an increase following ECT treatment (48). In one study investigating the effects of ECT, elevated DHEAS levels in depressed patients have been reported to show an additional elevation after the ECT treatment (29). Our results are in line with the data of the studies that report a decrease in DHEAS levels with the remission of depression (28,32,33). The finding of decrease in DHEAS with treatment may support the idea that there is a relationship between DHEAS and the pathophysiology of major depression.

Inconsistency in the data of ECT and pharmacotherapy studies raises a question whether the alteration in the DHEAS levels is a result of improvement in depression, or only a specific effect of antidepressant drugs. It was showed in a study that higher DHEAS levels become lower only in improved depressed patients, not in the patients who took antidepressant treatment but did not respond (28). This suggests the decrease in DHEAS may be related to remission in depression, rather than specific drug effect. However, we were unable to evaluate the direct effects of the antidepressant drugs on DHEAS levels since the patients who did not improve with treatment abandoned the study. Nevertheless, the finding of the present study that basal DHEAS level and ΔDHEAS are negatively correlated with the level of response to treatment (alteration in HRSD score) suggests the idea that the higher baseline DHEAS levels in depressed patients, the less response to treatment (29).

Several explanations may be made with respect to the improvement in HPA axis dysfunction and the normalization of DHEAS levels with treatment in depressive patients. Antidepressants may have a decreasing effect on DHEAS response to stress, just as they have decreasing effects of HPA axis, dopamine, and noradrenalin responses to stress (49,50). However, to claim this, we should have evaluated the response of DHEAS to stress along with the response to DHEAS.

Another explanation may be that: Long-term antidepressant use causes increase in the feedback inhibition of HPA axis activity by regulating the gene expression of the corticosteroid receptors (50,51). Thus, with antidepressant treatment, glucocorticoid receptor resistance, which is available in depressive or depression-tended patients, abolishes and cortisol comes to suppress CRH and ACTH (51). Therefore, DHEAS levels may decrease in parallel with decrease in ACTH levels. Or, if the hypothesis that zona reticularis cells secreting DHEAS may be hypersensitive to ACTH or other secretague holds true, one can consider that antidepressant drugs may normalize this hypersensitivity of ACTH receptors in the adrenal cortex.

It is known that neurosteroids have some relations with serotonergic system, as well. Some authors suggested that SSRIs may have therapeutic effects in depression other than the inhibition of serotonin reuptake such as blockade of postsynaptic 5- HT2C or 5-HT1A receptors, or increasing effect of allopregnanolone levels (52). One can suggest that the decrease in HPA axis activity with antidepressant may result from the effects of SSRIs on 5-HT1A receptors since long term administration of some SSRIs like fluoxetine have been reported to lead to a desensitization in postsynaptic 5-HT1A receptors of hypothalamus (53,54). 5-HT1A receptors have a regulating effect on CRH secretion (55). As a result, antidepressant treatment may cause a decrease in basal levels of neuroactive steroids such as DHEAS by decreasing CRH and ACTH secretions by means of 5-HT1A receptors (50).

It has been consistently shown that allopregnanolone has anxiolytic and antidepressant effects (56,57). It is claimed that this effect may be related to GABA agonistic effect of the substance, or the decreasing effect on gene expressions of two hypothalamic hormones blamed in the development of depression, CRH and AVP (2,58,59). Although this idea seems not to fit with the fact that exogenous DHEAS may recover depression at first glance (3,24), we may consider that exogenous DHEAS causes an increase in the activity of the allopregnanolone arm in parallel to decrease in the DHEAS synthesis arm (secondary to exogenous loading of DHEAS), and in fact, allopregnanolone, rather than DHEAS, is it that have anxiolytic and antidepressant effects.

Evaluation of cognitive functions:

Depressed patients failed in almost all neurocognitive tests, especially in memory, learning and attention tests, before the treatment. It has been reported that RAVLT can evaluate particularly the cognitive functions such as immediate memory, attention, learning and recognize-recall (16). In the present study, pretreatment patients had lower scores in each one of the three parts assessed of the test (immediate memory and attention, learning, and delayed total recall). After the treatment, memory and learning scores were not different from those of controls.

DSS forward subtest is used for evaluating immediate memory, while DSS backward subset is used for mental control and working memory. Depressive patients had lower scores in comparison to controls in both tests before the treatment, while they were normal following the treatment in the study.

Consistent with our results, it is a well-accepted idea that depressive patients show memory dysfunctions (60,61). Most of the previous studies reported that memory dysfunctions are temporary and limited to depressive episode (62-64) in accordance with our results, although there were also some studies claiming that some of the memory dysfunctions might continue during remission periods (65-67).

