



Salivary alpha-amylase response following repeated psychosocial stress in patients with panic disorder



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ABSTRACT

Background: This study examined autonomic responses (salivary alpha-amylase, sAA; heart rate, HR) to repeated psychosocial stress as a candidate mechanism linking autonomic hyper-arousal and sensitization to the occurrence of panic disorder (PD).

Methods: Thirty-three patients with PD and 34 healthy controls were exposed to the Trier Social Stress Test (TSST) twice on consecutive days.

Results: sAA changes were comparable between PD and controls on both testing days with overall decreasing sAA responses (delta) on day two. In contrast, HR delta increased on day two in both groups. This sensitization was driven by female controls while male PD showed most pronounced HR changes to the first TSST.

Conclusions: Overall, a general autonomic hyper-arousal in PD could not be confirmed. In contrast, sAA responses slightly habituated to repeated stress. Whether sAA findings mirror assumed habituation effects of repeated stress exposure on normalizing autonomic reactivity remains to be investigated in longitudinal studies.

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1. Introduction

Panic disorder (PD) is a highly prevalent clinical condition that was shown to be related to an increase in cardiovascular disease and mortality (Albert, Chae, Rexrode, Manson, & Kawachi, 2005; Smoller et al., 2007). It leads to a large number of hospital admissions (Roy-Byrne et al., 2000) and an explosion of health care costs (Greenberg et al., 1999). The exact pathophysiological mechanisms underlying PD are still under debate (Revest et al., 2009; van Duinen, Schruers, Maes, & Griez, 2007) but disturbances of the major stress axes, the hypothalamic–pituitary–adrenal (HPA) axis, and the autonomous nervous system (ANS), are most likely involved. Evidence of an abnormal functioning of the HPA axis in this disorder is quite convincing but inconsistencies exist. Studies show hypo-activity and decreased responsiveness to different stimuli (Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010; Petrowski, Wintermann, Schaarschmidt,

Bornstein, & Kirschbaum, 2013; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013), hyper-responsiveness to pharmacological stimulation (Erhardt et al., 2006; Schreiber, Lauer, Krumrey, Holsboer, & Krieg, 1996), but also no differences (Ising et al., 2012). The ANS, the fast-responsive stress-system, is also highly warranted in the etiopathogenesis of PD (Goldstein, Robertson, Esler, Straus, & Eisenhofer, 2002; Wilkinson et al., 1998). The activity of the locus coeruleus/ANS constitutes a major network in the processing of fear-related stimuli (Soya et al., 2013). Anxiety and stress lead to an immediate activation of the sympathetic branch of the ANS, the release of norepinephrine (NE) from sympathetic nerve terminals, and of mainly epinephrine (E) from the adrenal medulla. Circulating E results in an increase in blood flow, heightened respiration rate and heart rate as well as increased lipolysis and liver glycogen levels. These processes are related to massive body symptoms such as sweating, hyperventilation, high muscle tonus, and palpitations corresponding to the clinical phenomenology of panic attacks (APA, 2004). NE has similar consequences including an additional effect on cognitive functions such as attention and memory (Chamberlain & Robbins, 2013).

Some studies could not find any specificities in sympathetic functioning under basal and mental stress conditions in patients with PD (Alvarenga, Richards, Lambert, & Esler, 2006; Bremner,

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Krystal, Southwick, & Charney, 1996; Ekeberg, Hedley, Einvik, Rostrup, & Hoffart, 2003; Esler et al., 2004; Wilkinson et al., 1998). Others observed higher basal plasma E (Villacres, Hollifield, Katon, Wilkinson, & Veith, 1987), an increased sensitivity of the sympathetic arterial baroreflex (Lambert et al., 2002; Shioiri et al., 2004) and an impairment of the neuronal reuptake of NE after secretion from sympathetic nerve terminals in PD (Esler et al., 2004). Increased sensitivity of the arterial baroreflex and impaired reuptake of NE may lead to an overly strong phasic response to stimuli rather than having a high tonic level of activity. However, beta-blockade has shown to be ineffective in the treatment of PD and actually implicates decreased sensitivity of beta-adrenergic receptors (Yeragani, Pohl, Bar, Chokka, & Tancer, 2007). In addition, sex differences in the beta-adrenergic receptor function hint at decreased sensitivity in female but not in male patients (Kim, Min, & Yu, 2004).

