



Elevated alpha-amylase but not cortisol in generalized social anxiety disorder

J.F. van Veen^{a,*}, I.M. van Vliet^a, R.H. DeRijk^b, J. van Pelt^c,
B. Mertens^d, F.G. Zitman^a

^a Department of Psychiatry, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

^b Division of Medical Pharmacology, LACDR/LUMC, Gorlaeus Laboratories, 2300 RA Leiden, The Netherlands

^c Department of Clinical Chemistry, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

^d Department of Medical Statistics, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

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Summary Stress-system dysregulation is thought to increase the risk for anxiety disorders. Here we describe both hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system (ANS) activity in basal non-challenging conditions and after 0.5 mg dexamethasone in generalized social anxiety disorder (gSAD) patients. To ensure stress-free sampling we collected saliva and determined cortisol and alpha-amylase (sAA), the latter a relative new marker of autonomic activity.

Forty-three untreated gSAD patients without comorbidity were compared with 43 age and gender matched controls in non-stressed conditions on sAA and cortisol after awakening, during the day (including late evening), and after a low dose (0.5 mg) of dexamethasone. Cortisol and sAA were analyzed with mixed models. Additional analyses were done with paired *t*-tests. Apart from the assessments in the morning, gSAD patients had significantly higher diurnal and post-dexamethasone 1600 h sAA levels. No differences between gSAD and controls in any cortisol measurements were found.

In conclusion, in gSAD in basal, non-stimulated conditions and after dexamethasone, we found hyperactivity of the ANS, as measured with sAA, but not of the HPA-axis. This suggests a relative increased activity of the ANS as compared to the HPA-axis, in line with the observed hyperarousal in gSAD.

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1. Introduction

Social anxiety disorder (SAD; also known as social phobia) is one of the most common anxiety disorders (Stein, 2006). It is

characterised by the fear of scrutiny by others. In specific SAD (sSAD) one or two situations are feared, e.g. speaking in public, while in generalized SAD (gSAD) most social situations are involved (American Psychiatric Association, 2000). The anxiety in gSAD is often accompanied by hyperarousal, such as increased heart rate, trembling, blushing and sweating. These clinical observations suggest an involvement of the stress system (Kloet et al., 2005; Goldstein, 2003). However, whether the stress system is involved in gSAD is an unresolved

* Corresponding author at: Department of Psychiatry B1-P, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 71 5263785; fax: +31 71 5248156.

E-mail address: j.f.van_veen@lumc.nl (J.F. van Veen).

question. Moreover, it is unclear under which conditions (basal versus challenge) and which parts of the stress system (autonomic nervous system (ANS) or the hypothalamic pituitary adrenal (HPA) axis) are involved. In gSAD, these systems have never been studied in concert, instead previous studies aimed to elucidate the role of these systems separately.

The function of the HPA-axis in SAD has been investigated by using cortisol levels as biological marker. In basal conditions no differences were found between gSAD patients and controls with respect to 24-h urine cortisol levels (Potts et al., 1991; Uhde et al., 1994). Moreover, diurnal saliva cortisol levels of adolescent girls with SAD were comparable with those of healthy controls (Martel et al., 1999). The last study can be criticized since no distinction was made between subtypes of SAD. With some, but not all psychological challenges, HPA-axis dysfunction was reported. In one study gSAD patients had a significantly larger cortisol response to the Trier Social Stress Test than controls (Condren et al., 2002). Another study found a more outspoken dichotomous cortisol response after a stress challenge in gSAD compared to the control group: the cortisol responders in the group of gSAD patients had higher cortisol levels after the stress task than the cortisol responders in the control group, the cortisol non-responders in the gSAD group had lower cortisol levels than the non-responders in the control group (Furlan et al., 2001). However, in the study with adolescent girls mentioned above, Martel et al. (1999) did not find any difference in cortisol responses between SAD and controls after a public speaking challenge. One study on the effects of a pharmacological challenge with dexamethasone in gSAD was published, reporting no differences between gSAD patients and controls in 24-h urine cortisol levels (Uhde et al., 1994).

