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Hypothalamic–pituitary–adrenal axis response to acute psychosocial stress: Effects of biological sex and circulating sex hormones

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ABSTRACT

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis influences the risk for developing stress-related disorders. Sex-dependent differences in the HPA axis stress response are believed to contribute to the different prevalence rates of stress-related disorders found in men and women. However, studies examining the HPA axis stress response have shown mixed support for sex differences, and the role of endogenous sex hormones on HPA axis response has not been adequately examined in humans. This study utilized the largest sample size to date to analyze the effects of biological sex and sex hormones on HPA axis social stress responses. Healthy, 18- to 30- year-old community volunteers ($N = 282$) completed the Trier Social Stress Test (TSST), a widely used and well-validated stress-induction laboratory procedure. All women ($n = 135$) were tested during the follicular phase of their menstrual cycle (when progesterone levels are most similar to men). Adrenocorticotropic hormone (ACTH) and cortisol measures were collected at multiple points throughout pre- and post-TSST. Testosterone and progesterone (in men) and progesterone and estradiol (in women) were determined pre-TSST. Following the TSST, men had greater ACTH and cortisol levels than women. Men had steeper baseline-to-peak and peak-to-end ACTH and cortisol response slopes than women; there was a trend for more cortisol responders among men than women. Testosterone negatively correlated with salivary cortisol response in men, while progesterone negatively correlated with ACTH and cortisol responses in women. These data confirm that men show more robust activation of the HPA axis response to the TSST than do women in the follicular phase of the menstrual cycle. Testosterone results suggest an inhibitory effect on HPA axis reactivity in men. Progesterone results suggest an inhibitory effect on HPA axis reactivity in women. Future work is needed to explain why men mount a greater ACTH and cortisol response to the TSST than do women during the follicular phase of the menstrual cycle.

1. Introduction

Stress-related psychiatric syndromes, such as anxiety, depression, and substance use disorders, are believed to share common biological mechanisms that include dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Girdler et al., 2012; Petrowski et al., 2010; Stephens and Wand, 2012; Young et al., 2004). The HPA axis is a major component of the neuroendocrine system that is activated in response to stressors to help restore homeostasis. Corticotropin releasing factor and arginine vasopressin are released from the paraventricular nucleus of the hypothalamus and control the secretion of adrenocorticotropic

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hormone (ACTH) from the anterior pituitary which, in turn, stimulates the adrenal cortex to secrete glucocorticoid hormones, mainly cortisol in humans.

The HPA axis hormonal response to psychosocial stress appears to be moderated by sex. A series of studies with small to moderate sample sizes have documented sex-moderating effects in response to the Trier Social Stress Test (TSST), a well-validated, standardized protocol that induces psychosocial stress (Kirschbaum et al., 1993). Cumulative evidence over the past 16 years generally shows that men have greater HPA axis activation in response to the TSST than women (see Foley and Kirschbaum, 2010; Allen et al., 2014 for review); however, these differences may depend on the menstrual phase in which women are tested and on whether free (salivary) or total (blood) cortisol is measured (e.g., Childs et al., 2010a; Duchesne et al., 2012; Kirschbaum et al., 1999). Sex differences in TSST responses have not yet been confirmed within a single, well-powered study.

Sex-related differences in HPA axis stress reactivity may contribute to differences in vulnerability toward specific disorders between men and women. This view is supported by research showing that the prevalence of mood disorders (such as anxiety, major depressive and post-traumatic stress disorders) is almost twice as common in women as men whereas substance use disorders is twice as common in men as women (Compton et al., 2007; Girgus and Yang, 2015; Tolin and Foa, 2006). Further, HPA axis response to psychosocial stressors has been shown to differ between men and women, particularly in depressive disorders (Bagley et al., 2011; Chopra et al., 2009). The mechanisms involved in regulating HPA axis stress responses, how they differ in men compared with women, and how they are associated with or protective in developing stress-related pathologies remain unclear. It is important to elucidate these mechanisms to facilitate and inform prevention and treatment efforts.

