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Acute and Chronic Effects of Electroconvulsive Therapy on Neuroactive Steroids in Patients with Major Depressive Disorder

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Abstract

Objective: *Baseline serum levels of neuroactive steroids such as dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), testosterone, and cortisol were measured, and the acute and long-term effects of electroconvulsive therapy (ECT) on these hormones and the effect of gender on alterations in steroid hormones were investigated in patients with major depressive disorder (MDD).*

Methods: *The study included 25 inpatients (11 male, 14 female) diagnosed with MDD that responded to ECT, and 37 healthy controls (17 male, 20 female). Serum levels of cortisol, DHEAS, 17-OHP, and testosterone were measured 2 days before and 10 min after the first ECT, and 3 days after the last ECT in the patients. These measurements were obtained only once in the controls.*

Results: *Basal DHEAS increased, testosterone and 17-OHP decreased, and cortisol levels remained unchanged in MDD patients as compared to the controls. After completion of the therapeutic course of ECT, DHEAS levels in the patients were higher than they were before the treatment. After ECT treatment, cortisol and 17-OHP levels in the patients were lower than those in the controls; however, testosterone levels did not differ between the groups. In the MDD patients, increases in DHEAS and decreases in testosterone were only observed in men, while decreases in 17-OHP were only seen in women.*

Conclusions: *Alterations were observed in some neuroactive steroids in MDD patients and it appears that ECT affected these hormones. It is not clear whether the observed alterations in neuroactive steroids are associated with the pathophysiology of depression or whether they play a role in the therapeutic effects of ECT.*

Key Words: *Depression, neuroactive steroids, DHEAS, ECT*

INTRODUCTION

Current research is investigating the possible role of brain neurotransmitter systems, the hypothalamic-pituitary-adrenal (HPA) axis, cytokines, and neurotrophins in the etiology of depression (Stone et al. 2008). In recent years, in addition to monoamine-neurotransmitters, the role of amino acid neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA) in depression has also been investigated. GABA activity dysfunction is thought to be one of the factors involved in the etiopathogenesis of major depression. It has been reported that neuroactive steroids are involved in the etiology of depression, acting as agonists or antagonists on GABA receptors (Dubrovsky 2005). In addition, 3α-reduced neuroactive steroids (e.g. allopregnanolone), which are the metabolites of progesterone, are potent, positive modulators of GABA-A receptors. Classical steroid hormones such as testosterone and progesterone also work as neuroactive steroids by altering receptor activity. On the other hand, neuroactive steroids like dehydroepiandrosterone sulfate (DHEAS) act as antagonists on GABA-A receptors (Rupprecht 2003). Apart from being a neuro-active steroid, DHEAS is also involved in the depression process, acting as an anti-glucocorticoid (van Broekhoven and Verkes 2003).

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Neuroactive steroid dysregulation in depressed patients has been previously reported (van Broekhoven and Verkes 2003). Although the results of previous studies related to DHEAS levels in patients with depression are inconsistent, most report elevated DHEAS levels (Takebayashi et al. 1998, Maayan et al. 2000, Assies et al. 2004). In contrast, other studies demonstrated that reduced DHEAS levels might be associated with an increase in the severity of depressive symptoms, especially in elderly patients (Barrett-Connor et al. 1999, Morrison et al. 2001, Morsink et al. 2007).

Low testosterone levels in male patients with depression (Schweiger et al. 1999, Shores et al. 2005) and a reduction in the severity of depressive symptoms in response to testosterone hormone replacement have been reported (Perry et al. 2002). In contrast to males, testosterone levels were reported to be elevated in female patients with depression (Baischer et al. 1995, Weber et al. 2000); however, some studies report either an inverse relationship between depressive symptoms and testosterone (Morsink et al. 2007) or no relationship between those two phenomena in female depressive patients (Barrett-Connor et al. 1999). Progesterone is also reported to have antidepressant (Molina-Hernandez and Telles-Alcantara 2001) as well as anxiolytic (Bitran et al. 1995) effects. Nevertheless, clinical studies demonstrated that progesterone levels in depressive patients were not different from those of controls (Baischer et al. 1995).

