ELSEVIER

European Neuropsychopharmacology 15 (2005) 647 – 653

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

www.elsevier.com/locate/euroneuro

Circulatory neurosteroid levels in underweight female adolescent anorexia nervosa inpatients and following weight restoration☆

D. Stein[a], R. Maayan[b], A. Ram[c], R. Loewenthal[d], A. Achiron[e], D. Modan-Moses[f], M. Feigin[a], A. Weizman[b,g,*], A. Valevski[g]

[a]*Pediatric Psychosomatic Department, Chaim Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[b]*Laboratory of Biological Psychiatry, Felsenstein Medical Research Center, Rabin Medical Center, Beilinson Campus, Petah Tiqva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[c]*Center for Treatment of Eating Disorders and Obesity, Chaim Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[d]*Tissue-Typing Laboratory and Bone Marrow Registry, Chaim Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[e]*Multiple Sclerosis Treatment Center, Chaim Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[f]*Pediatric Endocrinology Service, Chaim Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[g]*Geha Mental Health Center, Petah Tiqva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

Received 26 January 2005; received in revised form 1 May 2005; accepted 5 May 2005

Abstract

Nineteen female adolescent inpatients diagnosed with anorexia nervosa, restricting type (AN-R) and 16 non-eating disordered (ED) controls were assessed for plasma dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and cortisol levels, and for eating-related and non-eating-related psychopathology. AN-R patients were assessed at admission, 1 month and 4 months following hospitalization. The non-ED controls were assessed once. No baseline between-group differences were found in plasma cortisol, DHEA, and DHEA-S levels, whereas the patient group had a significantly lower Cortisol/DHEA-S ratio and elevated scores on most psychopathological parameters. A significant increase was found in the body mass index of the AN-R patients at 4 months post-hospitalization, accompanied by a decrease in plasma cortisol levels and a trend towards decreased Cortisol/DHEA and Cortisol/DHEA-S ratios, whereas no change occurred in psychopathology. The difference in Cortisol/DHEA-S ratio between AN-R patients and non-ED controls, and the different patterns of change in cortisol vs. DHEA(-S) levels following weight restoration, may in part account for the feeding difficulties in AN, particularly during refeeding.

Keywords: Anorexia nervosa; Neurosteroids; Dehydroepiandrosterone; Dehydroepiandrosterone-sulphate; Cortisol; Refeeding

1. Introduction

Neurosteroids are steroids synthesized either directly in the central nervous system (CNS) or in the periphery that have definite effects on the brain (Monteleone et al., 2001; Patchev et al., 1994). The most important of these neuroactive steroids include allopregnanolone (3α5α-tetrahydroprogesterone), synthesized within the CNS glial cells from pregnanolone, dehydroepiandrosterone (DHEA), and its sulphated metabolite dehydroepiandrosterone-sulphate (DHEA-S). The synthesis of DHEA and DHEA-S has not been demonstrated in the brain, apparently because the enzyme cytochrome $P450_{17\alpha}$, which converts pregnanolone to DHEA, is not found within the CNS (Monteleone et al., 2001). Nevertheless,

☆ This research was supported by the Offer Grant for Psychiatric Research, Tel Aviv University, Sackler Faculty of Medicine (Dr. D. Stein).
* Corresponding author. Geha Mental Health Center, Rabin Medical Center, Beilinson Campus, Petah Tiqva, 49100, Israel. Tel.: +972 3 9258290; fax: +972 3 9241041.
E-mail addresses: weizmana@post.tau.ac.il, aweizman@clalit.org.il (A. Weizman).

0924-977X/$ - see front matter © 2005 Elsevier B.V. and ECNP. All rights reserved.
doi:10.1016/j.euroneuro.2005.05.001

these two neurosteroids may persist in the brain unchanged for over 2 weeks following adrenalectomy and gonadectomy, demonstrating that central DHEA and DHEA-S levels are likely independent of their peripheral biosynthesis in the adrenals or gonads (Corpechot et al., 1981; Baulieu, 1991).

Neurosteroids can alter neuronal excitability by binding to ion channel-coupled neurotransmitter receptors at the cell membrane. They may act at inhibitory γ-amino-butyric acid type-A (GABA-A) and glycine receptors, at excitatory glutamate receptors, and at serotonin, *N*-methyl-D aspartate, sigma type 1, and nicotinic acetylcholine receptors (Engel and Grant, 2001).

