Psychoneuroendocrinology 82 (2017) 126–132

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Modulation of HPA axis response to social stress in schizophrenia by childhood trauma

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ARTICLE INFO

Keywords:
Stress
Cortisol
Schizophrenia
HPA system
Trier social stress test
Childhood trauma

ABSTRACT

HPA axis functioning plays an important role in the etiology of schizophrenia spectrum disorders (SSD). However, only few studies have examined HPA axis responsivity to psychosocial stress in SSD, and results are heterogeneous. Furthermore, childhood trauma is known to influence psychopathology and treatment outcome in SSD, but studies on the influence of childhood trauma on stress related HPA axis activity are missing. The purpose of this study was to investigate cortisol response to a psychosocial stress challenge in SSD patients, and to examine its association with severity of childhood trauma. The present study included 25 subacutely ill patients with a current episode of a chronic SSD and 25 healthy controls. Participants underwent the modified Trier Social Stress Test, and salivary cortisol levels were assessed. The childhood trauma questionnaire was used to assess severity of adverse life events. Overall, cortisol response was blunted in the patient group compared to the control group ($p < 0.01$). Furthermore, we identified two patient subgroups (cortisol responders ($n = 12$) vs. non-responders ($n = 13$) to the modified TSST) that differed in their severity of childhood trauma experience: responders had experienced more emotional abuse in their past ($p < 0.042$). Therefore, childhood trauma might influence stress-related HPA axis activity in SSD. Our data contribute to the hypothesis that severity of childhood trauma may be of pathophysiological relevance in schizophrenia. In addition, it may be an overlooked factor contributing to inconsistent findings regarding HPA axis response to psychosocial stress in SSD.

1. Introduction

Preclinical and clinical data suggest that stress plays a causal role in the etiology of schizophrenia spectrum disorders (SSD) and can trigger illness episodes (Mizrahi, 2015). A recent meta-analysis on cortisol awakening response (CAR) in patients with schizophrenia showed a blunted CAR compared to healthy controls (Berger et al., 2016). Furthermore, patients with chronic schizophrenia show significantly higher levels of diurnal cortisol than healthy controls (Meltzer et al., 2001; Zhang et al., 2005; Gallagher et al., 2007; Popovic et al., 2007; Yılmaz et al., 2007; Venkatasubramanian et al., 2010; Yıldırım et al., 2011). After resting prior to experimental stress induction, similar baseline cortisol levels in SSD compared to controls have been reported (Brenner et al., 2009; Brenner et al., 2011; van Venrooij et al., 2012).

In psychosocial stress provocation tests, patients with chronic schizophrenia mostly fail to show cortisol group differences compared to healthy controls (Brenner et al., 2011; Lincoln et al., 2015; Steen et al., 2011), while medication free first episode patients display a lower cortisol response (van Venrooij et al., 2012), a pattern that has already been seen in individuals with ultra high risk for psychosis (Pruessner et al., 2013). Yet, earlier studies also found a blunted cortisol response in chronically ill patients with SSD (Jansen et al., 1998; Jansen et al., 2000). Overall, literature on HPA axis response to psychosocial stress in SSD is sparse and contradictory (Lange et al., 2016).

Psychosocial stressors, such as childhood trauma or discriminatory encounters, appear to play a significant role for the course of schizophrenia: Here, findings report a correspondence of increased occurrences of such life events and the onset or exacerbation of psychotic symptoms (for review see van Winkel et al., 2008; Dinzeo et al., 2004). Larsson et al. investigated childhood trauma via the childhood trauma questionnaire (CTQ) in 305 patients in SSD and affective disorders and found a prevalence of 85% in the SSD group (Larsson et al., 2013). Furthermore, SSD patients have a 2.72 times higher chance to experience childhood trauma compared to healthy controls (for review see Varese et al., 2012).

Childhood trauma is known to influence HPA axis functioning in

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http://dx.doi.org/10.1016/j.psyneuen.2017.03.027
Received 6 October 2016; Received in revised form 24 March 2017; Accepted 29 March 2017

healthy subjects: Whereas no basal cortisol differences can be found in healthy controls between participants with and without childhood trauma (Klaassens et al., 2009), healthy participants with childhood trauma exposed to a psychosocial stress test release less cortisol compared to the group with no childhood trauma (Carpenter et al., 2011). Furthermore, it seems that intensity of childhood trauma may play a role as higher childhood trauma scores and long enduring childhood trauma are associated with a more blunted cortisol response in healthy participants when confronted with a psychosocial stress test (Voellmin et al., 2015). Relatively few studies have investigated the effect of childhood trauma on diurnal HPA axis functioning in patients with SSD. Braehler et al. (2004) found a lower cortisol level in patients with childhood trauma. Ruby et al. (2015) also found differing cortisol patterns in patients with schizophrenia and early traumatization. So far, no study has investigated potential connections between childhood trauma and HPA axis function in SSD using a psychosocial stress test.

Considering the pathophysiological relevance of both stress and adverse life events for the course of SSD, the potential influence of both factors on the HPA axis, and the potential connection between HPA axis functioning and SSD, the question if childhood traumata influence cortisol response to psychosocial stress in SSD patients seems of strong clinical importance. Furthermore, it may help to disentangle the conflicting findings on HPA axis functioning in SSD (Lange et al., 2016 in press).

