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Effects of social exclusion on emotions and oxytocin and cortisol levels in patients with chronic depression

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ABSTRACT

Objective: Patients with chronic depression (CD) experience a high burden of disease, severe comorbidity, and increased mortality. Although interpersonal dysfunction is a hallmark of CD, the underlying mechanisms are largely unexplored. Oxytocin (OT) has been proposed to play a crucial role in the social deficits of mental disorders and has been found to be dysregulated after social exclusion (ostracism) in patients with borderline personality disorder. This study investigated how social exclusion affects emotions, OT levels, and cortisol (CT) levels in CD patients.
Method: Twenty-one patients diagnosed with CD and 21 healthy controls (HC) matched for gender, age, and education underwent repeated neuroendocrine measurements in a standardized laboratory setting while playing Cyberball, a virtual ball-tossing game that mimics a social exclusion situation. Emotional reactions, plasma OT and cortisol levels were assessed at baseline and 5, 15, and 40 min after Cyberball.
Results: At baseline, there were no group differences in OT levels. Immediately after playing Cyberball, plasma OT levels showed divergent changes in CD patients and HC; the difference in direction of change was significant with a reduction in CD patients compared to HC ($p = .035$*); CT levels did not differ between groups at any time point, but decreased over time. Patients showed more threatened emotional needs and increased negative emotions, especially anger and resentment, and showed higher sensitivity to ambiguous threat of social exclusion than healthy controls.
Conclusions: CD patients react to ostracism with pronounced negative emotions. The reduction in OT levels in CD patients after social exclusion may contribute to their interpersonal dysfunction and their difficulty in coping adequately with aversive social cues.

1. Introduction

Chronic depression (CD) is a severe mental disorder that develops in about 20%–30% of patients with major depressive disorder (MDD) (Angst et al., 2009; Kessler et al., 1994). CD can be characterized by interpersonal problems that may result from disturbed attachment and parenting as well as interpersonal trauma during childhood (Wiersma et al., 2009). This interpersonal dysfunction plays a major role in sustaining a depressive state and has been the focus of novel psychotherapeutic approaches, e.g. the cognitive behavioral system of psychotherapy (CBASP) (Keller et al., 2000). However, little is known about the neurobiological background of impaired interpersonal function in CD.

Theoretically, changes in interpersonal function, i.e. disturbed affiliative behaviors, impaired reading of social cues, impaired establishment of trust, reduced capacity for attachment, and inability to cope with social stressors, may be related to altered regulation of the oxytocin (OT) system (Eckstein and Hurlemann, 2013; Herpertz and Bertsch, 2014; Meyer-Lindenberg et al., 2011; Stanley and Siever, 2010; Striepens et al., 2011). OT, a hypothalamic neuropeptide, stimulates milk ejection and uterine contraction at parturition in mammals and has been linked to prosocial behavior and social approach in humans (Carter, 1998; Kosfeld et al., 2005). High peripheral levels of plasma OT are associated with trust and

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trustworthiness (Zak et al., 2005), and plasma OT levels can be increased by the warm touch of others (Holt-Lunstad et al., 2008). OT modulates the formation of social memories (Domes et al., 2012) and is involved in reading mental states of other individuals (mentalizing) (Domes et al., 2007). Moreover, it plays a major role in maternal care as well as parental and pair bonding, e.g. Ditzen and coworkers demonstrated an increase of positive communication behavior in relation to negative behavior together with a reduction of salivary cortisol levels after intranasal OT administration during a standard conflict discussion in heterosexual couples (Ditzen et al., 2009). Another study demonstrated a positive association between peripheral OT levels and positive communication in couples using a structured social support interaction task (Gouin et al., 2010).

OT has been shown to exhibit stress-attenuating functions in the Trier Social Stress Test (TSST) (Heinrichs et al., 2003), possibly mediated by a suppressive effect on the HPA axis, as has been shown in male rats (Neumann et al., 2000). Central OT release under stress has been observed in animals, accompanied by secretion of OT into the peripheral circulation (Nishioka et al., 1998; Wotjak et al., 1998). In humans, however, findings regarding the interaction of stress and OT release are inconsistent. Heinrichs and colleagues did not observe OT release in response to the TSST in breastfeeding women (Heinrichs et al., 2001), whereas Pierrehumbert and coworkers found a clear OT response during the TSST in people who had been exposed to traumatizing events such as abuse or potentially fatal illnesses during childhood or adolescence (Pierrehumbert et al., 2010). In addition, this response was related to the respective attachment representations (Pierrehumbert et al., 2012).