It was reported that antidepressant treatment could normalize abnormalities in the level of some neuroactive steroids in patients with depression (Romeo et al. 1998, Uzunova et al. 2006). Elevated DHEAS levels were observed to normalize in response to antidepressant treatment (Takebayashi et al. 1998, Fabian et al. 2001), whereas progesterone levels were unaffected by antidepressant treatment (Romeo et al. 1998).

Electro-convulsive therapy (ECT) remains the most efficacious treatment known for major depressive disorder (MDD) (UK ECT Review Group 2003). Currently, the mechanism of ECT's antidepressant effect is not entirely known. Neuroactive steroids were suggested to be among the factors contributing to the antidepressant effect of ECT (Maayan et al. 2000). Although some studies demonstrated that some neuroactive steroids did not change in response to ECT (Baghai et al. 2005), another study revealed that DHEAS levels increased following ECT in patients with psychotic depression and that elevated basal DHEAS prior to treatment was associated with non-responsiveness to ECT (Maayan et al. 2000). It was also shown that ECT did not alter serum levels of either testosterone or progesterone (Cooper et al. 1989, Motta et al. 2005).

The present study evaluated DHEAS, 17-hydoxyprogesterone (17-OHP), testosterone, and cortisol levels in male and female MDD patients, as well as the acute effect of one ECT session and the long-term effect of a completed course of ECT on these hormones. The study was based on the hypothesis that alterations in the levels of neurosteroids with GABA-antagonistic effects, such as DHEAS, might differ from those with GABA-agonistic effects, such as 17-OHP and testosterone, in MDD patients, and that ECT may affect this imbalance in neuroactive steroids. Moreover, by considering the fact that gonadal production of these neuroactive steroids diverges between males and females, it was aimed to investigate the effect of gender on variations in steroid hormones. It was thought that the results might provide insight into the etiopathogenesis of MDD and ECT's mechanism of action.

METHOD

Subjects

The study included 25 patients (11 male, 14 female; age range: 18-60 years; mean age: 43.96 ± 12.45 years) that were responsive to ECT selected from among 28 inpatients diagnosed with MDD according to DSM-IV who have ECT indication. The control group included 37 volunteers (17 male, 20 female; age range: 18-60 years; mean age 38.86 ± 10.39 years) selected from hospital personnel.

Both patients and controls were selected on the basis of physical and psychiatric examinations, as well as routine biochemical investigations. Patients that had not received ECT for 6 or more months prior to the study and were not receiving medication for at least 1 week prior to the study were included. The patients remained in the hospital during the study and did not receive any treatment other than ECT. The presence of additional physical or psychiatric disorders, a history of alcohol/substance abuse or dependence, and post-menopausal state and the use of oral contraceptives (for female patients) were the exclusion criteria. For the control group, in addition to these criteria, the presence of current or past psychiatric disorders was exclusionary.

In order to measure the severity of depression, the 17-item Hamilton Depression Rating Scale (HDRS) was administered at the time of hospital admission and after

Table I. Demographic data i patients and controls.

	Patients n = 25 (mean ± SD)	Controls n = 37 (mean ± SD)	t or χ^2	P
Age	43.96 ± 12.45	38.86 ± 10.39	1.74	> 0.05
BMI (kg/m^2)	24.77 ± 3.44	26.37 ± 3.17	1.88	> 0.05
Gender (m/f)	11/14	17/20	0.02	> 0.05

BMI: body mass index.

7-12 ECT sessions (Akdemir et al. 1996). A reduction of 50% or more in HDRS score was considered indicative of a clinical response to treatment.

The Erciyes University Medical Faculty Ethics Committee approved the study protocol. The aims and procedures of the study were explained to the patients and controls, and written informed consent was obtained.

PROCEDURE

Under general anesthesia, total 7-12 ECT sessions were administered to each patient as 3 times per week. ECT was administered between 0800 and 1000 by giving propofol (1 mg/kg), succinylcholine (0.5 mg/kg) and oxygen, and with bifrontal electrodes after a 1-night fast. The current was sinusoidal and the stimulus intensity was standardized at 700 mA for 5 s. The seizure was observed by the cuff method.

