Basal Plasma Dehydroepiandrosterone Sulfate Level: A Possible Predictor for Response to Electroconvulsive Therapy in Depressed Psychotic Inpatients

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Background: Dehydroepiandrosterone (DHEA) and its sulfate derivative DHEAS are neuroactive steroids. In the brain, they interact with γ-aminobutyric acid (GABA\(_A\)) receptors, which are involved in the regulation of anxiety and mood. The relevance of circulatory neurosteroids to psychiatric disorders and biological treatment is unknown.

Methods: Basal plasma levels of cortisol, DHEA, and DHEAS and the DHEAS–DHEA ratio were determined in 17 psychiatric inpatients before and after six electroconvulsive (ECT) therapy sessions, and all changes were statistically analyzed. For baseline values, 25 healthy individuals served as control subjects. Severity of depression and psychosis in the patients was measured with the Hamilton Depression Rating Scale (HDRS) and the Brief Psychiatric Rating Scale, respectively.

Results: Both basal and post-ECT levels of cortisol, DHEA, and DHEAS were significantly higher in the patients than in the control subjects. DHEAS levels in responding patients were higher at completion of treatment than at baseline. Patients defined as ECT nonresponders (change in HDRS < 30% from before treatments) exhibited elevated basal DHEAS levels compared with ECT responders.

Conclusions: Markedly elevated basal DHEAS levels (mean ± 2 SD of control value) are associated with resistance to ECT and may serve as a potential predictive marker of nonresponsiveness to ECT in depressed patients. Biol Psychiatry 2000;48:693–701 © 2000 Society of Biological Psychiatry

Key Words: Dehydroepiandrosterone (DHEA), DHEAS, neurosteroids, electroconvulsive therapy (ECT), depression, GABA\(_A\) receptor

Introduction

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are neuroactive steroids that are synthesized in situ within the brain, independent of their synthesis in the steroidogenic organs (Baulieu 1991, 1992, 1997; Baulieu and Robel 1990; Mellon 1994; Regelson and Kalimi 1994; Robel and Baulieu 1995a, 1995b; Robel et al 1995). Some of the neuroactive steroids have been found to interact with the γ-aminobutyric acid (GABA)-gated chloride ion channels and may represent an important class of neuromodulators that can rapidly alter central nervous system excitability via nongenomic mechanisms (Baulieu and Robel 1996; Deutsch et al 1992; Majewska 1992, 1995; Majewska et al 1986; Majewska and Schwartz 1987; McEwen 1991). DHEA, but not DHEAS, is associated with antiaggressive effects (Haug et al 1988). Researchers speculate that the sedative effects of some neurosteroids are achieved via direct or indirect enhancement of GABA-mediated chloride ion conductance (Majewska 1995; Regelson and Kalimi 1994; Robel and Baulieu 1995a, 1995b; Young et al 1996). They may act either by decreasing the level of the GABA\(_A\) antagonistlike pregnenolone sulfate (Robel and Baulieu 1995b) or by increasing the level of the GABA\(_A\) agonistlike metabolites of progesterone (such as di- and tetrahydro- progesterone) (Young et al 1996) or the level of the DHEA metabolite androsterone (Majewska 1995).

In contrast to the GABA agonists, the neurosteroids DHEA and DHEAS display allosteric antagonistic properties at GABA\(_A\) receptors (Akiva et al 1991; Demirgoren et al 1991; Majewska 1995; Majewska et al 1990; Spivak 1994); DHEAS appears to be the more potent (Baulieu and Robel 1998). Alterations in the synthesis of the neurosteroids may result in GABA-mediated behavioral changes. Neuroactive steroids were reported to be altered during major depression in humans and to play a putative role in the treatment of depression with antidepressants. A significant decrease in the plasma concentrations of 5α-preg
creases in plasma DHEA and/or DHEAS and cortisol. We hypothesized that ECT will be associated with increases in plasma DHEA and/or DHEAS and cortisol levels and that pretreatment high neurosteroid levels will interfere with the response to ECT.

