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Altered salivary alpha-amylase awakening response in Bosnian War refugees with posttraumatic stress disorder

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Summary In posttraumatic stress disorder (PTSD), chronic activation of the sympathetic nervous system (SNS) has been suggested. No study so far has investigated diurnal secretion patterns of salivary alpha-amylase (sAA) in PTSD, a promising candidate for non-invasive assessment of SNS activity. We compared sAA diurnal profiles between a group of Bosnian War refugees with PTSD and a healthy control group, and further analyzed for associations with psychiatric symptoms and glucocorticoid (GC) sensitivity of inflammatory regulation. PTSD patients showed a sAA awakening response profile that was opposite to those seen in healthy controls, i.e. an increase instead of a sharp decrease. Patterns of sAA secretion were further positively associated with psychiatric symptoms of PTSD. Finally, higher sAA awakening responses were associated with higher GC sensitivity of inflammatory cytokine production. These findings are in line with altered SNS function in PTSD, and lend further support for employing assessment of diurnal sAA profiles as non-invasive biomarkers in stress-related disease.

1. Introduction

Posttraumatic stress disorder (PTSD) develops in some but not all individuals that have been subjected to a traumatic event. PTSD involves alterations in different neurobiological structures and biochemical systems, yet it is characteristically associated with neuroendocrine dysregulations in the stress system, i.e. in the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). The majority of previous research has focused on neuroendocrine changes of the HPA axis. PTSD has been found to be associated with lower baseline concentration of cortisol in plasma, saliva, and urine (e.g. Boscarino, 1996; Heim et al., 2000; Mason et al., 1986; Rohleder et al., 2004a), stronger suppression of cortisol after administration of synthetic glucocorticoid (GC, de Kloet et al.,

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2006; Newport et al., 2004; Yehuda et al., 2002), increased release of hypothalamic corticotropin releasing hormone (CRH, Baker et al., 1999; Bremner et al., 1997; Sautter et al., 2003), higher number of peripheral GC receptors in lymphocytes (Yehuda et al., 1993), and higher GC sensitivity of different target tissues (Grossman et al., 2006; Rohleder et al., 2004a). Nevertheless, contrasting findings (e.g. Lemieux and Coe, 1995; Liberzon et al., 1999; Maes et al., 1998; Pitman and Orr, 1990) prevent final conclusions, especially as there are reasons to believe that hypocortisolism may rather be related to trauma exposure and subgroups of PTSD and not to PTSD itself (for a systematic review see Meewisse et al., 2007). Taken together, previous findings point towards a chronically hyperactive and hypersensitive HPA axis, combined with a sustained condition of hypocortisolism in individuals diagnosed with PTSD.

In contrast to PTSD-related HPA axis dysfunctions, neuroendocrine correlates of SNS activation in PTSD are less well studied. Given the suppressive effect of cortisol on SNS activity (Munck et al., 1984), a consequence of chronic hypocortisolism might be that catecholamine levels are elevated in PTSD patients. Indeed, previous investigations point towards a hyperactive SNS in PTSD with increased levels of norepinephrine (NE) and epinephrine (E) in 24 h urine samples (Kosten et al., 1987; Yehuda et al., 1992), elevated diurnal plasma concentrations of NE (Yehuda et al., 1998), and increased norepinephrine in the cerebrospinal fluid (CSF, Geracioti et al., 2001) in PTSD. However, just as many studies do not find differences in the sympathoadrenal function between individuals with or without PTSD (e.g. Blanchard et al., 1991; McFall et al., 1992; Pitman and Orr, 1990). Consequently, it remains unclear whether the SNS is indeed chronically activated in PTSD.

