International Journal of Psychophysiology 88 (2013) 35–39

Contents lists available at SciVerse ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Blunted salivary and plasma cortisol response in patients with panic disorder under psychosocial stress

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ARTICLE INFO

Article history:
Received 15 November 2012
Received in revised form 29 December 2012
Accepted 2 January 2013
Available online 10 January 2013

Keywords:
Panic disorder
Trier Social Stress Test
TSST
Hypothalamic–pituitary–adrenal–cortical (HPA)-axis
Plasma cortisol
Plasma ACTH
Salivary cortisol

ABSTRACT

Background: Panic disorder (PD) has been associated with an altered activity of the hypothalamic–pituitary–adrenal–cortical (HPA) axis. Recent findings from a patient sample with PD with secondary depression on psychotropic medication using salivary cortisol as outcome measure suggest a non-responsiveness of the HPA-axis under acute psychosocial stress. Salivary cortisol does not necessarily reflect the total plasma cortisol due to interfering variables. Whether the present findings can be replicated on a patient sample with pure PD using both salivary cortisol and total plasma cortisol as outcome variables remains to be elucidated.
Methods: For this study, the Trier Social Stress Test (TSST) was implemented to assess the HPA-axis reactivity indicated by the plasma adreno-corticotropin-hormone (ACTH), plasma cortisol, and salivary cortisol release. The sample included 32 patients diagnosed with PD in a Structured Clinical Interview (SCID). Twelve male and fifteen female patients [mean age = 32.87 years, SD = 11.23] were matched with 32 healthy controls by age and gender.
Results: The plasma ACTH, total plasma cortisol and salivary cortisol release increased significantly in both groups due to the psychosocial stress test. The patients with PD showed a decreased plasma and salivary cortisol response as compared to the healthy controls. Plasma cortisol and salivary cortisol were highly correlated in both groups.
Conclusion: These findings provide strong evidence for a hypo-responsiveness of the HPA-axis as measured in both blood and saliva. Salivary and total plasma cortisol showed a strong concordance of results. Thus, future investigations could consider salivary cortisol as reliable marker of the HPA-axis under psychosocial stress.

1. Introduction

Panic disorder (PD) is a common disorder with a large number of hospital admissions (Roy-Byrne et al., 2000), significant economic costs for society (Greenberg et al., 1999), and increased mortality (Albert et al., 2005; Smoller et al., 2007). Since the empirical results are not conclusive, the exact pathophysiological mechanism underlying PD is of major interest (van Duinen et al., 2007; Revest et al., 2009).

Considerable research efforts have associated PD with an abnormal functioning of the hypothalamic–pituitary–adrenal–cortical (HPA) system (Heuser et al., 1994; Schreiber et al., 1996; Erhardt et al., 2006; Petrowski et al., 2010, 2012). Abelson et al. (2007) demonstrated that PD is characterized by an enhanced sensitivity of HPA-axis to novel, threatening and uncontrollable situations (Abelson et al., 2007). One way to induce novelty, threat and uncontrollability under standardized laboratory conditions is the implementation of a psychosocial stress test: the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). Using the TSST patients with PD showed an abnormal non-responsiveness of the HPA-axis with a reduced salivary cortisol response (Petrowski et al., 2010) which is in contrast to the previously published results with different psychological stressors (Leyton et al., 1996; Hoehn et al., 1997; Garcia-Leal et al., 2005). Therefore, the non-responsiveness after the TSST remains to be elucidated further as the patients included were under antidepressant drugs or had psychiatric comorbidities such as major depression. Moreover, only salivary cortisol was used as measurement method (Petrowski et al., 2010). Recent findings showed that absolute levels of cortisol in the saliva are significantly lower than in the

Abbreviations: AUCg, area under the curve ground; ACTH, adreno-corticotropin-hormone; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CRH, corticotropin-releasing hormone; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; HPA-axis, hypothalamic–pituitary–adrenal–cortical-axis; PAS, Panic and Agoraphobia-Scale; PD, Panic disorder; SCID, Structured Clinical Interview for DSM-IV; SPSS, Statistical Package for Social Sciences; STAI, State-Trait-Anxiety-Inventory; TSST, Trier Social Stress Test; VAS, Visual analog scale.

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http://dx.doi.org/10.1016/j.ijpsycho.2013.01.002

blood due to differences in the availability of the corticosteroid binding globulines (CBG) in the blood (Kirschbaum and Hellhammer, 2007; Levine et al., 2007; Henley and Lightman, 2011). Even though the salivary cortisol significantly correlates with total plasma cortisol under baseline condition in patients with PD (Wedekind et al., 2000) data considering both salivary and plasma cortisol under acute psychosocial stress in patients with PD are still lacking.

Studies in healthy controls, showed that high trait anxiety is associated with a reduced salivary and plasma cortisol response under psychosocial stress (Jezova et al., 2004; Beaton et al., 2006). The lower plasma cortisol response was associated with exaggerated perception of stress (Duncko et al., 2006) and a higher emotional arousal after the TSST (Het et al., 2012).

Therefore, the lacking salivary cortisol response following the TSST in patients with PD needs to be replicated based on total plasma cortisol in a sample of patients without secondary depression and without the use of psychotropic drugs (Petrowski et al., 2010). Based on the results on healthy individuals (Kirschbaum and Hellhammer, 2007; Levine et al., 2007; Henley and Lightman, 2011), we expect a highly significant correlation between salivary cortisol and total plasma cortisol in both healthy controls and patients with PD under acute psychosocial stress. Based on the results on anxious healthy individuals, we expect a blunted plasma cortisol response with a higher perception of stress and higher emotional arousal in patients with PD under the TSST.

