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Predisposition or side effect of the duration: the reactivity of the HPA-axis under psychosocial stress in panic disorder

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ABSTRACT

Background: Panic disorder (PD) has been associated with an altered reactivity of the hypothalamic–pituitary–adrenocortical (HPA) system under psychosocial stress. Until now it remains unclear whether a diminished cortisol release is an early risk factor predisposing for PD or a consequence of PD. In order to unravel this point, the present study compares the cortisol secretion between patients with a recent onset and a chronic course of PD.
Methods: The Trier Social Stress Test (TSST) was applied in patients with a duration of PD ≤ 1.5 years ($N = 35$), patients with a duration of PD > 1.5 years ($N = 56$) and healthy controls ($N = 95$). Salivary cortisol and heart rate (HR) were assessed as primary outcomes.
Results: According to baseline cortisol/baseline HR and HR response there was no significant difference. Both patient groups (≤1.5/>1.5 years) showed a blunted cortisol response with no significant group difference. In multiple linear regression models the attenuation of the HPA-axis was largely accounted for by group, smoking status, use of contraceptive pill and the interaction group by gender. Female patients with a chronic course showed the lowest cortisol response under the TSST.
Conclusions: It might be assumed that a decreased reactivity of the HPA-axis could be considered as etiological risk factor in the preliminary stages of PD. Above, female gender, smoking status and the use of contraceptive pill seem to further moderate the attenuated HPA-axis response pattern in patients with PD.

1. Introduction

Panic disorder (PD) is among the most prevalent mental disorders with a life-time prevalence of about 3.7% and a strong comorbidity with major depression (Kessler et al., 2006; Bandelow and Michaelis, 2015; Roy-Byrne et al., 2000). Until now, it is not known what pathophysiological mechanism underlies the occurrence of sudden panic attacks (Jakuszkowiak-Wojten et al., 2015). One explanation is the exposure of stressors in the preliminary stages of PD. Most of the patients with PD experience their first panic attack after exposure to major stressful life-events (Watanabe et al., 2005; Klauke et al., 2010). As pathophysiological explanation, alterations in the two main stress systems of the human body, the symathico-adreno-medullary (SAM) system and the hypothalamic–pituitary–adrenomedullary (HPA)-axis could be shown in patients with PD (Abelson et al., 2007). Empirical findings suggest a decreased reactivity of the HPA-axis (Jezova et al., 2010; Petrowski et al., 2010; Petrowski et al., 2012; Petrowski et al., 2013; Siegmund et al., 2011). However, it is not clear whether an altered reactivity of the HPA-axis is a cause or a side effect of PD. According to the theory of alloastasis and allostatic load (McEwen, 1998; McEwen, 2004) a longer duration of the PD is associated with a greater number of panic attacks. On the long-run and under persisting stress, these 'repeated hits' of significant cortisol release in PD cause a down-regulation of corticosteroid receptors (Bandelow et al., 2000; Fries et al., 2005). Following, an adaptation of the HPA-axis occurs with a decreased cortisol release ('wear out') and mediated by increased negative feedback sensitivity. This assumption is in line with a recent study suggesting a diminished HPA-axis function in adolescents with chronic depressive problems (Booij et al., 2013). Another possible etiological process might be that the hypo-reactivity of the HPA-axis is a vulnerability factor for the development of a PD. This has been already shown for the hyper-reactivity of the HPA-axis in patients with major depression (Ising et al., 2007). The clarification whether a diminished reactivity of the HPA-axis is a consequence of the psychopathology or a predisposing risk factor would either allow the application of the cortisol response pattern as modifiable state dependent marker of PD or the early identification of patients at risk for PD.

Empirical findings considering the duration of PD and its impact on the HPA-axis are inconsistent. Findings could either find no association (Petrowski et al., 2013; Schreiber et al., 1996; Westberg et al., 1991) or even a near-significant positive correlation (Petrowski et al., 2012). A

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negative association between cortisol and chronicity could be found in a diagnostically heterogeneous sample of patients with different anxiety disorders (Finitsis et al., 2013). The cortisol awakening response in a population-based sample of older adults with long-lasting anxiety disorders was significantly lower than those without (Hek et al., 2013). However, the impact of the chronicity of an anxiety disorder on the cortisol secretion could not be unequivocally resolved (Hek et al., 2013). Considering the number of panic attacks as indirect marker for the duration of PD, a negative correlation with the corticotropin level could be shown (Abelson and Curtis, 1996). In contrast, Erhardt et al. (2006) found that the duration of PD was positively correlated with the CRH-induced plasma cortisol response (AUC, Cnet). However, in the latter study the duration could only be determined indirectly from the age of onset of PD. Existing studies differ with respect to the ascertainment of the duration of PD, the applied stress paradigm (e.g. psychosocial vs. physiological stress) and the kind of study samples (e.g. heterogeneous sample, convenience sample). Above, present studies only used correlational analyses and did not control for age at time of testing.

In order to unravel whether an altered cortisol secretion pattern is an early risk marker for PD or a consequence of the chronic psychopathology, studies investigating the HPA-axis reactivity in separate samples of age-matched patients with a recent onset and a chronic course of PD are highly needed. According to the theory of alloastasis and allostatic load (McEwen, 1998; McEwen, 2004) it is hypothesized that patients with a chronic course should show a lower stimulated cortisol secretion pattern than patients with only a recent onset of PD. This would allude that a diminished HPA-axis reactivity displays rather a consequence of the psychopathology than a risk factor for PD. In order to prove the impact of the duration of PD on the HPA-axis reactivity, the present study examined the salivary cortisol release under a psychosocial stress protocol, the TSST (Kirschbaum et al., 1993), in a large sample of patients with recent onset of PD and in patients with a chronic PD compared with a matched sample of healthy controls. Since major depression is a frequent comorbidity in patients PD, these patients were not excluded (Roy-Byrne et al., 2000).

