Psychoneuroendocrinology (2007) 32, 1052–1061

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Exogenous testosterone attenuates the integrated central stress response in healthy young women

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Received 4 May 2007; received in revised form 16 August 2007; accepted 16 August 2007

KEYWORDS
Testosterone;
Electrodermal activity;
Fear potentiated startle;
Anxiolytics;
Fear;
Anxiety

Summary
Animal research has shown that the androgen steroid testosterone, the end product of the hypothalamic–pituitary–gonadal (HPG) axis, down regulates the integrated stress response at multiple levels. These effects have been demonstrated at the level of the amygdala and the bed nucleus of the stria terminalis, and along the different nodes of the hypothalamic–pituitary–adrenal (HPA) axis. The present study was designed to assess effects of exogenous testosterone upon reactivity of the autonomic nervous system and modulation of the acoustic startle reflex in humans. Twenty healthy female participants received double-blind, placebo-controlled sublingual administrations of .5 mg testosterone. Measurements were made of phasic electrodermal activity, cardiac responses, and startle reflexes to acoustic probes while participants were exposed to pictures with strongly aversive, neutral, or positive content. Subjective reports of mood and picture evaluations were also obtained. Results support the hypothesis of a generally decreased responsiveness of the stress system by showing reduced skin conductance responses as well as reduced affective startle modulation in anxiety-prone participants after administration of testosterone. Candidate neurobiological mechanisms of action are outlined and discussed, and it is argued that androgens promote dynamic regulation of the stress system through actions upon central neuropeptidergic pathways that control corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) expression. The present findings highlight the importance of further investigation of the possible role of the HPG axis in disorders that are associated with HPA axis dysfunctions.

1. Introduction

Recent research suggests that the hypothalamic–pituitary–gonadal (HPG) axis, through its end product testosterone,

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doi:10.1016/j.psyneuen.2007.08.006

plays an important role in the down regulation of distinct components of the integrated stress response, such as central fear mechanisms (Van Honk et al., 2005; Hermans et al., 2006) and the hypothalamic–pituitary–adrenal (HPA) stress response (Viau, 2002; Rubinow et al., 2005). Initially, these notions were fuelled by findings of gender differences in HPA responsiveness in rodents (Kitay, 1963). Similar effects were later observed in humans, in terms of increased adrenal sensitivity to corticotropins in women (Horrocks et al., 1990; Roelfsema et al., 1993). Recently, the focus of attention has turned directly to the moderating role of androgen steroids on these processes. Evidence is mounting across various species that gonadal steroids attenuate central fear responses (Bitran et al., 1993; Boissy and Bouissou, 1994; Bouissou and Vandenheede, 1996; Aikey et al., 2002). In agreement, HPA axis functioning is down regulated after elevation of androgens (Kitay, 1963), especially phasic stress-related activity (Handa et al., 1994; Viau and Meaney, 1996; Papadopoulos and Wardlaw, 2000).

The integrated central response to stress (see De Kloet et al., 2005, for review) is thought to be regulated through the amygdalar region (basolateral and central nucleus) and the bed nucleus of the stria terminalis (BNST). These areas have efferent connections to, e.g., the nucleus ambiguous, which controls vagal cardiac innervation and induces bradycardia (Porges, 1995), the nucleus reticularis pontis caudalis, which is implicated in startle modulation (Davis et al., 1982), and the hypothalamus, which mediates sympathetic autonomic responses through its lateral part, as well as endocrine responding via the paraventricular nucleus (PVN; see Walker et al., 2003). A human model for assessing the compound stress response is available through laboratory measurement of psychophysiological responding to affective content (Lang et al., 1998). In agreement with the above notions, women have been shown to exhibit stronger startle modulation and autonomic responses to aversive content than men (Bradley et al., 2001b), which also suggests a similar attenuating role for androgens.

The present study investigated the hypothesis that androgens attenuate central stress responses by administering a single dose of testosterone to female participants, transiently raising their testosterone to an approximate male level. Using different categories of photographs as emotion provoking stimuli, we assessed both objective quantitative and subjective phenomenological effects of androgens upon the human stress system. Both baseline and phasic activity of sympathetic and parasympathetic branches of the autonomic nervous system were monitored using the dependent measures of electrodermal activity, heart rate, and startle reflex modulation. Subjective measures were obtained using affective picture ratings and mood questionnaires. Because affective startle modulation has been demonstrated to be positively related to self-reported fear and anxiety (Cook et al., 1991, 1992; Grillon et al., 1993), and negatively to fearlessness (Patrick et al., 1993; Pastor et al., 2003; Lissek et al., 2005), we administered an anxiety questionnaire prior to testing (Spielberger's Trait Anxiety Inventory; Spielberger et al., 1983).

Experiments using this type of paradigm typically demonstrate that electrodermal activity varies as a function of generalized arousal, and is thus elevated independent of valence being positive or negative. In contrast, startle modulation is normally potentiated during aversive stimulation, and inhibited by positive stimuli. Furthermore, processing of strongly aversive material is commonly accompanied by bradycardia (Lang et al., 1998). Instigated by previous findings using an identical testosterone administration procedure (Van Honk et al., 2005; Hermans et al., 2006), we anticipated a less pronounced effect in all physiological measures to aversive stimuli against a background of replication of these basic findings. In accordance with earlier findings, we expected no testosterone effects upon subjective reports.

2. Methods

2.1. Participants

Twenty healthy female volunteers (age range: 18–23) were recruited through university campus flyers and received payment for participation in this study. All procedures were approved by the institutional review board in accordance with the declaration of Helsinki. All participants provided written informed consent. Exclusion criteria were history of psychiatric or endocrine illness, left handedness, regular smoking, and use of any medication other than single-phase oral contraceptives. Participants were tested in a double blind, placebo controlled, mixed factorial crossover design.

2.2. Testosterone administration samples

Testosterone solutions for sublingual administration consisted of .5 mg of testosterone, 5 mg of hydroxypropyl-beta-cyclodextrin (used as carrier), 5 mg ethanol, and .5 ml of water. Placebo samples differed only in absence of testosterone. The method of sublingual testosterone administration was established through extensive piloting in our laboratory as part of studies on the time course of effects of testosterone on sexual arousal (Tuiten et al., 2000). It was demonstrated that plasma levels of total testosterone peaked at a supraphysiological level (for females) of an approximate ten-fold increase 15 min after intake (peaking at approximately 24 nmol/l), without changes in sex-hormone-binding globulin levels, whereas vaginal vasocongestion in response to sexual stimuli peaked 4 h after intake. In a line of research on the cognitive and emotional effects of acute testosterone we have successfully applied this delayed effect (Postma et al., 2000; Van Honk et al., 2001, 2004, 2005; Schutter and Van Honk, 2004; Hermans et al., 2006). Therefore, the present study used the same interval of 4 h between administration and testing.

2.3. Material and apparatus

Photographs with emotional content were carefully selected from the International Affective Picture System (Center for the Study of Emotion and Attention, 1999) photoset based on normative ratings for women. In total, 2 (versions of the experiment) $\times$ 3 (emotional valence categories; negative, neutral, or positive) $\times$ 19 (pictures per category) $=$ 114, and