Methods and Materials

Study Population
The study population consisted of 17 hospitalized psychiatric patients, seven men and 10 women, of mean age 40.4 ± 3.1 years. Two patients had major depression with psychotic features, 10 had schizophrenia with comorbid depression (Siris 1995), and five were schizoaffective patients with current depressive signs and symptoms. The diagnoses of schizophrenia, schizoaffective disorder, and major depression were established according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV—Patient Version (SCID-P; First et al 1995). The duration of the psychiatric disorders was 14.8 ± 8.4 years. All were physically healthy with no infection or history of drug or alcohol abuse. Six patients were receiving zuclopenthixol, three fluphenazine, four haloperidol, and four clozapine; three patients also were being treated with carbamazepine, three with clomipramine, and one with maprotiline. Patients were maintained on the same drug treatment for at least 4 weeks, and treatment regimen was not altered during the entire study period. An independent psychiatrist recommended ECT according to clinical judgment because of the patients’ drug resistance. For the patients with psychotic depression, drug resistance was defined as failure to respond to adequate trials with antipsychotics combined with antidepressants (a heterocyclic antidepressant, a selective serotonin reuptake inhibitor, or another class of antidepressant medication) before initiation of ECT (Prudic et al 1996). The schizophrenic and schizoaffective patients were defined as drug resistant if no satisfactory response was obtained following at least three adequate trials with antipsychotics (Meltzer et al 1990) combined with antidepressants, without or with carbamazepine. For baseline comparison, 25 healthy age- and gender-matched control subjects (10 men, 15 women; mean age 38.5 ± 2.7 years) were used. The control subjects were assessed by a clinical interview according to the SCID guidelines (First et al 1995) and medical examination. The rates of cigarette smoking were similar: 14 of 17 of the patients and 22 of 25 of the control subjects were smokers. None of the patients or control subjects used hormones. Both patients and control subjects were sampled during the summer (June-August) to avoid seasonal variations (Deslypere et al 1983).

The study was approved by the Be’er Yaakov Review Board for Clinical Research, and informed consent was obtained from all participants.

ECT Procedure
Unilateral ECT was administered according to D'Elia (1970), between 7:00 and 8:00 AM with a brief-pulse ECT device (MECTA SRI, Mecta Corporation, Lake Oswego, OR). One stimulus electrode was placed over the nondominant frontotemporal area, and one was placed over the nondominant centroparietal scalp, just lateral to the midline vertex. Premedication included atropine sulfate 0.5 mg IV, thiopental 2–3 mg/kg IV,
and succinylcholine 0.5–1.0 mg/kg IV. Seizure duration was monitored with a single-channel electroencephalograph (including electrodes placed over the contralateral hemisphere) and cuff technique. Treatment was given twice weekly for a total of six sessions. The starting charge of the ECT stimulus dosage (pulse width × frequency (2) × train duration × current) was 48 mc; this was increased gradually during the ECT course according to the rise in seizure threshold, as described previously (Coffey et al 1995; Fink 1992; Sackheim et al 1987).

**Clinical Assessments**

The severity of the depressive, anxiety, and psychotic symptoms was measured with the Hamilton Depression Rating Scale (HDRS; Hamilton 1960), the Hamilton Anxiety Rating Scale (HARS; Hamilton 1959), and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Clinical assessments were performed 1 day before initiation of the ECT course and 1 day after the sixth treatment. The rater (YY) was blind to the clinical data, and all hormone determinations were performed in the same run to avoid interassay variability.

**Hormone Determinations**

Blood samples were obtained before and 20 min after the first and sixth ECT session (ECT-1, ECT-6). Morning (7:00 to 8:00 AM) basal samples were collected concomitantly from the control subjects. All hormone determinations were performed in the same run to avoid interassay variability.