Relationship between hormonal variables and cognitive dysfunctions:

It is known that high cortisol levels may be associated with some cognitive dysfunctions. It is

claimed that high cortisol values may impair cognitive functions in some diseases such as Cushing disease, Alzheimer disease, schizophrenia, anorexia nervosa, and Korsakoff psychosis. It has been suggested that high cortisol levels may also play an important role in cognitive dysfunctions in major depression, and that more disordered cognitive functions are observed in psychotic major depression only because of higher cortisol levels in this subtype of depression than non-psychotic ones (68).

Hippocampus, which is known to have an important role for memory, is sensitive to steroids. It has been reported that corticosteroids block the induction of long-term potentiation in the hippocampus (69). It has been proposed that an acute enhancement in cortisol levels causes an impairment in memory by blocking transport of glucose to hippocampal neurons and glia cells, and by leading to an atrophy in hippocampus (68,70). Glucocorticoids probably enhance the concentration of excitatory neurotransmitters such as glutamate in the hippocampal synaptic space by non-genomic way, and in turn, cause the elevation in intracellular Ca2+ ion concentration and cellular atrophy (71).

In the present study, there was a positive correlation between pretreatment basal cortisol levels and DSS forward and back scores. This finding, which points to the fact that enhanced cortisol has an increasing effect on the immediate memory, attention and working memory, is clearly in odds with the previous suggestions that glucocorticoids cause cognitive impairments particularly in the areas such as selective attention and working memory (68,72). In our study, there was also a positive correlation between pretreatment basal DHEAS levels and attention and memory test scores. One can consider that elevated DHEAS may have a repairing effect on cognitive functions in depression, and this idea is in accordance with the suggestion that increased basal DHEAS levels may help decreasing the depressive symptoms in the depressed patients. In the literature, there are inconsistent findings about the effects of DHEAS on cognitive functions. Exogenous DHEAS has reported to have beneficial effects on the cognitive functions in animals (5). In elderly healthy humans, it has been reported that lower levels of DHEAS is related to the impairment in psychological well-being, but not to cognitive skills (26,73-75).

Studies investigating the relationship between DHEAS levels and cognitive functions in depressive patients are inadequate in the literature. In two studies researching this relationship indirectly, DHEAS treatment has been shown to have beneficial effects on depressive symptoms but not on the cognitive symptoms in the depressive and dystimic patients (24,76).

If the result of the study that favorable effect of DHEAS on the cognitive functions holds true, we can explain this beneficial effect by two mechanisms. The first one may be the antiglucocorticoid effect of DHEAS, since it has been suggested that DHEAS antagonizes the neurotoxic and memory impairing effects of high cortisol in the hippocampus (6,7). Secondly, the beneficial effects of DHEAS on the memory may result from its interactions with GABA-A, sigma 1 and NMDA receptors (6). It has been shown that DHEAS as a neuroactive steroid is an uncompetitive antagonist on the GABA-A receptors (77). It is generally thought that GABA-A agonists impair the memory while antagonists recover (78). As a result, DHEAS may favor the memory by way of antagonism on GABA-A receptors. Furthermore, DHEAS has been reported to have agonistic effect on sigma1 receptors, and thus enhance the responses of hippocampal CA3 neurons to glutamate and the arousability of hippocampal pyramidal CA1 neurons. The result of all these will be facilitation for hippocampal long-term memory (LTP) induction by DHEAS and a favorable effect on the memory (5).

Limitations of the study:

The small sample numbers of the groups might have prevented us from detecting differences more adequately in some hormonal variables. The fact that some patients left the study before the post-treatment evaluation prevented us from directly assessing the effects of drugs. Additionally, we did not measure the levels of allopregnanolone, which may have provided us with more global information about the adrenal neuroactive steroids and with the speculations closer to reality.

CONCLUSIONS

These results suggest that DHEAS may have a causal relationship with depression since elevated DHEAS levels before the treatment lowered to normal levels after the clinical response to the treatment. One may consider that DHEAS may be elevated in order to mitigate the depression-associated overactivity of cortisol and its harmful effects such as depressive mood and cognitive impairments in depression. In addition, it may be considered that this increased DHEAS might originate from hypersensitivity of DHEAS-secreting cells of the adrenal gland to ACTH, or from a shift in the activities of the enzymes that participate in the metabolism of pregnenolon, i.e. from allopregnanolone towards DHEAS synthesis during the depressive episode.

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