In the MDD patients, serum cortisol, DHEAS, 17-OHP, and total testosterone levels were measured 2 days before and 10 min after the first ECT session, and 3 days following the last ECT session. These measurements were obtained only once in the controls. Blood required for these measurements was drawn between 0800 and 0900 after overnight fasting; serum samples were separated and stored at –70 °C until analysis.

Serum cortisol, DHEAS, 17-OHP, and total testosterone levels were measured by radioimmunoassay kits (RIA, DSL UK Ltd., England). Sensitivity for cortisol was 0.3 µg/dl; intra-assay and inter-assay coefficients of variation were 8.4% for a mean of 5.01 µg/dl and 9.1% for 4.83 µg/dl, respectively. Sensitivity for DHEAS was 17 ng/ml; intra-assay and inter-assay coefficients of variation were 9.4% for 203 ng/ml and 9.6% for 206 ng/ml, respectively. Sensitivity for 17-OHP was 0.01 ng/ml; intra-assay and inter-assay coefficients of variation were 9.3% for 1.18 ng/ml and 9.7% for 1.13 ng/ml, respectively. Sensitivity for testosterone measurements was 8 ng/dl; intra-assay and inter-assay coefficients of variation were 9.6% for 94 ng/dl and 8.6% for 70 ng/dl, respectively.

Statistical Analysis

An independent samples t-test was used to compare age and body mass index (BMI) in the patient and control groups. The gender difference between the groups was compared by chi-square test. Two-way ANOVA was used to compare pre- and post-treatment hormone levels of the patients and controls. In this analysis, the presence of MDD and gender were used as between-subject factors, while age and BMI were covariates. Repeated-measures ANOVA was used to determine the effect of ECT on MDD patient hormone levels. In this test, treatment phase (3 phases; basal, after the first ECT session, and after response to ECT) was taken as the within-subject factor, while age and BMI were taken as covariates. For hormone levels that ECT was found to affect, repeated-measures ANOVA was applied again. For hormone levels affected by gender, the comparisons were performed separately for males and females. To evaluate the relationship between demographic and clinical data, and hormone levels, Pearson's correlation test was used.

RESULTS

No significant differences were found between the patient and control groups in terms of age, BMI, or gender distribution (Table I). Basal cortisol levels did not differ significantly between the patients and controls; however, after the completion of ECT, cortisol levels in the MDD patients were significantly lower than in the controls (F =

Table II. Hormone levels in the patients and controls.

	Patients n = 25 (mean ± SD)			Controls n = 37 (mean ± SD)
	Pre-treatment	After 1st ECT	Post-treatment	
DHEAS (ng/ml)	2677.23 ± 2316.61[a]	3531.66 ± 3638.02[c]	3712.85 ± 2795.98[a,c]	2151.43 ± 1697.92
Cortisol (µg/dl)	13.87 ± 6.13	20.04 ± 7.22[c]	12.35 ± 4.53[b]	16.29 ± 5.39
Testosterone (ng/dl)	246.60 ± 256.59[b]	274.47 ± 291.32	280.76 ± 310.77	414.89 ± 391.34
17-OHP (ng/ml)	1.25 ± 0.61[b]	2.01 ± 0.83	1.34 ± 0.72[b]	2.05 ± 1.07

DHEAS: dehydroepiandrosterone sulfate; 17-OHP: 17-hydroxy progesterone.
[a]Higher than in controls.
[b]Lower than in controls.
[c]Higher than pre-treatment.

5.67, P < 0.05) (Table II). Basal DHEAS levels in the patient group were significantly higher compared to those of the controls, both before treatment and after response to ECT (F = 4.59, P < 0.05, and F = 11.80, P < 0.001, respectively) (Table II). In the patient group 17-OHP levels were lower than those of the controls, both before and after ECT treatment (F = 8.40, P < 0.05, and F = 6.06, P < 0.05, respectively). While patient total testosterone levels before ECT treatment were significantly lower than those of the controls (F = 5.87, P < 0.05), no significant difference was observed after response to ECT (F = 2.36, P > 0.05) (Table II).

ECT significantly increased basal cortisol and DHEAS levels in the short term (F = 4.95, P < 0.05, and F = 10.32, P < 0.005, respectively). No acute effects of ECT on testosterone or 17-OHP were observed (Table II).

