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Stress-induced pro- and anti-inflammatory cytokine concentrations in panic disorder patients

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ABSTRACT

Background: An attenuated responsivity of the hypothalamus–hypophysis-adrenal (HPA) axis upon challenge and an increased risk for cardiac events are relatively consistent findings in panic disorder (PD) patients. Due to cytokine-HPA interactions, an altered HPA-axis responsivity may be accompanied by altered cytokine concentrations. Immunological reactions under stress might be considered the missing link for explaining an increased cardiac risk. This study analyzed stress-induced cytokine levels in PD patients.

Methods: A total of $n = 32$ PD patients and $n = 32$ healthy control individuals performed the Trier Social Test (TSST). Blood sample collection accompanied the TSST for the collection of cortisol and pro- (IL-6, TNF-α) and anti-inflammatory cytokines (IL-10). Established self-report questionnaires were handed out for the clinical characterization and the assessment of subjective levels of distress during testing. Repeated measures ANCOVA were conducted to evaluate main effects of time or group and time x group interaction effects. Additional ANCOVAS with disease severity as between-subjects factor (healthy, borderline, mild, moderate, severe) took global panic severity into account. Pearson correlation analyses were carried out to test for an association of panic specific symptoms and peak cytokine release.

Results: The TSST resulted in a significantly increased secretion of cortisol, IL-6 and IL-10. The data analysis further revealed a significant time x group interaction effect for cortisol and IL-10. Compared to the healthy volunteers, the PD patients showed significantly higher baseline and challenged IL-10 concentrations but lower challenged cortisol concentrations. Mildly and moderately affected patients showed the highest levels of IL-10 compared to the healthy individuals. There were no differential secretion patterns of IL-6 and TNF-α between both groups in the course of the TSST. The peak IL-6 release was found to be significantly associated with global disease severity.

Conclusion: We found evidence for altered levels of cytokines with primarily anti-inflammatory properties in PD patients under baseline and a psychosocial stress condition. The results provide tentative evidence for a low-grade inflammatory process in PD patients, possibly representing a missing link factor between PD diagnosis and the increased risk for cardiac disease.

1. Introduction

Cytokines are important proteins regulating the immune response to injuries, infections, and other stressful events the organism is exposed to (Hoge et al., 2009). Current research findings seek to explain the influence of psychosocial stressors on the development of mental disorders (e.g. anxiety disorders, affective disorders) via the investigation of pro-inflammatory cytokines and changes in immune system functioning (Quagliato and Nardi, 2018; Schiepers et al., 2005; Simon et al., 2008). The relation between the hypothalamus-hypophysis-adrenal (HPA) axis reactivity and panic disorder (PD) has already been proven with numerous studies reporting on altered levels of the hormone products adrenocorticotropic hormone (ACTH) and cortisol (Bourgeois, 1993; Erhardt et al., 2006; Heuser et al., 1994; Roy-Byrne et al., 1986; Schreiber et al., 1996). More recent findings showed evidence of a suppressed reactivity of the HPA-axis under physiological as well as psychosocial stress induction (Jezova et al., 2010; Petrowski et al., 2010; Petrowski et al., 2012; Wichmann et al., 2017a,b). Due to

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cytokine-HPA-axis interactions, an altered cortisol stress responsivity may be accompanied by an altered cytokine release. The secretion of cortisol under stressful conditions has the function of suppressing the production of pro-inflammatory cytokines and thus of counteracting the development of inflammatory reactions (Padgett and Glaser, 2003; Rohleder et al., 2004). Therefore, a malfunction of the hormonal stress response may be accompanied by an increase in susceptibility to infectious and autoimmune disorders as well as inflammatory processes (Padgett and Glaser, 2003). Accordingly, in patients with a post-traumatic stress disorder (PTSD) diagnosis a reduced cortisol secretion and an increased production of pro-inflammatory cytokines were observed [for review: Rohleder et al., 2010]. Besides, von Känel et al. (2007) reported on a low-grade systemic inflammatory state evident in PTSD patients as indexed via high levels of various pro-inflammatory cytokines. Further, TNF-α was found to be associated with PTSD-related re-experiencing, avoidance and hyperarousal symptoms and global disease severity (von Känel et al., 2007). Since PD and PTSD often co-exist and share common symptoms, similar alterations in the secretion of immune parameters may also be observable in patients with PD.