2. Materials and methods

2.1. Sample

The patients for the study were consecutively recruited at an out-patient unit specialized on the diagnostics and treatment of anxiety disorders of the University Hospital of the University of Technology, Dresden, Germany, from February 2006 to March 2013. During this time frame the participants of the present study were subjected to different diagnostic and stress tests which have been already published elsewhere (Petrowski et al., 2010; Petrowski et al., 2012; Petrowski et al., 2013). The Structured Clinical Interview (SCID) (Spitzer et al., 1990; Wittchen et al., 1997) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was used to ascertain a diagnosis of PD with or without agoraphobia or a diagnosis of agoraphobia without history of PD (APA, 2000) by an experienced clinical psychologist. As diagnostic exclusion criteria, the following were defined: any other mental disorder and any acute and/or chronic medical illness as assessed by a physical examination. There was no significant difference in the amount of a secondary depression between the patient groups (duration ≤1.5 years: $n = 12$ vs. duration >1.5 years: $n = 29$; $\chi^2 = 2.665$, $p = 0.103$) (for a detailed description see Supplementary A.1).

The patient sample consisted of $N = 91$ patients with a current diagnosis of PD. None of the patients were receiving psychotropic treatment. Duration of PD was calculated from the self-reported age of onset of PD. The groups of patients were defined on the basis of a duration of the PD of ≤1.5 years or >1.5 years. $N = 35$ patients experienced the PD for less than or exactly 1.5 years (recent onset), $N = 56$ patients experienced a duration of more than 1.5 years (chronic course). We specified a duration of 1.5 years as cut-off because there is a large amount of patients experiencing remission of PD during the first year of onset (Batelaan et al., 2010). Furthermore, there is a long time between onset and adequate diagnostics of PD with up to eight years for most patients (Christiana et al., 2000). This situation impedes the enrolment of patients with a duration of PD of less than one year.

In addition, a third group of healthy controls ($N = 95$) was recruited through newspaper advertisements and matched to the patient samples by age and gender. Absence of any current or life-time mental disorder in healthy controls was proven by the SCID (Spitzer et al., 1990; Wittchen et al., 1997).

2.2. Procedures

The participants were scheduled individually for the TSST (Kirschbaum et al., 1993) at 1400 h. A detailed description of the TSST was published by Kudielka et al. (2007). The participants were asked to refrain from eating, drinking, and smoking for at least 2 h 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). Heart rate (HR) assessment was realized as stimulation check of the applied stress paradigm ensuring that the TSST led to a significant increase in the activity of the sympatho-adrenal medullary system. Subjects rested in a comfortable, supine position with light reading permitted. Postural changes from sitting to standing and repeated sitting were only necessary for accomplishing the TSST and are not accompanied by major changes of cortisol (Mlynarik et al., 2007). After an accommodation time of 45 min to control the influence of previously experienced stress on the baseline cortisol, two saliva samples (−15 min before, after a five minute anticipation phase) were taken. After the completion of the TSST, five more saliva samples (+1 min, +10 min, +20 min, +30 min, +45 min) were collected at regular intervals. Additionally, blood samples have been simultaneously collected via a venous catheter in two-thirds (68.9%) of the participants. The details of blood sampling have been already reported elsewhere (Petrowski et al., 2013).

2.3. Psychopathological assessments

The severity of the panic-agoraphobia symptoms were measured by the *Panic and Agoraphobia-Scale* (PAS) (Bandelow, 1997) consisting of 13 items rated on a five-point rating-scale (range: 0–52). To evaluate the extent of anxiety induced by the acute psychosocial stress protocol, the state version of the *State-Trait-Anxiety-Inventory* (STAI) (Spielberger et al., 1970; Laux et al., 1981) was applied before and after the TSST. The STAI consists of two 20-item scales for measuring the intensity of anxiety as an emotional state and anxiety proneness as a personality trait on a four-point scale. Intensity of depressive symptoms was assessed with the *Beck-Depression-Inventory* (BDI) (Beck et al., 1961; Hautzinger et al., 1994) consisting of 21 symptoms rated on a four-point-scale (0–3, range: 0–63).

2.4. Cortisol analysis and analysis of heart rate

For quick and hygienic collection of saliva samples Salivette swabs were used (Sarstedt, Nümbrecht, Germany). The samples were kept frozen at −20 °C until assay. Before analysis, samples were centrifuged at 3000 rpm for 5 min to produce a clear supernatant of low viscosity. 50 μl was removed for cortisol analysis using a commercially available immunoassay with chemiluminescence detection (ELISA Kit) [for details see Dressendörfer et al., 1992]. The lower detection limit of this assay is 0.43 nmol/l. Intra- and inter-assay coefficients of variation were below 8% for low (3 nmol/l) and high (25 nmol/l) cortisol levels, respectively.

R–R-intervals were recorded via an elastic belt using the Polar® system (Polar, Kempe, Finland). Mean HR responses were available for four different three-minute-intervals of the stress task (pre-stress period/baseline, speech task, mental arithmetic, post-stress period/recovery).