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ORIGINAL ARTICLE

Anxiety, reactivity, and social stress-induced cortisol elevation in humans

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Abstract

OBJECTIVES: Traditionally, it has been hypothesized that highly anxious/emotionally reactive subjects may have exaggerated social stress response. We examined the relationship between self-reported anxiety, emotional reactivity, and social stress response.

METHODS: We investigated the relationship between personality scales of trait-state anxiety, subjective autonomic reactivity, and salivary cortisol levels before and after social stress exposure (Trier Social Stress Test) in 20 men.

RESULTS: Significant positive correlations between anxiety, subjective autonomic reactivity, and basal cortisol levels were observed, while neither anxiety nor subjective autonomic reactivity was correlated with social stress-induced cortisol elevation.

CONCLUSIONS: The present results indicate (i) subjects with higher degrees of trait anxiety/subjective autonomic reactivity have higher basal cortisol levels, and (ii) in contrast to the traditional view, anxious personality is not strongly associated with exaggerated cortisol response to social stress.

Introduction

Because altered functions of hypothalamic-pituitary-adrenal (HPA) axis and autonomic systems are strongly related to the development of various mood and anxiety disorders (e.g., depression and social phobia), a neuroendocrine basis of anxiousness and autonomic reactivity has been attracting much attention [8]. We have previously reported that subjects with low degrees of interpersonal trust have exaggerated HPA response to social stress [12], and social stress-induced cortisol elevation acutely impairs social recognition (face-name association) memory [13]. Neuroimaging studies have revealed that depressive subjects' plasma cortisol (a stress hormone in humans) levels are positively correlated with the activity of the left amygdala [2]. In a traditional view on the relationship between negative mood/anxiousness and stress reactivity, exaggerated acute neuroendocrine responses to a psychosocial stressor has been assumed in mood and anxiety disorder patients [1]. It has further been demonstrated that social phobics, characterized by augmented anticipa-

tory fear to interpersonal stress, have exaggerated HPA response to social stressors [4].

However, recent investigations into the relationship between depression/anxiety disorders and neuroendocrine response to a psychosocial stressor have provided conflicting results. For instance, several studies demonstrated that depressed patients and subjects with high degrees of trait anxiety had reduced neuroendocrine reactivity to stressors [6,14]. Therefore, it is of importance to examine the relation of state-trait anxiety to both basal cortisol levels and social stress-induced cortisol elevation for clarifying the conflicting points.

With respect to the relationship between emotional reactivity and actual neuroendocrine response to stressors, it has been reported that several types of patients with anxiety disorders have exaggerated perceived autonomic reactivity in spite of normal (i.e., not considerably enhanced) physiological response to stressors [3]. To date, however, little is known regarding the relationship between perceived autonomic reactivity and actual neuroendocrine response to social stress. Furthermore, chronic elevation in cortisol levels has been reported to induce hyperactivation of the amygdala [9]. Therefore, it is important to examine the relationship between perceived autonomic reactivity and basal cortisol levels, in addition to social stress-induced cortisol response, for understanding the neuroendocrine correlates of emotionally reactive personality. In the present study, we examined the relations of state-trait anxiety, subjective autonomic reactivity and perceived stress during a social stress exposure, to both basal cortisol levels and social stress-induced acute cortisol elevation in healthy young men.

Methods

In the present study, personality questionnaires and social stress-induced cortisol elavation of 20 healthy male students aged 19–23 years (average: 20.1 years) were analyzed. Smokers, drinkers, and subjects taking medicine, or suffering from acute or chronic hormonal dysregulations, atopic-, psychosomatic, or psychiatric diseases were excluded. To avoid the effects of a menstrual hormonal cycle, only male subjects were selected. The participating subjects were informed that the study involved the relationship between neuroendocrine measurements and personality traits. They were given instructions not to (i) drink anything containing alcohol or caffeine from 8.00 p.m. on the day before their participation, (ii) eat/drink anything except water, nor do physical exercises within 1hour prior to their participating in the experiment. The subjects had no prior experience with the Trier Social Stress Test (TSST) [7,12,13]. They signed an informed consent form and received payment for participation. The effect of circadian hormone rhythms was minimized by conducting all sessions between 2.30 p.m. and 5.30 p.m. In order to expose the subjects to a social stressor, the TSST protocol [7,12,13], which consists of both a public speech (5min, a serious-minded self-introduction after a 20min preparation period) and a mental arithmetic task (5min, serial subtractions of the number 13 from 1022) in front of both an audience (consisting of three male experimenters wearing white lab-coats, having pencils and paper for noting the evaluation of subjects' speech/arithmetic ability, sitting in front of the subject) and a video camera was employed. This well-established standard laboratory social stress protocol has proven to be a provocative psychosocial stressor [7,12,13].

