



DHEA and DHEA-S levels in hospitalized adolescents with first-episode schizophrenia and conduct disorder: A comparison study

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KEYWORDS

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Abstract

Introduction: Increasing evidence exists indicating an association of DHEA and DHEA-S blood levels with psychosis, however many of the findings remain contradictory based on different phases of the illness, different treatments and at a range of ages. To date no studies exist investigating the levels of these neurosteroids in adolescents with psychosis. Such an investigation would be important in order to exclude effects of chronic illness, long-term treatment and repeated hospitalizations.

Method: Peripheral venous blood samples for DHEA, DHEA-S and cortisol determination were collected from first-time hospitalized adolescents with diagnoses of schizophrenia as well as from patients with conduct disorder. Patients were rated with the Positive and Negative Syndrome Scale (PANSS), the Hamilton Scale for depression (HAM-D), the Overt Aggression Scale (OAS) and the impulsivity scale (IS).

Results: DHEA levels in adolescents with schizophrenia were significantly higher than in patients with conduct disorder ($p=0.002$). Blood levels of DHEA and DHEA-S in schizophrenia correlated with the total PANSS scores (both $p<0.05$). No correlations were detected between any of the neurosteroid blood levels and clinical rating scales in the control group.

Conclusions: It may be proposed that individuals in their early stages of schizophrenia psychosis may develop a protective or compensatory neurosteroid response to the first onset of psychosis. Such a putative upregulatory DHEA mechanism may become desensitized with progression to chronic illness. The temporal relationship of investigation of neurosteroid levels in adolescents compared to such investigation in adults may provide important and relevant information.

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1. Introduction

Since the initial description of neurosteroids in the early 1980's (Corpechot et al., 1981), evidence continues to mount indicating that neurosteroids influence and play an important role in mental well-being as well as a multitude of neuropsychiatric disorders including anxiety, depression and psychosis (van Broekhoven and Verkes, 2003; Pisu and Serra, 2004). One such fundamental neurosteroid is dehydroepiandrosterone (DHEA), a major circulating corticosteroid in humans serving as a precursor for both androgenic and estrogenic steroids, and its sulfated metabolite, dehydroepiandrosterone sulfate (DHEA-S) which is the most abundant steroid found in the body (Baulieu and Robel, 1996; Kroboth et al., 1999; Friess et al., 2000). It is considered both a neurosteroid, being produced in the brain, as well as a neuroactive steroid, produced in the adrenals and having its effect on the brain (Corpechot et al., 1981; Baulieu and Robel, 1996). In contrast to the more classically known but slower modulatory gene expression ("genomic") mechanisms of steroid activity, neuroactive steroids such as DHEA and DHEA-S are now known to regulate neuronal function by means of influence on neuronal excitability. These "non-genomic" mechanisms occur via interaction with membrane-bound ligand-gated ion channel receptors (Paul and Purdy, 1992; Rupprecht et al., 2001). DHEA and DHEA-S demonstrate prominent effects on the GABA_A receptor (van Broekhoven and Verkes, 2003).

While increasing evidence exists indicating an association of DHEA and DHEA-S blood levels with psychosis, many of the findings remain contradictory and non-replicable. For example, studies investigating DHEA serum levels in psychosis have demonstrated either low (Tourney and Hatfield, 1972; Harris et al., 2001), elevated (Strous et al., 2004; di Michele et al., 2005), or no differences in DHEA levels (Brophy et al., 1983; Ritsner et al., 2004) compared to matched healthy controls. Similarly, DHEAS levels have been reported to be elevated (Strous et al., 2004; Oades and Schepker, 1994), decreased or in the control range (Ritsner et al., 2005, 2006). Furthermore, other reports have noted cortisol/DHEA molar ratios to be significantly higher in medicated schizophrenia patients and that elevated serum cortisol and cortisol/DHEA(S) ratios may serve as markers of biological mechanisms involved in antipsychotic treatment response (2005). In order to explain some of the discrepancies between DHEA studies in schizophrenia it has been suggested that age and severity of symptoms should be considered (Ritsner et al., 2005, 2006). Perhaps most importantly, studies have investigated subjects at different phases of the illness, different treatments and at a range of ages. These factors would have a significant effect on blood levels and therefore may further account for discrepant findings.

While these above investigations have focused upon DHEA and DHEA-S levels in adults with schizophrenia, to date no studies exist investigating the levels of these neurosteroids in adolescents with psychosis. Such an investigation would be important in order to exclude effects of chronic illness, long-term treatment and repeated hospitalizations. Furthermore, it would be important to explore any differences of these levels in adolescents during the initial stages of psychotic illness as compared with another psychiatric illness also associated with the stress of mental disorder. This study aimed to investigate these factors in a subgroup of first

hospitalized adolescents with schizophrenia and conduct disorder patients as controls.

2. Methods

2.1. Sample population

Hospitalized adolescents between the ages of 15–19 with diagnoses of schizophrenia or conduct disorder were eligible for study participation. Study participants were all first-time hospitalized adolescents at the Department of Adolescent Psychiatry at the Ness Ziona Mental Health Center. Diagnosis was based on DSM-IV criteria, as assessed by clinical interview using the Kiddie Schedule for Affective disorders and Schizophrenia (Kaufman et al., 1996). Adolescents were excluded from the study if they had mental retardation or any past or current physical disorder. The Ness Ziona Mental Health Center Institutional Review Board approved the study. All patients and their parents/legal guardians consented to study participation and written informed consent was obtained from the parents of patients after full explanation of the nature of the study.

2.2. Study design

Peripheral venous blood samples for DHEA, DHEA-S and cortisol determination were collected between 8:00 and 10:00 am after a 12-h night fast. In this way possible changes induced by circadian variation or by previous meals were minimized. All subjects were instructed to avoid unusual physical activity for 24 h prior to blood collection. Blood samples from controls were obtained in a similar manner at the same time of day. In addition, patients were rated for clinical symptomatology. These ratings included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) in order to evaluate severity of psychotic symptomatology and the Hamilton Scale for depression (HAM-D) (Hamilton, 1960) in order to evaluate the severity of depressive symptomatology. In addition, aggressive behavior of the subjects was evaluated by the Overt Aggression Scale (OAS) (Yudofsky et al., 1986) and impulsive behavior by the impulsivity scale (IS) (Plutchik and van Praag, 1989).

2.3. Laboratory analysis

Blood samples of patients and controls were processed and serum extracted following centrifuge. It was then freeze stored under -20°C conditions until assayed. All these serum samples underwent laboratory measurement for a variety of predefined neurobiological measures at the Felsenstein Medical Research Center, Beilinson Campus, Petach Tikva. DHEA was tested with the DHEA-DSL 9000 Activek DHEA coated tube radioimmunoassay (RIA) kit (Diagnostic System Laboratories, Webster, TX, USA); sensitivity 0.7 nmol/L. DHEA-S was tested with the DHEA-S-DSL-3500 Activek DHEA-S coated tube RIA kit (Diagnostic System Laboratory, Webster, TX, USA); sensitivity 4.6 nmol/L. Cortisol was measured by the TKCO1 Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles, CA, USA); sensitivity 13.8 nmol/L. Hormone levels in all samples were measured simultaneously to avoid inter-assay variability. The intra-assay variability values for DHEA, DHEA-S and cortisol were 5.6–10.6%, 6.3–9.4% and 3–4.8% respectively according to the hormonal level.

2.4. Statistical analysis

Two-tailed unpaired Student's *t*-test assuming equal variances and Pearson's Correlation test were used as appropriate for analyses. All results are expressed as mean \pm S.D.

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