The levels of DHEA, DHEAS, and cortisol were determined by commercial radioimmunoassay (RIA) kits, as follows:

- DHEA-DSL 9000 Active DHEA coated tube RIA kit (Diagnostic Systems Laboratories, Webster, TX): sensitivity 0.02 ng/mL; specificity-cross-reactivity with DHEAS 0.88%; all others negligible; assay variability 10.2% between runs, 5.6–10.6% within runs, according to level.
- DHEA-S-DSL-3500 Active DHEAS coated tube RIA kit (Diagnostic Systems Laboratories): sensitivity 17 ng/mL; specificity-cross-reactivity with DHEA 41%; assay variability 10% between runs, 6.3–9.4% within runs, according to level.
- Cortisol-TKCO1 Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles): sensitivity 0.2 μg%; specificity-cross-reactivity: with prednisolone 76%, 11-deoxycorticisol 11.4%, prednisone 2.3%, cortisone and corticosterone 1%, all others ≤0.3%; assay variability 4.0–6.4% between runs, 3–4.8% within runs, according to level.

**Statistical Analysis**

Analyses of variance (ANOVAs) with or without repeated measures followed by the Student–Newman–Keuls post hoc test were used for the evaluation of the hormonal data. The changes in the HDRS, HARS, and BPRS scores were analyzed by two-tailed Student’s paired t test. Correlation was analyzed by Pearson’s correlation test. All results are expressed as means ± SEMs.

**Results**

**Clinical Effects of ECT**

As expected, the HDRS, HARS, and BPRS scores for the whole group significantly decreased after completion of the six ECT sessions: $p < .0001$ for all (Figure 1).

**Hormone Effects of ECT**

**PATIENTS VERSUS CONTROL SUBJECTS.** The patients had significantly higher levels of cortisol, DHEA, and DHEAS than did the healthy control subjects both at baseline and after the last session [F(4,90) = 4.44, $p = .0025$; F(4,90) = 3.16, $p = .017$; and F(4,90) = 5.51, $p = .005$, respectively; Figures 2–4]. No significant difference was found in the DHEAS–DHEA ratio [F(4,90) = 1.38, $p = .24$, ns; Figure 5]. The patients did not have elevated cortisol and DHEA compared with the controls subjects at the pre–ECT-6 time point, and the DHEAS–DHEA ratio did not differ significantly at the post–ECT-6 time point. No correlation was found between the pretreatment level of depression and DHEAS or DHEA levels ($r = -.11$ and $r = -.28$, respectively, both ns).

**PATIENT LEVELS BEFORE, DURING, AND AFTER ECT.** Cortisol and DHEA plasma levels remained unaltered during the study period [F(67) = 2.19, $p = .1$, ns, and F(67) = 0.30, $p = .8$, ns, respectively; Figures 2 and 3], but DHEAS levels rose significantly from the beginning to the end of treatment. Both pre– and post–ECT-6 DHEAS levels were significantly higher than the pre– and post–ECT-1 levels [F(67) = 5.11, $p = .003$; Figure 4]. A significant difference was also found in the DHEAS–DHEA ratio [pre–ECT-6 vs. post–ECT-1, F(67) = 3.44, $p = .02$; Figure 5]. Because DHEA and/or DHEAS may act as a cortisol antagonist (Hechter et al 1997), we
assessed also possible alterations in DHEAS–cortisol and DHEA–cortisol ratios, which were not affected significantly by the repeated ECT \(F(67) = 2.13, p = .11, \text{ ns}, \) and \(F(67) = 2.36, p = .08, \text{ ns}, \) respectively.

Relationship between Clinical Response and Alterations in DHEAS

No statistically significant correlations were found between the changes in the severity of depressive, anxiety, and psychotic symptoms (post–ECT-6 minus pre–ECT-1) and the corresponding changes in DHEAS, DHEA, and cortisol levels (correlations were \(-.28, .29, \) and \( .11 \) for depression; \(-.14, .17, \) and \( .13 \) for anxiety and \(-.11, .38, \) and \( .29 \) for psychosis, all \(\text{ ns} \)).

