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DHEA and DHEA-S response to acute psychosocial stress in healthy men and women

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ABSTRACT

This study investigates the effect of acute psychosocial stress on serum concentrations of DHEA and DHEA-S in healthy men and women. Twenty men and 19 women (age 30–50 years) underwent Trier Social Stress Test (TSST). Physiological measurements were performed before, directly after the stress test and after 30 mins of recovery. In both men and women, significantly elevated DHEA and DHEA-S levels were observed in response to the stressor. There was a large inter-individual variation in the magnitude of the response, especially for DHEA but no statistical difference between men and women. Magnitude of the change in the levels of DHEA was found to be positively associated with the magnitude of the changes in ACTH, cortisol and heart rate. Furthermore, the results of this study suggest that the capacity to secrete DHEA and DHEA-S during acute psychosocial stress declines with age.

1. Introduction

In studies of physiological response to acute psychosocial stress the main focus has been the activity of the hypothalamic–pituitary–adrenal (HPA) axis usually through assessment of the cortisol levels. Cortisol is synthesized by the adrenal cortex in response to secretion of adrenocorticotropic hormone (ACTH), which stimulates mobilization of the energy that is needed for overcoming the stressor. Dehydroepiandrosterone (DHEA) and its sulphated metabolite dehydroepiandrosterone sulphate (DHEA-S) are androgen precursors, also secreted by the adrenal cortex in response to ACTH. Cortisol and DHEA are produced in different sections of the adrenal cortex; the zona fasciculata layer secretes cortisol while the zona reticularis layer secretes DHEA and DHEA-S (Nguyen and Conley, 2008). Concentrations of DHEA-S are much higher than concentrations of DHEA, partly because DHEA-S has longer half-life and lower clearance than DHEA. Only desulphated DHEA is biologically active; the pool of DHEA-S serves as a reservoir for DHEA. Peak concentrations of DHEA-S and DHEA are reached between the ages of 20 and 30 and thereafter levels declines with increasing age, depending on changes in the zona reticularis (Hornsby, 1997; Parker et al., 1997). While cortisol is a catabolic hormone, DHEA is an anabolic and thus has a protective and regenerative role (Theorell, 2008; Maninger et al., 2009). DHEA and DHEA-S have been shown to have neuroprotective, antioxidative, anti-inflammatory, and antiglucocorticoid effects (Kalimi et al., 1994; Maninger et al., 2009), and have got extensive publicity because of their association with a broad range of health outcomes (Goldman and Glei, 2007). The ratio of cortisol and DHEA represents the balance between catabolic and anabolic activity. High cortisol/DHEA ratio has been related to e.g. chronic stress (Jeckel et al., 2010), depression (Young et al., 2002), and cognitive disorders (Ferrari et al., 2001a).

Since DHEA has anabolic and antiglucocorticoid effects and thus protects against the effects of cortisol, DHEA and DHEA-S have been suggested to play a significant role in protection against the negative consequences of stress (Morgan et al., 2004). However, few studies have been conducted to study the DHEA and DHEA-S response to acute psychosocial stress. Thus, the knowledge of the response of DHEA and DHEA-S to acute psychosocial stress is limited, especially in women. All except one of the published studies on DHEA or DHEA-S response to acute psychosocial stress were conducted on men, and these studies showed increased DHEA levels in response to the stressor (Oberbeck et al., 1998; Morgan et al., 2004; Izawa et al., 2008; Shirotsuki et al., 2009). Pico-Alfonso et al. investigated DHEA response to acute psychosocial stress in women (Pico-Alfonso et al., 2007). That study aimed at investigating the

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role of natural fluctuations in estrogen levels (different phases in the menstrual cycle) on physiological responses to an acute psychosocial stressor. HPA axis response was measured based on the changes in the levels of cortisol and DHEA. In this study significant increase in the DHEA levels was observed when both subgroups were combined together (18 women in follicular phase and 18 women in ovulatory phase) while significance was not reached when the groups were analysed separately.

