Journal of Affective Disorders 215 (2017) 118–124

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Attenuated DHEA and DHEA-S response to acute psychosocial stress in individuals with depressive disorders☆

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ARTICLE INFO

Keywords:
DHEA
DHEA-S
Depressive disorders
Acute stress response

ABSTRACT

Background: In recent years, a relationship between depression and basal dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) levels has frequently been suggested, but responses of these adrenal steroids to psychosocial stress have not been examined in individuals with depressive disorders. In this study, we examined salivary DHEA, DHEA-S, and cortisol/DHEA response to the Trier Social Stress Test (TSST) in individuals with depressive disorders and in healthy controls to discover whether the responses of DHEA and DHEA-S to acute psychosocial stress could be a more sensitive marker of HPA dysfunction in depressive disorders.

Methods: We compared salivary cortisol, DHEA, DHEA-S, and cortisol/DHEA levels to the TSST tests between 38 individuals with depression and 43 healthy controls aged 18.4–25.9 years. Depression severity was assessed by the self-reported Beck Depression Inventory-II (BDI-II). Salivary samples were evaluated at four time points: the baseline (−10 time point), before the TSST started (0 time point), the end of the TSST (+20 time point), and the recovery (+50 time points).

Results: No significant differences existed in the basal adrenal hormonal levels between subjects with depressive disorders and controls; however, at the end of TSST, attenuated DHEA and DHEA-S response was identified in subjects with depressive disorders compared to that found in healthy subjects. The differences in the DHEA and DHEA-S levels at the +20 time point, as well as the differences in the cortisol/DHEA at the +50 time point, exhibited negative correlations with depression severity.

Conclusion: Attenuated DHEA and DHEA-S response to acute psychosocial stress was identified in subjects with depressive disorders. These findings help us to discover the bi-directional relationship between depression and the hypothalamic-pituitary-adrenal (HPA) axis function, hence furthering our understanding of whether altered DHEA and DHEA-S response to psychosocial stress may be a more sensitive method than basal adrenal steroid analysis for detecting HPA axis dysfunction in depressive disorders.

Limitations: As this is a case control study, we could only draw the conclusion of the bi-directional relationship between the depression and the altered DHEA (S) response to stress, and could not identify whether depression was due to the HPA dysfunction, or vice versa. Prospective studies such as such as cohort studies or epidemiology experiments are needed to further test the cause of depression or HPA dysfunction; and the mechanisms responsible for altered DHEA and DHEA-S in response to acute psychosocial stress in individuals with depressive disorders are also needed to be clarified.

1. Introduction

Dehydroepiandrosterone (DHEA) and its sulfated form (DHEA-S) are androgen precursors secreted by the zona reticularis layer of the adrenal cortex in response to adrenocorticotropic hormone (ACTH) (Nguyen and Conley, 2008). The pool of DHEA-S serves as a reservoir

☆ Subject Areas: (1) Psychoneuroendocrine activity (2) Depressive disorder.

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http://dx.doi.org/10.1016/j.jad.2017.03.013
Received 8 October 2016; Received in revised form 12 January 2017; Accepted 5 March 2017
Available online 16 March 2017
0165-0327/

for DHEA, and DHEA-S has a longer half-life and lower clearance than DHEA. DHEA and DHEA-S are supposed to be anabolic hormones and thus have been suggested to play a significant role in protection against the negative consequences of elevated levels of cortisol levels, which is a catabolic adrenal steroid secreted by the zona fasciculata layer of the adrenal cortex that stimulates the mobilization of the energy needed for overcoming stressors (Karishma and Herbert, 2002; Maninger et al., 2009). The ratio of cortisol and DHEA represents the balance between catabolic and anabolic activity (Young et al., 2002; Markopoulou et al., 2009).

The hypothalamic-pituitary-adrenal (HPA) axis in individuals with depressive disorders has attracted much attention, and a bi-directional relationship between depression and DHEA and DHEA-S levels has frequently been suggested (Hu and Zhang et al., 2011). Animal studies have suggested that DHEA and DHEA-S have antidepressant effects (Maayan et al., 2006; Ovsyukova et al., 2013). Specifically, it has been reported that individuals with depressive disorders might be associated with decreased DHEA and DHEA-S levels, which affect mood regulation, concentration, and learning abilities in the patient (Michael et al., 2000; Markianos et al., 2007; Wong et al., 2011; Oulis et al., 2014; Hu et al., 2015). However, other studies have reported increased DHEA and DHEA-S levels (Kurita et al., 2013) in drug-free subjects with depressive disorders and no association between depression and DHEA and DHEA-S levels (Young et al., 2002). Investigations have shown that basal levels of adrenal steroids vary with age, sex, weight, emotional state, and environmental or physiological stimuli (Birkenhager-Gillesse et al., 1994; Vermeulen, 1995; Laudenslager et al., 2009), therefore, different methodological designs might obtain different results. Consequently, these discrepancies might prevent us from considering basal DHEA and DHEA-S as alternative biomarkers of HPA function to evaluate depressive disorders.