Preliminary research supports the potential role of sex hormones in determining the sex-related HPA axis stress response. In men, acute doses of progesterone suppressed cortisol response to the TSST (Childs et al., 2010b). Recently, Juster et al. (2016) reported that sex differences in cortisol response to the TSST were attenuated when analyses were adjusted for baseline progesterone, testosterone and estradiol levels. Although their sample of women was large ($n = 144$), it comprised a group with heterogeneous hormonal status (normal cycling, post-menopausal, or on hormonal contraceptives), many of whom had current or past psychiatric histories. Only two previous studies examined healthy young adults and considered pre-TSST endogenous levels of sex hormones; these studies found no effect on subsequent cortisol response to the TSST in follicular phase women ($n = 14$; Altemus et al., 2001), men ($n = 23$) and luteal phase women ($n = 18$; Schoofs and Wolf, 2011). The small sample sizes in the latter two studies, and confounds within the recent larger study, precluded drawing any definitive conclusions about the effects of endogenous circulating sex hormones on HPA axis reactivity. Thus, using the TSST in the largest sample of healthy individuals to date, the current study sought to confirm whether the HPA axis response differs by sex, and examine the extent to which pre-TSST sex hormones relate to the magnitude of the HPA axis response.

Whereas many of the earlier TSST studies examined menstrual phase as a surrogate marker of hormonal influence, we examined the effect of endogenous circulating levels of testosterone and progesterone (in men) and progesterone and estradiol (in women) at the onset of the stressor. We tested women during the follicular phase of the menstrual cycle, when progesterone levels are most comparable to men (Schumacher et al., 2014). The study objectives were to (1) compare the HPA axis responses in young men and women in greater detail than previously completed, and (2) determine the effects of circulating sex hormone levels on HPA axis responsivity. First, we hypothesized that men will have a greater ACTH and cortisol response than women to the TSST. Based on extensive preclinical literature and preliminary human studies, we also hypothesized that sex hormone levels at the onset of stress will negatively correlate with HPA axis hormone response in both men and women (Handa and Weiser, 2014; Juster et al., 2016).

2. Methods

2.1. Recruitment

We recruited healthy adults, aged 18–30 years, to participate in a stress response study through newspaper advertisements and posted flyers throughout the Baltimore metropolitan region. Initial screening was done by telephone and then in person at the Johns Hopkins University School of Medicine (JHU). Participants gave written informed consent after complete description of the study. The study was approved by the JHU School of Medicine Institutional Review Board. Participant assessments included a medical history, physical examination, blood chemistry profile, complete blood count, alcohol breathalyzer test, and urine toxicology screen. DSM-IV axis I psychiatric diagnoses were determined by a Master's level interviewer administering The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II; Bucholz et al., 1994). The SSAGA-II is a comprehensive research diagnostic assessment designed to obtain a detailed history of current and past psychiatric disorders. Developed for the Collaborative Study on the Genetics of Alcoholism (COGA; Begleiter et al., 1995), it is specifically designed to differentiate commonly occurring co-morbid conditions by identifying the ages of onset and recency of diagnoses, and by distinguishing symptoms due to alcohol and drug use from those observed in affective, conduct, or antisocial personality disorders. The SSAGA-II has been shown to have good intra- and inter-rater reliability and validity in clinical as well as general population samples (Bucholz et al., 1994, 2006; Hesselbrock et al., 1999).

Exclusion criteria included: (a) current medical conditions and/or use of prescription medications, (b) diagnosis of any DSM-IV Axis I disorder, (c) use of any psychoactive medication within the past 30 days, (d) treatment in the last 6 months with antidepressants, neuroleptics, sedative hypnotics, glucocorticoids, appetite suppressants, estrogens, opiates, or dopamine medications, (e) seizure disorder or history of closed head trauma, (f) self-reported drinking of more than 30 drinks per month in women or 60 drinks per month in men, (g) drug-positive urine screens at intake or on procedure day, (h) nicotine dependence measured by the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), and (i) pregnancy, or use of hormonal birth control methods in women.

Participants in this study were included in an earlier report that examined the association of cortisol responses to the TSST with allelic variants in the CRHR1 and FKBP5 genes (Mahon et al., 2013). A subset of these participants was also analyzed for sex differences in HPA axis reactivity in an earlier report (Uhart et al., 2006). For this study, we included only women with serum progesterone levels <3 ng/mL obtained on the day of the TSST session.

2.2. Psychometric instruments at intake assessment

Upon eligibility assessment, participants completed the Trait component of the State-Trait Anxiety Inventory (STAI) which contains 20 items that are scored from 1 (not at all) and 4 (very much so), and yields a total summary score ranging from 20 from 80. Higher scores on the STAI-Trait scale indicates greater