When the effects of the completed courses of ECT on hormone levels were assessed, only DHEAS significantly increased after treatment, as compared to that in the pre-treatment period (F = 5.28, P < 0.05). No statistically significant differences were detected between pre- and post-treatment levels of the other hormones (Table II).

Since the effect of gender on DHEAS, 17-OHP and testosterone levels was significant (F = 29.57, P < 0.0001, F = 4.42, P < 0.05, and F = 168.29, P < 0.0001, respectively), comparisons of these hormones were performed separately for males and females. DHEAS levels in male patients were significantly elevated in comparison to those of the controls, both before and after ECT treatment (F = 4.95, P < 0.05 and F = 6.36, P < 0.05, respectively). As for females, although no significant difference in DHEAS levels was found between the patients and controls prior to treatment (F = 0.004, P > 0.05), the levels were higher in the patients after ECT treatment than in the controls (F = 9.21, P < 0.005) (Table III and Figure I). Additionally, ECT significantly increased DHEAS levels in female patients compared to those in the pre-treatment period (F = 11.88, P < 0.005). When compared to the controls, no differences were observed in 17-OHP levels of male patients, either before or after the treatment, whereas 17-OHP levels in female patients were lower in both instances (F = 5.75, P < 0.05, and F = 6.02, P < 0.05, respectively). Testosterone in male patients was significantly lower than that in the controls both pre- and post-treatment (F = 10.47, P < 0.005, and F = 5.48, P < 0.05, respectively). No difference was observed in females (Table III).

In the patient group, change in HDRS score due to treatment (ΔHDRS) was positively correlated to basal DHEAS levels (r = 0.49, P < 0.05).

DISCUSSION

The major findings of the present study were that DHEAS levels in MDD patients were elevated and that ECT had an accentuating effect on this elevation, both

Table III. Hormone levels in female and male subjects.

	Patients n = 25 (mean ± SD)				Controls n = 37 (mean ± SD)	
	Pre-treatment		Post-treatment			
	Male n = 11	Female n = 14	Male n = 11	Female n = 14	Male n = 17	Female n = 20
DHEAS (ng/ml)	4629.81 ± 2621.12[a]	1428.91 ± 1069.03	5603.22 ± 2941.09[a]	2295.08 ± 1675.16[b]	3070.82 ± 2134.57	1369.95 ± 475.72
Testosterone (ng/dl)	453.72 ± 255.76[c]	83.85 ± 80.04	514.11 ± 320.26[c]	105.75 ± 151.77	802.94 ± 218.44	85.05 ± 27.18
17-OHP (ng/ml)	1.56 ± 0.33	0.94 ± 0.68[d]	1.85 ± 0.59	0.83 ± 0.43[d]	2.33 ± 0.78	1.82 ± 1.23

[a]Higher than in male controls.
[b]Higher than in female controls and pre-treatment levels in female patients.
[c]Lower than in male controls.
[d]Lower than in female controls.

acutely and chronically. The increased DHEAS levels in depression, as observed in the present study, are consistent with previous reports (Takebayashi et al. 1998, Maayan et al. 2000, Assies et al. 2004) and might be a component of increased HPA axis activity in major depression. On the other hand, cortisol levels of the MDD patients in the present study were normal, which may indicate that DHEAS is a more sensitive marker than cortisol for depression, as reported in previous studies (Assies et al. 2004).

The acute elevation in DHEAS levels we observed in response to ECT in MDD patients may have been related to the acute stress response to ECT. Moreover, the acute effects of ECT also led to an elevation in cortisol levels. Long-term treatment raised DHEAS levels even further. This finding is in agreement with that of another study that demonstrated DHEAS levels in patients with psychotic depression increased following ECT (Maayan et al. 2000). While that study reported that DHEAS elevation was related to resistance to ECT, in the present study a positive relationship was observed between elevated DHEAS levels and ECT treatment response. It is also possible that DHEAS increases in MDD patients as an endogenous antidepressant. This idea was also proposed in previous studies (Wolkowitz et al. 1999, Maayan et al. 2000) and is supported by the present study because ECT accentuated the DHEAS elevation and the observed increase in DHEAS was positively related to ECT treatment response. Alternatively, DHEAS might play a role in reducing the deleterious effects of a rise in cortisol in depression (van Broekhoven and Verkes 2003). It is known that ECT normalizes increases in HPA axis activity (Yuuki et al. 2005). Similarly, we also observed that cortisol levels in the MDD patients were initially normal and decreased after ECT. As such, the corrective effect of ECT on HPA axis activity may have been due to its lowering effect on cortisol and elevating effect on DHEAS (which is known to antagonize the effects of cortisol). The fact that ECT resulted in a decrease in cortisol and an increase in DHEAS in the MDD patients suggests that control of their adrenal secretions is via distinct pathways and that the effects of anti-depressant treatment on these hormones might be different.