The primary aims of this study were to investigate changes in concentrations of DHEA and DHEA-S in response to acute psychosocial stress in healthy men and women, and to assess if differences in the response exist between men and women. To our knowledge, there are no published studies that focused on examining sex differences in stress-induced DHEA response. Examining existence of such differences is important particularly because of the plausible protective effects of DHEA and DHEA-S during stress. To further investigate the DHEA and DHEA-S response to acute psychosocial stress, we also aim to relate the DHEA and DHEA-S response to the response of the more common physiological measures of stress, such as ACTH, cortisol and heart rate. The few studies that exist on DHEA response to acute psychosocial stress were conducted on individuals in early adulthood. Since the capacity to produce DHEA and DHEA-S declines with age, it could be speculated that stress-induced DHEA response also depends on age. Our sample consists of healthy individuals between 30 and 50 years of age, and gives us the possibility to study whether age affects the stress-induced DHEA secretion within this age range. We also aimed to investigate the cortisol/DHEA ratio to assess the balance between the catabolic and the anabolic activity during acute psychosocial stress.

2. Methods

2.1. Participants

Thirty-nine healthy subjects (20 men and 19 women, mean age 37.5 years, SD 5 years), were included in the study. The subjects were recruited from a cohort study, surveying psychosocial work environment and health, and through advertising in a local daily newspaper. To be included in the study, subjects had to be between 30 and 50 years of age, and only individuals reporting "no stress at all" or "very little stress" on a single perceived stress item (Elo et al., 2003) were included. These criteria were selected in order to avoid inclusion of individuals suffering from chronic stress problems. Symptoms of burnout, anxiety and depression were measured with Shirom-Melamed Burnout Questionnaire (SMBQ) (Melamed et al., 1992), and Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983). Exclusion criteria were as follows, a body mass index less than 18.5 kg/m^2 or over 30 kg/m^2, high blood pressure (SBP above 160 mmHg or DBP above 90 mmHg), current infection, vitamin B-deficiency (high homocysteine), known systemic disease such as diabetes or thyroid disease or known psychiatric disease. As the menstrual cycle and the use of estrogens are known to affect the physiological response to acute stress (Kirschbaum et al., 1999; Kajantie and Phillips, 2006), women taking estrogens, pregnant, nursing and postmenopausal women were excluded from the study. Subjects who were taking psychoactive medications or medications that may affect the HPA axis function were also excluded. The study was approved by the Regional Ethical Review Board in Göteborg, Sweden, and was conducted according to the Helsinki Declaration. All participants gave written informed consent before entering the study.

2.2. Study procedure

The participants underwent the TSST, a standardized laboratory stress test that was set up according to the original design of Kirschbaum and co-workers (Kirschbaum et al., 1993). The stress task in TSST 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. Subjects were instructed to abstain from hard physical exercise 24 h before the stress test. Subjects were also instructed to avoid beverages containing caffeine at least two hours before the stress test and to eat a standardized lunch. Smoking and using snuff were not accepted on the test day. For female subjects, the stress tests were conducted during follicular phase of the menstrual cycle (self-reported, between the 5th and 10th days). Phase of the menstrual cycle phase was confirmed by measuring serum levels of estradiol and progesterone in samples collected before the stress test. The stress tests were performed at the Institute of Stress Medicine, Gothenburg, Sweden. The total test time for each subject was two hours, including preparations and measurements after completing the test. The test procedure was conducted between 1300 h and 1700 h. At arrival, an intravenous catheter was inserted in the subject's forearm (−30 time point). The first blood sample was drawn at the −10 time point. The next blood sample was drawn directly before the TSST started (0 time point). Between these two measurements, the participants rested (approximately seven minutes). At the start of the TSST, the participants were introduced to the tasks, and asked to prepare for the simulated job interview (10 min). After this, the participants had the simulated job interview (5 min) and thereafter performed a mental arithmetic task (5 min). Directly after the end of the stress test (the +20 time point), a third blood sample was drawn. Thereafter, participants rested (recovery period of total 30 min), and at 10 and 20 min into the recovery period, the fourth and fifth blood samples were drawn (+30 and +40 time points). A final blood sample was drawn at the end of the recovery period (+50 time point). Cardiovascular responses (heart rate, systolic blood pressure, and diastolic blood pressure) were electronically recorded (CardioPerfect Workstation, Welch Allyn) every fifth minute starting from 10 min prior to the TSST, until 30 min after the TSST ended (between the −10 and +50 time points).