Because DHEAS was the only hormone altered significantly by ECT, we decided (post hoc) to evaluate the possibility that pre-ECT DHEAS levels can predict a positive clinical response to ECT. Patients were divided...
into two groups by basal DHEAS levels. A cutoff point of elevated DHEAS level was defined as a level higher than the control mean ± 2 SD (>2200 ng/mL). Eight patients were found to have a basal DHEAS above this cut-off (5171 ± 407 ng/mL), and nine patients a nonelevated basal DHEAS level (1691 ± 407 ng/mL). A positive clinical response of the depressive, anxiety, and psychotic symptoms to ECT was defined as a reduction of at least 30% from baseline in the HDRS scores a day after ECT-6. This cutoff for clinical response was chosen a priori because most of the patients were chronic (mean duration of the psychiatric disorders: 14.8 ± 8.4 years), drug-resistant psychotic patients with depression who are difficult to treat. Accordingly, eight of the nine patients with a nonelevated basal DHEAS level responded to the ECT treatment as opposed to only one of the eight patients with an elevated level (Fisher's exact test: \( p < .005 \), odds ratio = 56, 95% confidence interval 2.9–1072.4). Such a relationship was not found for either anxiety or psychotic symptom response to ECT (Fisher’s exact test: HARS, \( p = .13 \), ns; BPRS, \( p = .29 \), ns). The patient subgroups with high and normal baseline DHEAS levels did not differ significantly in their ECT-induced changes in

![Figure 4](image-url)  
**Figure 4.** Levels of serum dehydroepiandrosterone sulfate (DHEAS) before, during, and after electroconvulsive therapy (ECT). \(*p < .05\) vs control subjects. \(*\*p < .01\) vs. control subjects. \(#p < .05\) vs. pre-ECT-1, \(#\#p < .01\) vs. post–ECT-1 within “total.” \(+p < .05\) vs. post–ECT-1.

![Figure 5](image-url)  
**Figure 5.** Serum dehydroepiandrosterone sulfate (DHEAS)/dehydroepiandrosterone (DHEA) ratio before, during, and after electroconvulsive therapy (ECT). \(*p < .05\) vs. post–ECT-1.
DHEAS levels [1188 ± 449 vs. 662 ± 485 ng/mL; t(15) = 0.77, p = .45, ns].

Discussion

The major findings of this study are that ECT induces an elevation in DHEAS plasma levels and that nonelevated basal DHEAS levels are associated with a clinically relevant response (improvement > 30%) of depressive symptoms (as assessed by the HDRS) to ECT, at least following six repeated ECT treatments. In addition, we demonstrated that cortisol, DHEAS, and DHEA basal levels are higher in drug-resistant psychotic depressed patients than in healthy control subjects.

Our finding of elevated basal plasma levels of DHEA and DHEAS in psychiatric patients is in accordance with earlier studies. Hansen et al (1982) reported high basal DHEA levels in psychotic depressed patients, and Tolleson et al (1990) found elevated 24-hour urinary DHEAS levels in nonpsychotic patients with major depression. In a more recent study, however, Romeo et al (1998) failed to demonstrate altered DHEA in 11 hospitalized patients with severe major depression. Furthermore, other researchers reported on reduced DHEA and/or DHEAS levels or DHEA and/or DHEAS–cortisol ratios in depressed patients (Berr et al 1996; Goodyer et al 1998; Herbert 1998; Osran et al 1993). Our results regarding the effect of ECT are in agreement with Ferguson et al (1964) who demonstrated that ECT increased urinary DHEAS levels. It is of note that DHEA and/or DHEAS show increased concentrations both in blood and in the brain following acute stress (Zinder and Dar 1999). Thus, the pretreatment elevated DHEA and/or DHEAS levels in the patients may be related to stress of hospitalization, and the increase obtained immediately after ECT may be related to the stress of the iatrogenic convulsions or to ECT premedication.

The increase in neuroactive steroid levels during depression may act to attenuate the depression-associated overactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Wolf et al 1997), as well as the severity of the depressive symptoms (Wolkowitz et al 1995, 1997b). It is of note that DHEA has been successfully tested as an antidepressant (Reus 1997; Wolkowitz et al 1997a, 1997b, 1999) and may act as an endogenous antidepressant. Furthermore, the antidepressant responses to DHEA treatment were directly correlated with treatment-induced increases in plasma DHEAS (Wolkowitz et al 1997b).