Analysis of the relationship between gender and DHEAS levels showed that ECT did not alter DHEAS levels in males, whereas it significantly increased them in females; however, pre-treatment DHEAS levels in the male patients were higher than in the male controls, whereas those of the female patients did not differ from the female controls. The results of this investigation may be misleading due to the fact that the number of subjects analyzed in the 2 groups was inadequate. Nevertheless, previous studies also observed that the relationship between DHEAS and depressive symptoms differed between genders. DHEAS levels were mostly associated with depression in females (Yaffe et al. 1998, Barrett-Connor et al. 1999). Some studies reported that depres-

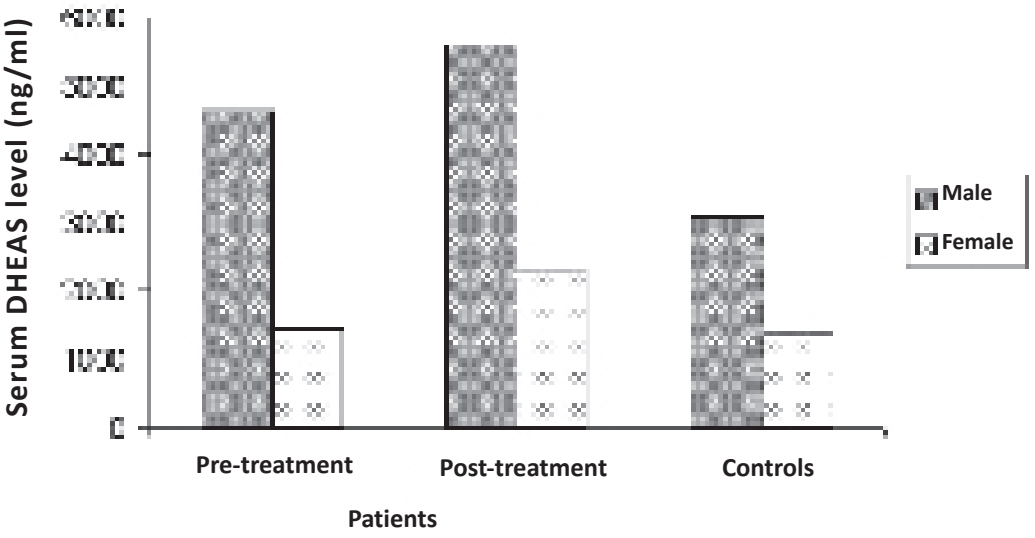

FIGURE I. Serum DHEAS levels in female and male subjects.

sive symptoms were related to DHEAS levels in male patients, while there was no such relationship in females (Goldman and Glei 2007). The fact that DHEAS in women originates from both gonads and adrenal glands might explain this gender difference.

Another important result of the present study is that the MDD patients had reduced serum levels of 17-OHP and total testosterone, which were not improved by treatment. Although testosterone levels did not change in response to ECT treatment, they were become similar to those of the controls after ECT treatment. The finding that low testosterone levels in the MDD patients were more prevalent in males is in accordance with previous investigations (Schweiger et al. 1999, Shores et al. 2005). Decreased 17-OHP levels observed in the present study are inconsistent with other reports of normal progesterone values (Baischer et al. 1995, Romeo et al. 1998). The reason for this discrepancy may be the gender differences of the patients included in the studies. The decrease in gonadal steroids in patients with depression might be related to some symptoms of depression, such as sexual dysfunction and reduced energy.