2.3. Hormone assays

A total of 122 ml blood was collected from the participants during the TSST. Blood samples were collected at six time points (−10, 0, +20, +30, +40, and +50; 7 ml at each time point) for measurements of plasma ACTH and serum cortisol. Blood samples at four of the six time points (−10, 0, +20, +50) were collected (20 ml at each time point) for the measurement of DHEA and DHEA-S. The samples were collected in two different tubes; pre-chilled tubes containing EDTA and serum separator tubes. After the tubes had been centrifuged, plasma and serum were stored at −80 °C until assayed. Plasma concentrations of ACTH were measured by immunoradiometric assay (limit of detection, 0.4 pmol/L) (CIS bio International, Gif-sur-Yvette Cedex, France). Serum concentrations of cortisol were measured by electrochemiluminescence immunoassay (limit of detection, 20 nmol/L). Serum concentrations of DHEA were determined using Liquid chromatography–tandem mass spectrometry (LC–MS/MS) method (limit of quantitation, 175 pmol/L), as described in details elsewhere (Kushnir et al., 2006, 2010). Serum concentrations of DHEA-S were measured by radioimmunoassay techniques (RIA) (limit of detection, 0.14 μmol/L, Diagnostic Products Corporation, Los Angeles, CA). Interassay coefficients of variation were below 10% for ACTH, below 11% for cortisol, below 10% for DHEA and below 12% for DHEA-S. Estradiol and progesterone were measured from a sample taken at the −10 time point, to confirm the self-reported phase of the menstrual cycle. Estradiol was measured by radioimmunoassay (RIA) (limit of detection, 0.04 nmol/L; DiaSorin, Saluggia, Italy). Progesterone was measured by chemiluminescence microparticle immuno assay (limit of detection, 0.3 nmol/L; Abbott Laboratories, Diagnostic Division, Abbott Park, IL). Interassay coefficient of variation for progesterone was below 11% (at 3 nmol/L), and below 5% (at 30 nmol/L); and for estradiol it was below 10% at 0.4 nmol/L, and below 16% at 0.04 nmol/L.

2.4. Statistical analysis

Baseline values for DHEA, DHEA-S, ACTH, cortisol, heart rate, systolic blood pressure and diastolic blood pressure were calculated as means of the values at the −10 and the 0 time points. Three women and one man had missing values of heart rate, systolic and diastolic blood pressure at the 0 time point. For these four individuals the −10 time point values of heart rate, systolic blood pressure and diastolic blood pressure was used as the baseline value, instead of the mean of the two measures. The baseline values of the cortisol to DHEA ratio were calculated by dividing the baseline concentration of cortisol by the baseline concentration of DHEA. Kolmogorov–Smirnov test was used on each study variable (men and women separately and/or together depending on the analysis) to test whether the data were normally distributed. Logarithmic transformation was used for the variables that showed a non-normal distribution.

To evaluate possible differences between men and women in the baseline characteristics, age, body mass index (BMI), the hormonal and cardiovascular parameter values at baseline were analysed using a *t*-test. Log values of baseline DHEA, DHEA-S, ACTH, cortisol and heart rate were used for this analysis. Gender differences in scores on the burnout, anxiety and depression scales were analysed by using a Mann–Whitney *U* test. Between-gender differences in nicotine use were assessed with a Chi-square test.

Assessment of the association between concentrations of DHEA, DHEA-S, cortisol, and the cortisol/DHEA ratio with age of the participants was performed using Pearson correlation analysis. Log values of DHEA, DHEA-S, cortisol and the cortisol to DHEA ratio at baseline were used.

To assess HPA axis and cardiovascular functions, we first identified the peak levels of heart rate, systolic blood pressure, and diastolic blood pressure (in between the +5 and +20 time points) and the peak levels of ACTH and serum cortisol (in between the +5 and +50 time points) for each participant, and then we performed paired samples *t*-tests (separately in men and women) using before and after stress test values (baseline value and identified peak value). Log-transformed concentrations of ACTH, cortisol, heart rate, and systolic blood pressure were used.

To assess the effect of acute psychosocial stress on serum concentrations of DHEA and DHEA-S, the stress-induced peak level of each of the hormones was identified in every participant (at either +20 or +50 time point), and a paired samples *t*-test was performed, using before and after stress test values (baseline and peak