Saliva samples for the assessment of free salivary cortisol were collected immediately before the onset of the social stress sessions as well as 10 minutes after the cessation of TSST, when cortisol levels peak [7,12,13]. Saliva was collected from the subjects using Salivette (Sarstedt, Rommelsdorf, Germany) collection devices. The saliva samples were stored at –20 degrees Celsius until a biochemical analysis was conducted. Before assaying the saliva samples for cortisol, they were thawed and centrifuged, which results in low viscosity saliva. Cortisol in saliva was determined using an enzyme-linked immunoassay method employing a polyclonal anticortisol-antibody. All procedures determining salivary cortisol levels were conducted using the standard protocols by Teikoku Hormone Medical Co. Ltd. (Japan), which has significant experience in various steroid hormonal assays [11,12,13]. Staff at the company did not know the nature of the experimental conditions. To assess subjects' *trait* personality characteristics (before TSST), we utilized Spielberger's trait anxiety scale [10], Cacioppo's autonomic reactivity scale [5], and a visual analogue scale [13] (VAS1, 0–100 %) of subjects' perceived anticipatory stress level immediately before the onset of TSST. It should be noted that the autonomic reactivity scale measures subjects' perceived degree of autonomic response (e.g. a change in a heart rate) to stressful daily events as a trait (i.e., stable and independent of a particular experimental condition) propensity [5]. To assess subjects' *state* (i.e., dependent on a particular condition) affective characteristics during TSST, Spielberger's state anxiety scale [10] and a visual analogue scale of perceived stress level [13] (VAS2, 0–100 %) were assessed at the end of TSST. All alpha coefficients of the personality scales were larger than 0.8, verifying the reliability of the scales. Each subject's cortisol elevation was defined as "[post-stress cortisol level]-[pre-stress cortisol level]" [12].

Pearson's correlation analysis was utilized to examine the relationship between personality scores and cortisol level/elevation. Data are expressed as mean ± SEM. Significance level was set at 5% throughout. Statistical procedures were conducted with R language (R foundation for Statistical Computing).

Results

The subjects' pre-stress and post-stress cortisol levels were 7.3±2 nmol/L and 13±1.9nmol/L, respectively. This indicates that TSST significantly increased subjects' cortisol levels ($p< 0.05$). This range of the subjects' averaged cortisol elevation was similar to values observed in previous studies [4,6,7,12,13]. The correlations between subjects' affective characteristics and cortisol level/ele-

vation are presented in Table 1. Subjects' trait anxiety was significantly correlated with basal (pre-stress) and post-stress cortisol levels in a positive manner (n=20, $p<0.05$); while trait anxiety was not significantly correlated with social stress-induced cortisol elevation, indicating that a high level of anxiousness as a trait personality is associated with chronic high levels of cortisol, irrespective of a psychosocial stress exposure. Autonomic reactivity scale was also significantly associated with basal cortisol levels, as well as perceived stress (VAS2) and anxiety during TSST, in a positive manner (n=20, $p<0.05$), while autonomic reactivity scale scores were not significantly correlated with post-stress cortisol level or social stress-induced cortisol elevation. This implies that individuals with high degrees of perceived autonomic reactivity have higher levels of basal cortisol and perceived stress response, but do not actually have enhanced cortisol response to social stress. Finally, we observed a significant negative correlation between basal cortisol level and social stress-induced cortisol elevation (n=20, $p<0.05$), indicating that subjects with high levels of basal cortisol have lowered HPA response to a psychosocial stress exposure.

Discussion

We observed a significant positive correlation between trait anxiety, autonomic reactivity scores, and basal cortisol levels, but did not find a significant correlation between trait anxiety, autonomic reactivity, and social stress-induced cortisol elevation. This is the first study to compare (a) the relationship between anxiety and autonomic reactivity-related trait personality characteristics and basal cortisol levels, with (b) the relationship between those characteristics and acute neuroendocrine stress response in healthy young men. Moreover, it was demonstrated that social stress-induced cortisol elevation was negatively correlated with basal (pre-stress) cortisol levels. Our data suggest that (i) high trait anxiety and subjective autonomic reactivity are associated with chronic elevation in the level of HPA activation, and (ii) subjects with chronic high levels of cortisol may have blunted acute neuroendocrine response to experimental social stress, possibly due to saturated HPA reactivity.

Neurobiologically, chronic elevation in cortisol levels is known to increase corticotropin releasing hormone (CRH) mRNA expression at the amygdala, resulting in the enhancement of emotional reactivity to fear [8,9]. Neuroimaging studies reported that basal plasma cortisol levels in depressed patients were shown to associate with the activity of the amygdala [2]. Consistent with these findings, the present study showed that subjects with higher basal cortisol levels had more exaggerated subjective autonomic reactivity as a trait personality and higher levels of perceived (but not physiological) stress during TSST. Moreover, it has been reported that patients with depression and comorbid anxiety disorders had exaggerated adrenocorticotropic hormone (ACTH) response to a psychosocial stressor, but their cortisol elevation induced by social stress was not significantly enhanced in comparison to healthy controls, indicating that subjects with high trait anxiety have exaggerated amygdala and ACTH responses to social stressors, but their cortisol secretion induced by ACTH stimulation might be blunted [15]. Collectively, these findings are in line with our present results in healthy young men. Our present results suggest that future neuropsychopharmacological studies should examine the impacts of antidepressant and anxiolytic drugs on basal cortisol levels, rather than social stress-induced acute cortisol elevation.

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Table 1: Correlations between state-trait personality characteristics and cortisol level/elevation.

	Pre-stress cortisol	Post-stress cortisol	Cortisol elevation	VAS1	VAS2	Trait Anxiety	State Anxiety	Autonomic Reactivity
Pre-stress cortisol		0.38	– 0.52*	0.42	0.27	0.58*	0.25	0.46*
Post-stress cortisol			0.58*	0.29	0.21	0.51*	0.10	0.21
cortisol elevation				–0.097	–0.03	–0.05	– 0.13	–0.20
VAS1					0.51*	0.14	0.60*	0.41
VAS2						0.1	0.77*	0.56*
Trait Anxiety							0.13	0.52*
State Anxiety								0.74*
Autonomic Reactivity								

*: significant correlation (n=20, $p<0.05$)

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