When the results of the current study were evaluated generally, it was seen that positive GABA-A receptor modulator steroids such as testosterone and progesterone decreased, while GABA-A receptor antagonists such as DHEAS increased in patients with depression. It has been reported that GABA levels decrease in MDD patients and increase in response to ECT treatment (Sanacora et al. 2003, Esel et al. 2008). Therefore, in accordance with previous studies, it can be proposed that depression is associated with inadequate GABA activity as well as imbalances, such as elevated levels of GABA-antagonistic neurosteroids and reduced levels of GABA-agonistic neurosteroids. Although it was not demonstrated in the present study, the mechanism of ECT's curative effect on depression might be modulation of the imbalance of neuroactive steroids. In accordance with the results of the present study, previous studies have reported that the levels of GABA-agonistic neurosteroids in the plasma and cerebrospinal fluid declined, and recovered after antidepressant treatment (Romeo et al. 1998, Uzunova et al. 1998). On the other hand, it is known that GABA-antagonistic neurosteroids such as DHEAS are elevated in patients with depression and are affected by ECT (Mayan et al. 2000).

One of the main limitations of the present study is its small sample. This caused a problem when separate analyses were performed according to gender. If the study group had been gender homogeneous the results would have been more reliable. Nonetheless, because we only included patients that had undergone ECT and excluded those with psychiatric co-morbidity, it was not possible to enlarge our sample. Another limitation of the study was that ECT was the sole treatment method administered. In future studies the effects of different treatment modalities, such as pharmacotherapy, could also be investigated and compared to those of ECT. Moreover, due to laboratory deficiencies, the lack of measurement of other neurosteroids such as allopregnanolone might have prevented us from thoroughly evaluating the neurosteroid imbalances in depression.

In conclusion, the present study demonstrated that in the MDD patients DHEAS levels, a GABA-antagonistic

neuroactive steroid, elevated, and that levels of testosterone and progesterone, which are GABA-antagonistic neuroactive steroids, declined. Furthermore, ECT acted specifically on those hormones, rather than generally. Moreover, these changes could be gender specific. Nevertheless, whether alterations in neuroactive steroids are related to depression's pathophysiology or to their potential role in the therapeutic effects of ECT can only be elucidated through further research consisting of larger samples of both males and females.

REFERENCES

Akdemir A, Örsel S, Dağ İ et al. (1996) Hamilton depresyon derecelendirme ölçeği (HDDÖ)'nin geçerliği, güvenirliği ve klinikte kullanımı. Psikiyatri Psikoloji Psikofarmakoloji Dergisi, 4(4): 251-259.

Assies J, Visser I, Nicolson NA et al. (2004) Elevated salivary dehydroepiandrosterone-sulfate but normal cortisol levels in medicated depressed patients: preliminary findings. Psychiatry Res, 128(2): 117-122.

Baghai TC, di Michele F, Schule C et al. (2005) Plasma concentrations of neuroactive steroids before and after electroconvulsive therapy in major depression. Neuropsychopharmacology, 30(6): 1181-1186.

Baischer W, Koinig G, Hartmann B et al. (1995) Hypothalamic-pituitary-gonadal axis in depressed premenopausal women: elevated blood testosterone concentrations compared to normal controls. Psychoneuroendocrinology, 20(5): 553-559.

Barrett-Connor E, von Muhlen D, Laughlin GA et al. (1999) Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study. J Am Geriatr Soc, 47(6): 685-691.

Bitran D, Shiekh M, McLeod M et al. (1995) Anxiolytic effect of progesterone is mediated by the neurosteroid allopregnanolone at brain GABAA receptors. J Neuroendocrinol, 7(3): 171-177.

Cooper AJ, Finlayson R, Velamoor VR et al. (1989) Effects of ECT on prolactin, LH, FSH and testosterone in males with major depressive illness. Can J Psychiatry, 34(8): 814-817.

Dubrovsky BO (2005) Steroids, neuroactive steroids and neurosteroids in psychopathology. Prog Neuro-Psychopharmacol Biol Psychiatry, 29: 169-192.

Esel E, Kose K, Hacimusalar Y et al. (2008) The effects of ECT on GABAergic function in major depressive patients. J ECT, 24(3): 224-228.

