Psychoneuroendocrinology 77 (2017) 9–17

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Effects of the cortisol stress response on the psychotherapy outcome of panic disorder patients

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ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form
23 November 2016
Accepted 23 November 2016

Keywords:
Panic disorder
TSST
Cortisol
ACTH

ABSTRACT

Background: A proportion of patients with panic disorder (PD) fail to show a remission after psychotherapy. Biological correlates of psychotherapy non-response have rarely been described in the literature. The aim of the present study was to research the relationship between the cortisol stress response and the psychotherapy outcome in PD patients.
Methods: Twenty-eight PD patients (20 females, mean age ± SD: 35.71 ± 13.18) seeking psychological treatment for PD and $n = 32$ age- and sex-matched healthy control participants (21 females, aged 34.66 ± 12.07) participated in this study. The patients underwent five weeks of cognitive behavioural therapy (CBT). Within the first two weeks of the CBT, both study groups were confronted with the Trier Social Stress Test (TSST). Blood sampling for cortisol and adrenocorticotropic hormone (ACTH) evaluation as well as fear-rating (Visual Analogue Scale; Primary Appraisal and Secondary Appraisal Questionnaire, PASA) accompanied the TSST. The global severity of PD (Panic & Agoraphobia Scale; PAS), agoraphobic cognitions (Agoraphobic Cognitions Questionnaire; ACQ), fear of bodily sensations (Bodily Sensations Questionnaire; BSQ), agoraphobic avoidance (Mobility Inventory; MI), and depressiveness (Beck Depression Inventory; BDI) were assessed before and after the CBT (except the BDI).
Results: The statistical analysis revealed significant main effects of time for cortisol and the ACTH concentration in response to the TSST, independently of the study group. 42.9% of the PD patients and 65.6% of the healthy control participants showed a cortisol stress response to the TSST ≥ 55.2 nmol/l (descriptive finding). The data showed a significant inverse association of the TSST cortisol stress response with the MI total score when accompanied. Further, a significant association of the PASA subjective level of fear and the BSQ as well as a trend for an association of the PASA with the ACQ were observed.
Conclusion: Consistent with prior research, we could replicate findings of decreased cortisol concentrations in the PD patients in comparison to the healthy control participants. Furthermore, our findings agree with previous data showing an association of the attenuated cortisol stress response with the psychotherapy non-response. In the present sample, those patients with the lowest cortisol concentrations showed the least improvement in agoraphobic avoidance after psychotherapy. The patients with the highest level of fear showed the most improvement in fear of bodily sensations. Study limitations as well as implications for future studies will be discussed.

1. Introduction

Panic disorder (PD) is a serious mental disorder associated with high levels of disability and impairment in the quality of life, next to depressive disorders (Wittchen and Jacobi, 2005). The most recent 12-month-prevalence of PD, with and without agoraphobia, in the German adult population was 2.0% (Jacobi et al., 2014). Patients with PD experience acute, stressful panic attacks as well as chronic stress due to being concerned about future panic attacks and their implications to health as well as changes in behaviour related to the panic attacks.

The hypothalamic-pituitary-adrenal (HPA)-axis is the body's major endocrine stress system controlling responses to various stressors. In clinical psychological research, the activity of the HPA-axis has been investigated extensively in reference to the pathophysiology of panic attacks. The hypothalamus directs the secretion of the adrenocorticotropic hormone (ACTH) from the

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http://dx.doi.org/10.1016/j.psyneuen.2016.11.030
0306-4530/

anterior pituitary which, in turn, stimulates the secretion of cortisol from the adrenal cortex. Under resting conditions, the ACTH and cortisol secretion follow a circadian rhythm as a function of light exposure to stress (Jung et al., 2010), caffeine (Lovallo et al., 2006), intense aerobic exercise (Fuqua and Rogol, 2013), and disrupted sleep (Leproult et al., 1997), among others. During acute stress, the diurnal hormone secretion is disrupted, which increased release of both cortisol and ACTH in healthy individuals (Tsigos and Chrousos, 2002). In individuals with stress-related mental disorders, this mechanism seems impaired. Thus, ACTH and cortisol release during non-stressful basal and stressful conditions provide an index for the normative (or disrupted) stress-regulating function of the HPA-axis.

Contradictory evidence has been reported on the cortisol levels of PD. Basal cortisol concentrations represent the resting activity of the HPA-axis and have been reported as "normative" with no difference from healthy individuals (Abelson and Curtis, 1996; Holsboer et al., 1986 ; Uhde et al., 1988). However, contradictory to this normative pattern, elevations (Goldstein, 1987; Wedekind et al., 2000) as well as reductions (Stones et al., 1999) in basal cortisol concentrations have been reported as well. Findings on the cortisol stress response are also mixed. The cortisol stress response provides an indicator for the acute HPA-axis reaction to laboratory-induced stressors. Overall, previous research suggests a hypo-responsiveness of the HPA-axis in patients diagnosed with PD. Different panic-related stimuli were used in the activation of the HPA-axis which, in fact, triggered panic but failed to result in cortisol secretion (lactate-induced panic: (Hollander et al., 1989; Levin et al., 1987; Peskind et al., 1998; Seier et al., 1997); CO2-induced panic: (van Duinen et al., 2004; Sinha et al., 1999)). These results correlate with our findings of a cortisol non-response pattern to the Trier Social Stress Test (TSST; Kirschbaum et al. (1993))in patients with PD (Petrowski et al., 2010). The TSST reliably induces subjective stress with concomitant cortisol release showing 2–4-fold elevations above baseline levels in healthy individuals (Kirschbaum et al., 1993). In patients diagnosed with PD, the cortisol response was absent (Petrowski et al., 2010). Further, patients with PD were found to show decreased plasma and cortisol stress response in response to the TSST as compared to healthy control participants, independent of comorbid depression and psychoactive medication (Petrowski et al., 2013). Occasionally, however, increased cortisol stress responses to laboratory-induced panic (CO2: (Woods et al., 1988); yohimbine: (Charney et al., 1987); respiratory stimulant: (Abelson et al., 2007)), and spontaneously occurring unprovoked panic attacks (Bandelow et al., 2000) have previously been reported in the literature.