The relatively small number of studies examining the activity of the SNS in PTSD may be explained by the complexity, i.e. the stress or invasiveness of previously available means of biochemical SNS activation measurement (urine, blood, and CSF). Only recently, a potential marker derived from saliva has been proposed, which may constitute a convenient and non-invasive indicator of SNS activity, i.e. the salivary enzyme alpha-amylase (sAA, see reviews in Nater and Rohleder, 2009; Rohleder and Nater, 2009). Salivary alpha-amylase follows a characteristic daily secretion pattern showing a sharp decrease in the first hour after awakening followed by an increase in activity throughout the day (Nater et al., 2007; Rohleder et al., 2004b). It has been shown that sAA levels rise in response to both physical (e.g. Chatterton, 1996; Kivlighan and Granger, 2006; Skosnik, 2000) and psychological stress (e.g. Chatterton et al., 1997; Gordis, 2006; Nater et al., 2005; Rohleder et al., 2004b; Stroud et al., 2006). Further, it was found that the sAA release can be stimulated by beta-adrenergic agonists (Gallacher and Petersen, 1983), alpha-2-adrenergic receptor antagonists (Ehlert et al., 2006), and inhibited by beta-adrenergic blockers (van Stegeren et al., 2006). Moreover, some studies also report correlations between changes in sAA secretion and stress-induced norepinephrine release (Chatterton, 1996; Rohleder et al., 2004b). Finally, Nater et al. (2006) reported that sAA secretion is positively correlated with heart rate variability (HRV) measures of sympatho-vagal balance. Altogether, hitherto existing findings suggest that sAA constitutes a promising candidate as a non-invasive biomarker for SNS activity. However, as summarized in a recent commentary, further evaluation might be warranted (Bosch et al., 2011). Recent studies have shown that the daily secretion pattern of sAA is altered in individuals reporting chronic stress (Nater et al., 2007), in young women experiencing chronic shame (Rohleder et al., 2008), in children with asthma experiencing chronic home life stress (Wolf et al., 2008), and in caregivers for cancer patients (Rohleder et al., 2009).

Given the interactive role of the HPA axis and the SNS in the development and maintenance of PTSD, an additional and easier obtainable SNS marker would shed more light on stress system pathophysiology in PTSD. We hypothesize that daily secretion patterns of sAA are altered in PTSD patients compared to healthy controls, based on alterations of daily sAA secretion in chronic stress conditions. In order to test this hypothesis we analyzed saliva samples of Bosnian War refugees with PTSD and healthy controls that were collected in the context of a previously published study (Rohleder et al., 2004a). This allows us to additionally link sAA secretion patterns in PTSD patients with other health relevant parameters measured in the previous study, such as inflammatory regulation.

2. Methods and materials

2.1. Study participants

For the current study we analyzed data from a group of Bosnian War refugees and healthy controls who had provided saliva samples in the context of a previous study (Rohleder et al., 2004a). From the original 25 participants, two PTSD patients and two healthy controls (laboratory staff members) were excluded from all analyses due to insufficient saliva volume. The final number of participants was $n = 21$ ($n = 10$ Bosnian War refugees with PTSD and $n = 11$ controls). Bosnian War refugees were recruited from the Psychosocial Center (PSC) of Refugees in Düsseldorf, Germany, a psychological treatment facility specialized for war-related trauma. With the exception of two participants, all Bosnian War refugees underwent psychotherapy while participating in the study. Bosnian War refugees were screened at the PSC for traumatic events using the Harvard Trauma Questionnaire (HTQ, Mollica et al., 1992). The traumatic events that were reported the most were the following: separation from members of the family (12), near-death experiences (11), deficient food or water supply (10), witnessing murder/-s of strangers (10), lack of shelter (7), prison (5), as well as experiencing the killing of a family member/friend (5), torture (4), or combat (4). In case of a reported trauma, refugees were further screened for PTSD symptoms using the International Diagnostic Checklist, which is based on the DSM-IV criteria for PTSD (American Psychiatric Association, 1994). Twelve of the screened Bosnian War refugees fulfilled DSM-IV criteria for PTSD and were accordingly included in the PTSD group. These reported an average of 21.67 traumatic events (range 16—26). Five Bosnian War refugees who did not fulfill DSM-IV criteria for PTSD were included in the control group: on average, they reported 21 traumatic experiences (range 17—27). The remaining six controls, i.e. healthy and non-war refugees reported on average 1.2 traumatic experiences (range 0—3). All participants were free of somatic diseases,