Converging evidence suggests that neurosteriods may be relevant to the pathophysiology of several psychiatric disorders such as depression, schizophrenia post-traumatic stress disorder and attention deficit hyperactivity disorder (Spivak et al., 2000; Michael et al., 2000; Strous et al., 2001, 2004; Ritsner et al., 2004). Specifically, they may modulate the expression of mood, anxiety, aggression, cognition, general well-being and activity (Van Goozen et al., 1998; Wolf and Kirschbaum, 1999; Monteleone et al., 2001; Michael et al., 2000).

There is some evidence for a putative role of neurosteroids in the pathophysiology of feeding behaviors. Allopregnanolone, which is a positive modulator of inhibitory GABA-A and glycine receptors, may increase feeding behavior and weight, whereas DHEA and DHEA-S, which are negative modulators of GABA-A and glycine receptors and positive modulators of excitatory glutamate receptors and serotonin receptors, may decrease food intake and weight (Engel and Grant, 2001; Kaur and Kulkarni, 2001). The interaction between these neurosteroids and serotonin may be of relevance in the regulation of feeding behavior because of the down-regulation of serotonin found in underweight individuals with anorexia nervosa (AN), and its elevated activity in long-term recovered AN patients (Kaye et al., 2004). Additionally, elevated serotonin activity may increase several AN-related behavioral constraint and dysphoric traits, including obsessionality, rigidity, perfectionism, harm-avoidance, depression and anxiety (Casper et al., 1992; Pollice et al., 1997; Kaye et al., 2004).

Corticotropin Releasing Factor (CRF) stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn stimulates the adrenal cortex to secrete DHEA and DHEA-S, in addition to cortisol (Leowattana, 2004). Underweight individuals with AN show elevated plasma cortisol secretion, reflecting hypersecretion of endogenous CRF and an overdrive of the CRF/ ACTH system (Hotta et al., 1986). The secretion of CRF and ACTH in AN normalizes after weight restoration, leading to normalization of cortisol levels (Kaye et al., 2004) and theoretically also of DHEA and DHEA-S levels, although this has not been investigated yet. As the secretion of DHEA and DHEA-S by the adrenal gland is driven by the CRF/ACTH system, it seems plausible that alterations in the production of these neurosteroids may occur in patients diagnosed with AN (Monteleone et al., 2001).

Only a few studies have previously assessed neurosteroid function in AN. Zumoff et al. (1983) have found decreased mean daily values of plasma DHEA and DHEA-S in 14 AN patients with a concomitant increase in plasma cortisol concentrations, whereas Winterer et al. (1985) reported normal cortisol levels and reduced baseline and ACTH-stimulated concentrations of DHEA and DHEA-S in six underweight AN women. Other studies have also found reduced levels of DHEA and DHEA-S in acutely ill AN patients (Devesa et al., 1987; Gordon et al., 2000). In the largest and most rigorous study performed yet, Monteleone et al. (2001) have found increased plasma levels of allopregnanolone, DHEA, DHEA-S, and cortisol in 30 female AN patients, compared with 30 age-matched healthy controls.

The aim of the present study was to assess whether a change would occur in circulatory neurosteroid levels in AN patients following weight restoration compared to the acute underweight stage of the disorder, and whether these changes will be associated with changes in core eating-related and non-eating-related psychopathology. We hypothesized that plasma DHEA, DHEA-S and cortisol levels will be elevated in underweight AN patients compared with non-eating disordered (non-ED) controls, whereas weight restoration will be associated with normalization in the level of these neurosteroids.

2. Experimental procedures

2.1. Patients

Two groups of female participants between the ages of 15 and 19 years were included in the study. Nineteen inpatients with AN restricting-type (AN-R) were hospitalized in the Pediatric Psychosomatic Department of the Chaim Sheba Medical Center, Tel Hashomer, Israel. Patients were excluded if they ever had a bipolar disorder, schizophrenic spectrum disorder, organic brain syndrome, substance use disorder, or any lifetime or current medical disorder with the potential to affect food consumption and weight (e.g., diabetes mellitus or thyroid disorders). Two AN-R patients had primary amenorrhea and 17 had secondary amenorrhea at admission.

A control group included 16 female adolescent volunteers recruited from families of the hospital's staff. These participants were required to have no lifetime or current history of any psychiatric or medical disorder and no stigmata indicative of an ED. Their lifetime and current weight was between 90% and 115% of average body weight (Metropolitan Life Tables, 1959), and they had regular menses since menarche.