Previous studies have demonstrated that depression is associated with a decrease in cerebrospinal fluid (CSF) and plasma levels of the GABA-agonistic neurosteroids 3α,5α-tetrahydroprogesterone (THP, allopregnanolone), and 3α,5β-THP (Romeo et al 1998; Uzunova et al 1998), which occurs comonitantly with an increase in plasma levels of 3β,5α-THP, but not DHEA. Furthermore, in one study, CSF levels of allopregnanolone correlated negatively with the severity of depression as assessed by the HDRS, and successful antidepressant therapy led to normalization of both the CSF and plasma content of the GABA-active neurosteroids (Romeo et al 1998; Uzunova et al 1998). Based on preclinical and clinical studies, these authors suggested that the antisyphoric and anxiolytic profiles of selective serotonin reuptake inhibitors may be related to their ability to increase brain allopregnanolone availability (Guidotti and Costa 1998; Uzunov et al 1996). Unfortunately the role of the balance between neurosteroids with GABA-agonistic and antagonistic activity were not assessed in nonpsychotic and psychotic depressed patients.

To the best of our knowledge, the involvement of DHEA or DHEAS in psychosis complicated by depression or in the response of the depressive symptoms of psychotic patients to ECT has not yet been investigated. Because both DHEA and DHEAS are GABA_A antagonists, although DHEAS is a more potent inhibitor of the GABA-gated chloride ion channel function (Baulieu and Robel 1998; Deutsch et al 1992; Majewska et al 1990; Paul and Purdy 1992) and because DHEA may act as a functional antagonist for GABA-agonistic neurosteroids (Prince and Simmonds 1992; Romeo et al 1998), an elevation in their circulatory levels could lead to an increase in anxiety, dysphoria, aggression, or psychosis (Howard 1992; Sands 1954). Moreover, as shown here, a high basal DHEAS plasma level is a predictor of poor response to ECT, whereas a normal-range DHEAS level before treatment, and its persistence following ECT, is associated with a good response (at least following six repeated ECTs). Nevertheless, it is possible that the ECT-induced increase in DHEAS is associated with attenuated GABA activity and increased release of brain serotonin (Abadie et al 1993). In addition, the activity of DHEAS at the N-methyl-D-aspartate and sigma receptors, as well as possible neurosteroid-related adaptation of NMDA receptors, may also be relevant to the antidepressive effect of ECT (Maurice et al 1997; Reddy et al 1998; Reddy and Kulkarni 1997; Skolnick et al 1996). Unfortunately, we did not assess the plasma levels of GABA-agonistic steroids in our study, so we cannot rule out the possibility of a disequilibrium of neuroactive steroids, that is, increase in GABA-agonists before ECT treatment and a decrease in GABA-agonists after ECT treatment. Moreover, the relationship between high circulatory levels of DHEAS and brain neurosteroid biosynthesis and content is as yet unclear. Furthermore, the relationship between neurosteroids and depressive symptoms may be complex because no significant correlation
was found in our study population between the changes in DHEAS levels and changes in depression scores. Nonetheless, a recent study (Heinz et al 1999) has demonstrated in abstinent alcoholics negative correlations between DHEAS plasma concentrations and both self-rated depression and observer-rated depression scores. In addition, the ratio of DHEAS to cortisol concentrations was also negatively correlated with depression scores.

In conclusion, depression in drug-resistant psychotic inpatients is associated with high levels of the putative allosteric GABA<sub>A</sub> receptor antagonist DHEAS as compared with healthy controls, and a markedly elevated (mean ± 2 SD of control levels) basal level of this neurosteroid is a predictor of resistance to ECT. The relationship between elevated DHEAS levels, other GABA-active neurosteroids, depression, anxiety and psychosis, as well as the clinical response to antidepressants, anxiolytics, and ECT, merit further investigation. Our data should be considered as preliminary pilot data and should inspire more rigorous studies in homogeneous psychiatric populations.

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