In recent years, the adrenal steroid response to acute psychosocial stress has been hypothesized to be a more sensitive measure of HPA axis function because HPA dysfunction is thought to occur primarily through impairment of its response to environmental or physiological stimuli (Burke et al., 2005; Shirotsuki et al., 2009). Previous studies in normal individuals have shown that DHEA increases following the stressor reactivity phase from the baseline (i.e. pre-stressor), and returns to near the baseline levels following the stress recovery phase (Lennartsson et al., 2012, 2013). Studies have reported an attenuated DHEA-S response in individuals with irritable bowel syndrome (IBS) (Sugaya et al., 2012) and blunted cortisol/DHEA responses in the higher-social-anxiety group (Shirotsuki K et al., 2009) to acute psychosocial stress, such as the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), and suggested that there may be reduced HPA axis reactivity to psychosocial stress in individuals with psychosomatic or affective disorders (Izawa et al., 2008). Abnormal responses of DHEA, DHEA-S, or cortisol/DHEA to psychosocial stress might be a good biomarker for these disorders. However, to our knowledge, DHEA, DHEA-S, or cortisol/DHEA response to psychosocial stress has not been examined in individuals with depressive disorders.

In this study, we aimed to examine salivary DHEA, DHEA-S and cortisol/DHEA response to the TSST in individuals with depressive disorders and in healthy controls. The primary purpose of this study was to gain insight into the possible bi-directional relationship between depression and DHEA, DHEA-S, and cortisol/DHEA dysfunction; and to discover whether the response of DHEA and DHEA-S, the main adrenal steroids other than cortisol, to acute psychosocial stress could be a marker of HPA dysfunction in depressive disorders.

2. Methods

2.1. Participants

Three hundred and forty-eight college student aged 18–26 years in Southern Medical University were screened to survey somatic and psychological symptoms from January 2012 to December 2013. The self-reported Beck Depression Inventory-II (BDI-II) was used, and the cutoff for depression disorders was a score of 13. Participants scoring higher than 13 underwent a detailed clinical interview by one of the investigators, which included the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR), to confirm the diagnosis of depressive disorders. Participants scoring lower than 13 were considered without depressive disorder, from which the healthy controls were selected.

Thirty-eight patients with newly occurring depressive disorder (male/female: 20/18; age: 22.5 ± 4.7 year) and 43 healthy (male/female: 24/19; age: 23.1 ± 4.3 year) controls were recruited from the screening. The matched factors included age, gender ratio, body mass index (BMI), heart rate and blood pressure. Each participant's history of medical disease, psychiatric illness, and medication use was carefully evaluated by an interview and a medical chart review (Robles-Pina, 2011). All the recruited participants were drug-free; none of them had been prescribed any antidepressant drugs or treated for any; other serious psychiatric, somatic, or comorbid substance-related disorder. They consumed no illicit, prescription, or OTC (over-the-counter) drugs as confirmed by physical and mental examination and biological analysis. They had no cigarette smoking or alcohol consumption habits, which have a documented effect on the HPA axis (Baron et al., 1995; Sierksma et al., 2004)..

Informed consent was obtained from all participants prior to commencement of the study, and the Ethics Committee of School of Public Health of Southern Medical University approved all the procedures.

2.2. Study procedure

The participants underwent the TSST, a standardized laboratory stress test that consisted of a simulated job interview and a mental arithmetic task, both in front of a committee (two men and one woman), a video camera, and a microphone (Kirschbaum et al., 1993). The baseline information, such as heart rate and blood pressure, was detected after the participant rested quietly for 10 min before the test. To minimize the circadian variations of the steroids, all experimental sessions were started between 8:00 and 10:00 a.m. Since the adrenal hormones change during these hours, we compared the average baseline collection time between the depressive and control groups, to ensure that no significant difference existed in the started time. The total test time for each participant was two hours, including preparations and measurements after completing the test. Participants were instructed to avoid smoking or consuming alcohol, caffeine, or other substances that would influence adrenal steroids secretion for 24 h before the TSST.

All female participants were tested during the follicular phase of the menstrual cycle (self-reported, between the 5th and 10th days) to minimize the influence of sex hormones on HPA and autonomic nervous activities. All procedures necessary for the data collection were explained to the individuals. The stress tests were performed in our laboratory under controlled temperature (21–25 °C) and humidity (50–60%).

2.3. Measures

2.3.1. Beck Depression Inventory (BDI)

Before performing the TSST, depression severity was assessed by the self-reported Beck Depression Inventory-II (BDI-II) (Vanheule et al., 2008; Ward, 2006). The BDI-II consists of 21 items, each of which is scored on a scale from 0 to 3. The maximum score is 63. Higher total scores indicate more severe depressive symptoms..

2.3.2. Hormone assay

Salivary samples were collected from the participants during the