The function of the ANS has been studied in various ways. Stein and colleagues found higher noradrenaline levels in gSAD patients in one study, but could not replicate this finding in another (Stein et al., 1992, 1994). One study reported on higher baseline heart rate and blood pressure in gSAD patients compared to controls (Bouwer and Stein, 1998), whereas other studies did not (Grossman et al., 2001; Laederach-Hofmann et al., 2002; Gerlach et al., 2003).

A major drawback of autonomic measures, especially plasma (nor)adrenaline obtained by venipuncture, is the stress accompanying the sampling. Furthermore, heart rate and blood pressure are easily influenced by many factors, e.g. posture.

Recently, salivary alpha-amylase (sAA) has been proposed to reflect ANS activity (Chatterton et al., 1996; Granger et al., 2007). In basal conditions in healthy volunteers, sAA activity shows a diurnal profile with a decrease during the first 60 min after awakening and an increase during the rest of the day (Rohleder et al., 2004; Nater et al., 2007). sAA levels were relatively independent of several possible confounders like gender, body mass index (BMI), activity level, smoking, eating and drinking but significantly associated with chronic stress and stress reactivity in healthy volunteers (Nater et al., 2007).

Psychological and physiological challenges were followed by increases in sAA (Gilman et al., 1979; Bosch et al., 1996; Chatterton et al., 1996, 1997; Rohleder et al., 2004, 2006; Nater et al., 2005, 2006; Kivlighan and Granger, 2006), although most studies failed to find significant correlations

between adrenaline and noradrenaline, peripheral markers of the ANS, and sAA (Rohleder et al., 2004; Nater et al., 2006) indicating that stress-dependent sAA increases reflect changes of the ANS in general, not catecholamine increases. Furthermore, two pharmacological challenges provided direct evidence that sAA measures ANS activity. Propranolol (a non-selective beta-blocker), combined with a stressful task, resulted in lowering of sAA, showing the sensitivity of sAA to changes in adrenergic activity (Van Stegeren et al., 2006). Similarly, a yohimbine (an alpha-2-receptor antagonist) challenge induced not only increases of peripheral noradrenaline levels but also increases of sAA levels compared to placebo. No correlations were found between adrenaline, noradrenaline and sAA, indicating that sAA reflects central noradrenaline release instead of peripheral noradrenaline secretion (Ehlert et al., 2006). More research on sAA is discussed in the review of Granger et al. (2007).

The question remains whether there is a difference in basal autonomic activity in gSAD as compared to controls. Furthermore, we aimed to investigate the ANS and the HPA-axis in concert, since the specific balance between these stress systems, as was shown in experimental animal research, is often overlooked (Goldstein, 2003). Considering sAA as a measure of autonomic activity together with stress-free sampling of saliva stimulated us to use sAA to test basal autonomic activity in gSAD.

Here we report the awakening and diurnal rhythm of both cortisol and sAA, in basal conditions. In order to also measure the feedback sensitivity of the HPA-axis, we added a low-dose dexamethasone suppression test with 0.5 mg (Gaab et al., 2002), which is more sensitive to detect differences between different groups than higher dosages. We expected, based on former research, not to find differences in HPA-axis function in gSAD as compared to controls. However, we hypothesized that the ANS, as measured using sAA, would show hyperactivity in gSAD during the day.

2. Methods

2.1. Subjects

Forty-three patients with gSAD and 43 age (± 5 years) and gender matched healthy controls participated in this study. No life-time psychiatric comorbidity or clinically significant medical disorders, such as endocrinological disorders, were allowed. Patients were not currently treated for gSAD. Subjects were excluded in the case of alcohol consumption of over three units a day, using drugs of abuse or smoking more than 20 cigarettes a day. Use of psychotropic medication (including beta-blocking agents) had to be stopped at least 14 days before the trial, with the exception of oxazepam (half life 4–15 h) with a maximum dosage of 30 mg a day and only when used sporadically on an 'as needed' basis. It was allowed to be used up to 24 h before the test days. No oral glucocorticoids were allowed in 6 months prior to the study. Because of the influence of estradiol on the HPA-axis, women were tested during the follicular phase of the menstrual cycle and women using oral contraceptives in the stop week. Women were asked about their menstruations in order to assess perimenopause (period of irregular menstruations before menopause) or menopause (last menstruation over a year ago). In case of any doubt, hormonal assessments were

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