In patients with a PD diagnosis, overall findings so far suggest a broad spectrum of increased baseline peripheral cytokine levels (Hoge et al., 2009). 87% of the PD patient sample showed an increased pro-inflammatory (e.g. TNF-α, IL-6) and anti-inflammatory (e.g. IL-10) cytokine level at resting conditions in comparison to 25% of the healthy control group. Furthermore, the increase in anti-inflammatory cytokines led to the assumption that they, too, increase in reaction to the increase in pro-inflammatory cytokines (Opal and DePalo, 2000). Concurrently, da Silva et al. (2017) reported on increased baseline IL-6 levels in patients with a current PD diagnosis as compared to remitted PD patients. Their analysis additionally showed that higher levels of panic severity were related to higher IL-6 concentrations. However, contrasting with the results by Hoge et al. (2009), no substantial differences were evident for TNF-α and IL-10 (da Silva et al., 2017). Van Duinen et al. (2008) and Tükel et al. (2012) also failed to reveal substantial differences in IL-6 and TNF-α under baseline conditions. Research on stress-induced cytokine secretion also produced mixed results. Meta-analytic evidence exists that cytokines respond to acute psychosocial stress, specifically the pro-inflammatory cytokine IL-6 (Steptoe et al., 2007). Weizman et al. (1999) reported on a negative correlation of the pro-inflammatory IL-3 concentration with the severity of state anxiety suggesting a state-dependent modulation of immune parameters. However, after acute stress induction, Van Duinen et al. (2008) were unable to determine any alterations in the cytokine secretion (TNF-α, IL-6, IL-10) in patients with PD before as well as after a 35% CO2 inhalation-induced panic in comparison to healthy individuals. Since this finding was contrasting findings of altered cytokine levels and simultaneously altered HPA-axis functionality in patients with depression and PTSD, the authors presume that the bidirectional communication between the immune system and the HPA-axis probably plays a role in some affective disorders, but does not specifically seems to have an impact in the etiology of PD.

Some causes for the inconsistent findings in PD patients may arise from differences of the paradigms employed (induced cytokine production vs. measuring of circulating cytokines), differences in the examined cytokines, the assays used, differences in the time in point of measuring the cytokines [circadian rhythm of the cytokines; Vgontzas et al. (2005)] as well as the influence of variables such as depressive comorbidity, age, sex, body mass index (BMI), smoking, and psychopharmaceutic medication intake (Hoge et al., 2009). Furthermore, due to taking a singular blood sample under baseline conditions, differences that would be present under stimulation/psychosocial stress may remain uncertain (Van Duinen et al., 2008). As yet, there have been no investigations reported for patients with PD under psychosocial stress induction. In healthy individuals, psychological stress (medical exam) produced increased pro-inflammatory (TNF-α, IL-6) and anti-inflammatory (IL-10) cytokine concentrations (Maes et al., 1998).

Therefore, the present study focuses on the question to which extent patients diagnosed with PD display increased pro-inflammatory cytokine (IL-6, TNF-α) and anti-inflammatory cytokine (IL-10) concentrations in response to psychosocial stress induction. These cytokines were specifically chosen for investigation since they were associated with PD diagnosis and were found to respond to psychosocial stress as reviewed above. The reduced cortisol availability under mental stress found so far (Jezova et al., 2010; Petrowski et al., 2010; Petrowski et al., 2012; Wichmann et al., 2017a,b) might be accompanied by an increased production of pro-inflammatory cytokines, thus explaining the creation of a cardiovascular morbidity in patients with PD via the mediation of a chronic low-stage inflammatory process (Smoller et al., 2007). Immunological processes under stress in patients with PD may be considered the “missing link” in the explanation of the severity of the psychopathology and for the determination of the risk factors of co-occurring somatic conditions such as the increased risk of a myocardial infarct. Since both pro- and anti-inflammatory cytokines were found to increase upon psychosocial stress (Maes et al., 1998; Steptoe et al., 2007), we expect an increase in all measured cytokines independent of the study group. However, we additionally suggest an attenuated cortisol stress response as has previously been described, and thus we hypothesize higher levels of pro- and compensatory increased anti-inflammatory cytokines in the patient sample compared to the healthy control individuals. According to the reported association between pro-inflammatory cytokines and disease severity, we expect higher levels of IL-6 and TNF-α in more severely affected patients.

2. Methods

2.1. Study sample

Recruitment of the study sample took place between August 2014 and March 2016. The patients were recruited from the department for psychotherapy and psychosomatic medicine at the university hospital Dresden, Germany. Participants with fluent German language skills and age between 18 and 65 were included in the study. General exclusion criteria were a lifetime history of substance use disorder, psychotic or bipolar disorder, psychopharmacological or glucocorticoid-containing medication intake (e.g. asthma inhaler, topical cortisone creams), severe medical illnesses (e.g. cancer, autoimmune diseases, diabetes), and pregnancy. The Structured Clinical Interview [SCID; First et al., 1995] was conducted by trained interviewers for the assessment of *DSM-IV-TR* mental disorder diagnoses. The diagnostic assessment was confirmed by an experienced clinical psychologist. Patients with a primary diagnosis of PD with or without agoraphobia were included. The inclusion in the healthy control group required the participants to be free of any history of mental disorder in the SCID. In total, thirteen individuals dropped out of study participation. Specifically, nine healthy individuals [due to outlying values in cytokine release ($n = 4$), due to missing matching patient ($n = 5$)] and four patients [due to tricyclic antidepressant medication and due to immunomodulatory medication intake (each $n = 1$), due to outlying values in cytokine release ($n = 2$)] were excluded. The final sample included $n = 32$ PD patients with and without agoraphobia and $n = 32$ healthy controls. A total of $n = 4$ (12.5%) showed a borderline, $n = 12$ (37.5%) a mild, $n = 8$ (25%) a moderate, and $n = 8$ (25%) a severe disease severity according to the Panic & Agoraphobia Scale (PAS; Bandelow, 1999). All the study participants provided written informed consent and the study procedure was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of the Medical Faculty of the Technische Universität Dresden, Germany (EK#7012006).

2.2. Psychosocial stress induction and hormone sampling

The standardized protocol for the TSST was applied for the reliable induction of acute moderate psychosocial stress under laboratory