Until now, it is unknown whether stress (non-)responsiveness is related to the psychotherapy outcome. A proportion of PD patients fail to show a symptom reduction or a remission following psychotherapy (Kampman et al., 2002; Keller et al., 1994), which is the first choice treatment for PD (Bandelow et al., 2014). Different variables have been associated with the psychotherapy outcome, among them agoraphobic avoidance (Andersson et al., 2008) and catastrophic agoraphobic cognition (Keijsers et al., 1994) as negative predictors, especially for agoraphobic patients (Keller et al., 1994; Steketee and Shapiro, 1995), anxiety and depression comorbidity with no impediment to the therapy success (Allen et al., 2010; Brown et al., 1995; Kampman et al., 2008), as well as the comorbid cluster C personality disorder and initial motivation for therapy, again with no influence on the therapy outcome (Kampman et al., 2008; Keijsers et al., 1994). Overall, recent research efforts failed to identify consistent therapy outcome predictors of a psychological or disorder-related kind. To date, there is a lack of studies focusing on the biological correlates of the psychotherapy outcome. One study group reported an association of poor actual and perceived health with the failure to meet recovery criteria after psychotherapy (Schmidt and Telch, 1997). Similarly, in a previous study, psychotherapy non-response was associated with decreased cortisol levels upon provocation (Siegmund et al., 2011). Siegmund et al. (2011) found a dissociative pattern in the hormonal stress response and the subjective level of fear during an in-vivo exposure to feared situations: despite experiencing fear, the hormonal stress response did not significantly increase during exposure. And further, patients with the lowest cortisol stress response showed the least improvement from psychotherapy.

The aim of the present study was to research the relationship between the cortisol stress response to the TSST and the psychotherapy outcome in patients diagnosed with PD, with or without agoraphobia. We hypothesized that the cortisol stress response is predictive of symptom recovery. Specifically, we predicted that the TSST non-response is associated with a higher panic symptom severity and psychotherapy non-response.

2. Methods

2.1. Study participants

The data were collected from June 2008 to October 2012. The patients were recruited from the University Hospital of the Technische Universität Dresden, Germany, before the start of cognitive behavioural psychotherapy. In addition, the healthy control participants were recruited via newspaper advertisements and matched to the patient sample by age and sex. General inclusion criteria were being 18–65 years of age and fluency in the German language. Exclusion criteria included a history of substance (ab)use, psychotic or bipolar disorder, post-traumatic stress disorder, eating disorder, as well as familiarity with the TSST (Kirschbaum et al., 1993), pregnancy as well as any severe physical illness (e.g. cancer, a metabolic or autoimmune disorder) within the previous two years. The Structured Clinical Interview (SCID; (Spitzer et al., 1990; Wittchen et al., 1990)) for *DSM-IV-TR* diagnosis of mental disorders on axis I and II (American Psychiatric Association, 2000) was conducted by trained clinical interviewers and the diagnoses confirmed by an experienced psychotherapist (KP). Patients with a current primary diagnosis of PD, with or without agoraphobia, were included in the study. Inclusion in the healthy control group was established using the DIA-X stem questions (Wittchen, 2007) which confirm that the participants did not have a history of mental disorders.

Thirty patients with PD and 32 healthy control participants were screened with respect to the defined inclusion and exclusion criteria. Two patients were excluded due to a 12-month- diagnosis of post-traumatic stress disorder and alcohol abuse disorder, resulting in a sample of $n = 28$ patients with a primary diagnosis of PD and $n = 32$ age- and sex-matched healthy control participants. According to the Panic & Agoraphobia Scale (Bandelow, 1995), $n = 5$ PD patients showed borderline panic and agoraphobic symptoms, $n = 7$ a mild, $n = 11$ a moderate and $n = 5$ a severe psychopathology. Two patients were on antidepressant medication (selective serotonin reuptake inhibitor: Citalopram, Paroxetine). All the other patients were free of antidepressant or anxiolytic medication. Comorbid mental disorders were major depression (single episode: $n = 6$; recurrent episode: $n = 4$) and specific phobia ($n = 4$). A brief description of sociodemographic and clinical characteristics of the included study participants is provided in Table 1. All the study participants gave written informed consent. The study procedure was approved by the local Ethics Committee of the Medical Faculty of the Technische Universität Dresden, Germany (No# EK46032008).