Fabian TJ, Dew MA, Pollock BG et al. (2001) Endogenous concentrations of DHEA and DHEA-S decrease with remission of depression in older adults. Biol Psychiatry, 50(10): 767-774.

Goldman N, Glei DA (2007) Sex differences in the relationship between DHEAS and health. Exp Gerontol, 42(10): 979-987.

Maayan R, Yagorowski Y, Grupper D et al. (2000) Basal plasma dehydroepiandrosterone sulfate level: a possible predictor for response to electroconvulsive therapy in depressed psychotic inpatients. Biol Psychiatry, 48(7): 693-701.

Molina-Hernandez M, Tellez-Alcantara NP (2001) Antidepressant-like actions of pregnancy, and progesterone in Wistar rats forced to swim. Psychoneuroendocrinology, 26(5): 479-491.

Morrison MF, Ten Have T, Freeman EW et al. (2001) DHEA-S levels and depressive symptoms in a cohort of African American and Caucasian women in the late reproductive years. Biol Psychiatry, 50(9): 705-711.

Morsink LF, Vogelzangs N, Nicklas BJ et al. (2007) Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: Results from the Health ABC study. Psychoneuroendocrinology, 32(8-10): 874-883.

Motta E, Ostrowska Z, Kazibutowska Z et al. (2005) The effect of a single electroconvulsive shock on pituitary-thyroid-adrenal-gonadal axis function in men with severe depression--preliminary report. Psychiatr Pol, 39(3): 469-479.

Perry PJ, Yates WR, Williams RD et al. (2002) Testosterone therapy in late-life major depression in males. J Clin Psychiatry, 63(12): 1096-1101.

Romeo E, Ströhle A, Spalleta G et al. (1998) Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry, 155: 910-913.

Rupprecht R (2003) Neuroactive steroids: mechanisms of action and neuropsychopharmacological properties. Psychoneuroendocrinology, 28(2): 139-168.

Sanacora G, Mason GF, Rothman DL et al. (2003) Increased cortical GABA concentrations in depressed patients receiving ECT. Am J Psychiatry, 160(3): 577-579.

Schweiger U, Deuschle M, Weber B et al. (1999) Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. Psychosom Med, 61: 292-296.

Shores MM, Moceri VM, Sloan KL et al. (2005) Low testosterone levels predict incident depressive illness in older men: effects of age and medical morbidity. J Clin Psychiatry, 66(1): 7-14.

Stone EA, Lin Y, Quartermain D et al. (2008) A final common pathway for depression? Progress toward a general conceptual framework. Neurosci Biobehav Rev, 32(3): 508-524.

Takebayashi M, Kagaya A, Uchitomi Y et al. (1998) Plasma dehydroepiandrosterone sulfate in unipolar major depression. Short communication. J Neural Transm, 105(4-5): 537-542.

UK ECT review group (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet, 361(9360): 799-808.

Uzunova V, Sampson L, Uzunov DP et al. (2006) Relevance of endogenous 3alpha-reduced neurosteroids to depression and antidepressant action. Psychopharmacology (Berl), 186(3): 351-361.

Uzunova V, Sheline Y, Davis JM et al. (1998) Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci, 95: 3239-3244.

van Broekhoven F, Verkes RJ (2003) Neurosteroids in depression: a review. Psychopharmacology (Berl), 165(2): 97-110.

Weber B, Lewicka S, Deuschle M et al. (2000) Testosterone, androstenedione and dihydrotestosterone concentrations are elevated in female patients with major depression. Psychoneuroendocrinology, 25(8):765-771.

Wolkowitz OM, Reus VI, Keebler A et al. (1999) Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry, 156: 646-649.

Yaffe K, Ettinger B, Pressman A et al. (1998) Neuropsychiatric function and dehydroepiandrosterone sulfate in elderly women: a prospective study. Biol Psychiatry, 43(9): 694-700.

Yuuki N, Ida I, Oshima A et al. (2005) HPA axis normalization, estimated by DEX/CRH test, but less alteration on cerebral glucose metabolism in depressed patients receiving ECT after medication treatment failures. Acta Psychiatr Scand, 112(4): 257-265.