2. Materials and methods

2.1. Study participants

Patients with panic disorder were recruited from May 2008 to November 2011 at the anxiety outpatient unit of the University Hospital of the Technische Universität Dresden, Germany. All patients that fit the inclusion criteria were consecutively included and tested as part of the diagnostic procedure.

The Structured Clinical Interview (SCID, Spitzer et al., 1990; Wittchen et al., 1990) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was used to diagnose the current primary diagnosis of panic disorder with or without agoraphobia (APA, 2004), respectively. Diagnostic exclusion criteria were: any other mental disorder according to the SCID, personality disorder and any acute and/or chronic medical illness (e.g. endocrinological, cardiological, chronically-inflammable diseases) 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 and the use of oral contraceptives were accepted. Patients with panic disorder under psychotropic drug treatment were not included as it may have evoked an influence on the HPA-axis.

Patients with panic disorder were matched in age and gender with healthy control subjects. A total of 39 patients were approached. In all, $n=7$ patients had to be excluded due to the following reasons: more than one missing value in the plasma cortisol sampling, a panic attack during testing or familiarity with the TSST. The sample for the analyses consisted of $n=32$ patients with a primary diagnosis of PD.

The mean age at the onset of panic disorder was 28.45 (SD = 10.39) years of age, and the mean duration of the panic disorder was 4.52 (SD = 6.44) years. According to the Panic and Agoraphobia-Scale (PAS) (Bandelow, 1997) seven patients showed a borderline severity of panic and agoraphobic symptoms, four patients showed a mild and $n=16$ patients a moderate severity, five patients with PD showed a severe psychopathology on the Panic and Agoraphobia-Scale, respectively. Furthermore, $n=15$ of the patients had shown a first manifestation of the symptomatology during the previous 1.5 years.

The healthy controls (n = 32) had been recruited through newspaper advertisements and were matched to the patient sample by age and gender. Both, healthy controls and patients were rewarded with 50 € expense allowance for their participation. The characteristics of the patients and the matched controls are provided in Table 1. Significant differences between the patients with PD and the healthy controls could be shown for the severity of the panic disorder on the PAS and the Trait-Anxiety (Table 1).

All study participants provided written informed consent. The study protocol was approved by the local Ethics Committee of the Medical Faculty of the Technical University of Dresden, Germany (No. #EK7012006).

2.2. Procedures

The participants were scheduled individually for the TSST at 1400 h in order to minimize the circadian variations in the cortisol levels. The participants were asked to refrain from eating, drinking, and smoking for at least two hours before testing as well as during the two-and-a-half-hour testing session.

The subjects were fitted a belt for continuous wireless transmission of heart rate signals (Polar S810, Polar, Finland) and rested in a comfortable, supine position with light reading permitted. Postural changes from sitting to standing and repeated sitting were necessary only for accomplishing the TSST and are not accompanied by major changes of ACTH or cortisol (Mlynarik et al., 2007). A venous catheter was placed at 1415 h to later collect eight consecutive blood samples each for analyzing ACTH and cortisol concentration, respectively. After an accommodation time of 45 min to control the influence of previously experienced stress on the baseline cortisol, two blood samples (−15 min, −1 min) were taken before the study participant was exposed to the TSST. After the completion of the TSST, six more blood samples (+1 min, +10 min, +20 min, +30 min, +45 min, +60 min) were collected at regular intervals. In total, eight plasma cortisol, eight plasma ACTH, and eight salivary cortisol samples were collected. All blood samples were taken in a supine body position.

The psychosocial stress protocol mainly consists of a social-evaluative situation including a five-minute mock job interview and a subsequent five-minute mental arithmetic task in front of a two-person-panel. A detailed description and evaluation of the TSST was published by Kudielka and colleagues (Kudielka et al., 2007). Healthy controls and patients were tested in the same setting with identical procedures.

2.3. ACTH and cortisol analysis

Analysis of plasma ACTH and cortisol was realized as already described by Petrowski et al. (2012). 50 µl of saliva supernatant of low viscosity was removed for the cortisol analysis using a

Table 1
Characteristics of patients (N = 32) and controls (N = 32). Displayed are the means and standard deviations (SD).

	Patients with PD (PD)	Controls (C)	$F/\chi^2/U$	P
Total, N	32	32		
Females, n	20	20		
Males, n	12	12	.000	1.000[a]
Age (years)	32.87 (11.23)	31.17 (11.12)	.370	.545
Cycle week	2.90 (.90)	2.93 (.48)	121.000	.822 (U)
BMI (kg/m^2)	22.66 (3.27)	23.22 (2.54)	.578	.450
Smokers, n (%)	16 (50.0)	9 (45.0)	3.216	.123[a]
Cigarettes/day	3.59 (4.29)	1.84 (3.93)	.032	.860
Contraceptive pill, n (%)	9 (45)	9 (45)	.000	.624[a]
Total triglyceride, mmol/l	1.18 (.73)	1.26 (.71)	.196	.659
PAS	19.59 (11.10)	1.18 (3.33)	80.705	<.001***
STAI-Trait	46.59 (9.40)	36.44 (8.22)	21.177	<.001***

U = Mann–Whitney U-test; STAI = State-Trait-Anxiety-Inventory (Spielberger, 1970; Laux et al., 1981); PAS = Panic and Agoraphobia-Scale (Bandelow, 1997).
[a] Chi-square test.
*** $p \leq .001$.