Thus, the current study aimed (1) to analyze cortisol response to psychosocial stress as administered using a modified Trier Social Stress Test (TSST) in subacutely ill patients with chronic schizophrenia spectrum disorder (SSD) in comparison to healthy controls, (2) to examine if sociodemographic and clinical parameters are connected with cortisol response, and (3) to examine the association of severity of childhood trauma with cortisol response.

2. Materials and methods

25 patients with chronic SSD (7 females, 18 males) and 25 healthy volunteers (9 females, 16 males) participated in the present case-control study (Table 1). Patients were recruited from the Psychiatric Hospital of the University of Basel between July 2013 and April 2015. The healthy participants were recruited by advertisements in the city of Basel, Switzerland. Participation was voluntary, and healthy participants were compensated for their participation. All participants provided their written informed consent. The local ethics committee approved the study protocol (EK 117/13). The investigation was carried out in full accordance with all local and national regulations, and with the Declaration of Helsinki in its latest revision.

Inclusion criteria for the current analyses were: a diagnosis of SSD according to DSM-IV; being in partial remission after an acute illness episode, defined as having a Positive and Negative Syndrome Scale (PANSS) total score of < 95 (not more than moderately ill according to Leucht et al. (2006)); chronic SSD, defined as currently having at least the second illness episode and having a duration of illness ≥ one year; and sufficient knowledge of the German language. Inclusion criteria for controls were absence of a psychiatric disorder, and of a family history of SSD. Patients and controls were excluded if diagnosed with endocrine, cardiovascular, neurological, other chronic somatic diseases or with intake of medication potentially interfering with the HPA axis, or with non-SSD related axis I disorders.

2.1. Study procedure

Nicotine consumption, caffeine consumption, exercise, intake of benzodiazepines, and alcohol and drug consumption (Kirschbaum et al., 1993a; Kirschbaum and Hellhammer 1999) can significantly alter the cortisol response to stress; therefore participants were asked to refrain from these substances and activities on the day of testing.

Between 10:00 and 11:00 of the testing day, a member of the research staff with formal training in the administration of diagnostic interviews conducted the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), and collected clinical and socio-demographic information.

Table 1
Demographic and clinical data of study participants.

	Patients (N = 25)	Controls (N = 25)	p-value
Gender (m/f)	18/7	16/9	$x^2 = 0.368$, df = 1, p = 0.762 [1]
Age (in years)	38.3 (SD 13.5)	41.16 (SD 11.1)	0.420
Duration of illness (in years)	13.8 (SD 12.4)	N/A	
Main diagnosis			
Schizophrenia	23	N/A	
Schizoaffective disorder	2	N/A	
PANSS total score	59.1 (SD 17.1)	N/A	
Antipsychotic medication (CPZ equivalents, in mg)	575.5 (SD 427.8)	N/A	
Trauma History (as measured using the CTQ)			
Emotional Abuse present	8.3 (SD 2.5)	7.6 (SD 2.4)	0.356
Emotional Abuse (yes/no)	9/16	5/20	
Physical Abuse present	6.4 (SD 1.9)	5.2 (SD 0.5)	0.007
Physical Abuse (yes/no)	6/19	0/25	
Sexual Abuse present	5.4 (SD 1.0)	5.5 (SD 1.2)	0.758
Sexual Abuse (yes/no)	6/19	4/21	
Emotional Neglect present	12.5 (SD 4.2)	9.0 (SD 3.3)	0.003
Emotional Neglect (yes/no)	19/6	9/16	
Physical Neglect present	10.9 (SD 2.0)	10.2 (SD 1.8)	0.245
Physical Neglect (yes/no)	25/0	25/0	

For gender and main diagnosis, the number participants is given, and a chi-square test was used for group comparisons. All other data are shown as mean values with standard deviation (SD), and independent t-tests were used for group comparisons; CPZ: chlorpromazine; CTQ: Childhood Trauma Questionnaire; f: female; m: male; N/A = not applicable; PANSS: Positive and Negative Syndrome Scale for Schizophrenia; [1] chi-square test.

The Childhood Trauma Questionnaire (CTQ) was used to examine the severity of trauma history (Bernstein et al., 2003). The participants answered the 34 items on a five-point Likert-rating scale (1 = not at all; 5 = very much). The CTQ describes adverse childhood experiences on the five subscales emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Subscale scores are computed by summing up the score of the individual items and have a theoretical range between 5 and 25 points. The CTQ is a tool with high validity in psychiatric patients (Dudrck et al., 2015). In order to avoid emotional distress and therefore possible cortisol changes as a result of completing the CTQ, patients completed the questionnaire either the day prior or the day after the TSST.

Participants then rested from 12:00 to 14:00. The TSST was consistently conducted at 14:00 in order to avoid circadian effects on baseline cortisol levels (Kudielka et al., 2004). Participants were taken to a separate room where a two-person evaluating panel was awaiting them behind a desk (Kirschbaum et al., 1993b). The TSST is generally a public speaking task followed by a mental arithmetic task in front of an evaluating panel of judges (Kirschbaum et al., 1993a). Instead of the job interview employed in the original TSST protocol, we asked the participants to talk about their physical appearance without recording equipment, an adaptation that has been chosen for patients with SSD in the past, as patients may not be able to relate to a job interview situation (e.g. Brenner et al., 2009). A meta-analysis showed that a combination of a public speaking task and a cognitive paradigm will lead to the most robust stress responses (Dickerson and Kemeny 2004) despite this modification. Following the mental arithmetic task, parti-