Recently, salivary alpha-amylase (sAA) has emerged as a new surrogate biomarker for stress-related changes within the ANS (Granger, Kivlighan, el-Sheikh, Gordis, & Stroud, 2007; Nater & Rohleder, 2009). Nerve fibers of the sympathetic and parasympathetic branch of the ANS innervate salivary glands with sympathetic stimulation increasing salivary protein secretion whereas parasympathetic stimulation increases the salivary flow rate (Baum, 1993; Turner & Sugiya, 2002). SAA activity has been described as an autonomic biomarker complementing but not replacing the measurement of catecholamines and cardiac activity under stress (Nater et al., 2006; Thoma, Kirschbaum, Wolf, & Rohleder, 2012). Acute stressors induce a rapid increase in the enzyme's activity while chronic stress has been associated with both a decreased as well as an increased sAA output (Berndt, Strahler, Kirschbaum, & Rohleder, 2012; Nater, Rohleder, Schlotz, Ehlert, & Kirschbaum, 2007; Rohleder, Marin, Ma, & Miller, 2009). Regarding mental disorders, results suggest sAA as useful biological marker for patients with major depression, bipolar disorder and the generalized type of social phobia (Kawano et al., 2013; Tanaka, Ishitobi, Maruyama, Kawano, Ando, Okamoto et al., 2012; Tamura et al., 2013; Tanaka et al., 2013; for a review see Schumacher, Kirschbaum, Fydrich, & Ströhle, 2013). Considering evidence for increased noradrenergic transmission from the locus coeruleus in PD (Kalk, Nutt, & Lingford-Hughes, 2011) the usefulness of sAA as a marker for sympathetic activation is also hypothesized in this disorder. Concerning diurnal sAA, no difference could be observed between PD patients and healthy controls (Plag et al., 2014; Schumacher et al., 2014). While an exercise intervention or cognitive behavioral therapy had no effect on sAA (Plag et al., 2014), acute in vivo exposure led to an increased sAA followed by a decrease to baseline values in agoraphobic patients (Schumacher et al., 2014). Since exposure situations differ in settings and stimulations' intensity and therefore limit comparability, acute stress-induced sAA levels may best be investigated under controlled laboratory conditions. To our knowledge, only one study investigated sAA in PD disorder in the laboratory by means of an electrical stimulation test. This test induced an increase in sAA in the majority of patients ($N = 21$ of 34; Tanaka, Ishitobi, Maruyama, Kawano, Ando, Imanaga et al., 2012). However, the electric stimulation might not be a potent stressor when investigating sAA activity as indicated by unchanged sAA values in the group of healthy controls (Tanaka, Ishitobi, Maruyama, Kawano, Ando, Imanaga et al., 2012). Therefore, a laboratory-based psychosocial stress protocol like the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) might be more suitable when investigating stress-induced sAA activity as well as cardiovascular changes in patients suffering from PD and healthy controls of both sexes (Maruyama et al., 2012).

Our main research aim was to investigate the autonomic functioning of PD by means of psychosocial stress-induced cardiovascular and sAA reactivity. Due to previous reports of an overly

autonomic responsiveness to emotional stimuli in PD (Shioiri et al., 2004; Wilkinson et al., 1998), higher stress-induced sAA and cardiovascular activity is expected in patients with PD whereas baseline sAA values should be comparable. Since female PD patients seem to be more prone to ANS disturbances (Kim et al., 2004), most pronounced stress responses are expected within the female group. Though habituation to repeated stress exposure is a key adaptive mechanism in endocrine system (McEwen, 2000), responses of the fast-responsive ANS to similar repeated stressors are normally comparable in healthy controls (Schommer, Hellhammer, & Kirschbaum, 2003; Strahler, Rohleder, & Wolf, 2015). Since a heightened autonomic responsiveness and altered beta-adrenergic receptor function was observed in patients with PD, a sensitization of sAA stress responses could be hypothesized.

2. Materials and methods

2.1. Study participants

Patients with PD were recruited between January 2006 and July 2007 at the Carl Gustav Carus University Hospital of the Technische Universität Dresden, Germany. The Structured Clinical Interview (First, Spitzer, Gibbon, & Williams, 1997; Wittchen, Zaudig, & Fydrich, 1997) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was used to confirm diagnosis of PD with or without agoraphobia, respectively. Diagnostic exclusion criteria were: any other mental disorders (except major depression) according to the SCID and any acute and/or chronic medical illness as assessed by a physical examination and routine laboratory tests. In order to avoid a significant selection bias in the recruitment of patients, habitual cigarette smoking, use of oral contraceptives, or pharmaceutical treatment of PD were allowed. Patients were matched on these variables with healthy control subjects (except for the use of pharmaceutical drug treatment). A total of 33 patients ($n = 13$ females) with a primary diagnosis of PD fulfilled our inclusion criteria. Nine patients were diagnosed with PD (ICD-10: F41.0), 19 with PD with agoraphobia (ICD-10: F40.01) and five with agoraphobia (ICD-10: F40.0). Depressive episodes as frequent comorbid condition in PD were not excluded. Overall, 24 patients were diagnosed with a secondary diagnosis of depression [dysthymia: F34.1, $n = 2$; mild depression: F33.0, $n = 3$; moderate depression: F32.1, $n = 4$; F33.1, $n = 1$; severe depression: F32.2, $n = 6$; F33.2, $n = 7$; remitted depression: F34.1, $n = 1$].

The mean age at the onset of PD was 27.6 ($SD = 9.7$) years of age and the mean duration of symptoms was 6.9 ($SD = 8.5$) years. Of the 33 patients, 17 were on psychotropic drug treatment during the testing phase (selective serotonin reuptake inhibitors [SSRIs; $n = 6$], serotonin norepinephrine reuptake inhibitors [SNRIs; $n = 5$], tricyclic antidepressants [$n = 1$], tetracyclic antidepressants [$n = 3$], benzodiazepine [anxiolytic; $n = 1$], phyto-sedatives [$n = 1$]). Three patients took more than one of the above-mentioned psychopharmaceuticals, three at maximum (one patient additionally phenothiazine; one patient additionally buspiron and a neuroleptic; one patient additionally a phyto-sedative). Seven patients were on heart medication (beta-blocker, $n = 5$; other antihypertensive drugs, $n = 3$). Both psychotropic and antihypertensive drug treatment remained stable over the testing period. A total of 34 age- and sex-matched healthy controls (19 women) were recruited through local newspaper advertisements. Six patients (one woman) and nine controls (seven women) did not attend the second TSST session. While we can only speculate about possible reasons, these subjects did not differ on any of the characteristics from those attending both sessions (all $p > 0.05$). The following statistical analyses concerning autonomic stress responses are thus based on 27 patients and 25 controls. All study participants provided written

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