Dysregulation of the OT system has been suggested as a putative mechanism that contributes to interpersonal dysfunctions in conditions with social deficits, such as borderline personality disorder (BPD), autistic disorder, and schizophrenia (Goldman, Marlow-O'Connor, Torres and Carter, 2008; Green et al., 2001; Stanley and Siever, 2010). Women with BPD had lower plasma OT levels than healthy controls, and their plasma OT levels were negatively correlated with a history of childhood trauma (Bertsch et al., 2012). Moreover, BPD patients showed an altered regulation of peripheral OT levels after social exclusion (Jobst et al., 2014), which may underlie the deficits in repairing broken cooperation (King-Casas et al., 2008). There is recent evidence of an altered OT regulation in MDD: Salivary OT levels were found to be reduced in mothers with CD and their children compared to non-depressed mothers (Apter-Levy et al., 2013). Similarly, plasma OT levels were lower in women with MDD than in healthy controls (Yuen et al., 2014). However, to date OT has not been investigated in CD, even though interpersonal deficits are particularly pronounced in this disorder.

Rejection and feeling isolated from others can be experimentally mimicked with social exclusion (ostracism) paradigms, e.g. the Cyberball paradigm. In the Cyberball paradigm, participants are excluded from a computer-based virtual ball-tossing game (Williams and Jarvis, 2006). Using this paradigm, Renneberg and colleagues observed higher scores of negative emotions (anger) after exclusion in BPD patients than in healthy controls. BPD patients felt excluded even when they were not, and the exclusion resulted in dysfunctional behavioral intentions (Renneberg et al., 2012; Staebler et al., 2011).

To our knowledge, so far no studies have addressed the effects of social exclusion on the regulation of emotions, OT and CT levels in patients with CD. Consequently, this pilot study used the Cyberball social exclusion paradigm to investigate the effects of social exclusion on these variables in a group of CD patients and healthy controls.

2. Methods and materials

2.1. Participants

Twenty-one inpatients (15 men, 6 women, mean age 45.79 ± 15.55, range: 20–72 yrs) with a diagnosis of CD and 21 healthy controls (15 men, 6 women, mean age 46.43 ± 14.37), matched for gender, age and education, were included in the study. The patients were recruited at the Department of Psychiatry and Psychotherapy, Ludwig Maximilian University of Munich. CD diagnoses and comorbid axis I and II diagnoses were assessed with the German version of the Structural Clinical Interview for DSM-IV (First et al., 1995) (SCID-I-Screening, SCID–II–Interview); all patients met the diagnostic criteria for dysthymia and depressive episode lasting longer than 2 years. Individuals with a diagnosis of substance dependence, schizophrenia, schizoaffective disorder, or bipolar disorder were excluded. The mean frequency of comorbid diagnoses on SCID-II was 1.42 (SD 1.61); patients had the following co-morbid personality disorders: Depressive ($N = 5$), avoidant ($N = 4$), obsessive-compulsive ($N = 4$), paranoid ($N = 2$), dependent ($N = 2$), antisocial ($N = 2$), negativistic ($N = 1$), schizoid ($N = 1$), narcissistic ($N = 1$), borderline ($N = 1$), and histrionic ($N = 1$). The HC were recruited by advertisements in newspapers and on noticeboards; they did not have a current psychiatric disorder, had never received psychiatric treatment and had not received any psychological treatment in the past 10 years, as confirmed with the SCID-I and –II screening instruments (First et al., 1995).

Most of the CD patients were receiving pharmacological treatment, i.e. antidepressants ($N = 17$), second generation antipsychotics (SGA, $N = 10$), or mood stabilizers ($N = 9$). At the time of assessment, 8 patients were taking benzodiazepines.

The study was approved by the Institutional Review Board of the Faculty of Medicine, Ludwig Maximilian University, Munich. All participants provided written informed consent. The healthy controls received €70 financial compensation.

2.2. Procedure and measures

Plasma OT and CT levels were measured in all participants before and after a social exclusion paradigm that used the standardized virtual ball-tossing game Cyberball to evoke social stress (Williams and Jarvis, 2006). Participants had to visit the laboratory three times. At the first visit, we checked inclusion and exclusion criteria and obtained informed consent. At the second visit, participants completed the following psychometric questionnaires: Beck Depression Inventory II (Beck et al., 1996), 24-item Hamilton Depression Rating Scale (Hamilton, 1960), the German version of the short form of the Childhood Trauma Questionnaire (CTQ-SF) (Bernstein et al., 2003; Klinitzke et al., 2012), and the Rejection Sensitivity Questionnaire (RSQ) (Downey and Feldman, 1996). At the third session, participants played Cyberball in a standardized experimental setting, as previously reported (Jobst et al., 2014). Before starting the game, an intravenous catheter was inserted into a forearm vein to allow through-the-wall blood drawings via a long catheter that ran through a soundproof lock to an adjacent laboratory. Ten to 15 min after inserting the catheter (during which time the participants completed questionnaires on their current emotional state), a blood sample was collected for baseline measurements, and the Cyberball game was started on a computer screen positioned in front of the participants. During the experiment, participants sat in a comfortable chair and had no visual contact with the investigators. The Cyberball paradigm includes two virtual players who are controlled by the software (Williams and Jarvis, 2006). An explanation on the computer screen tells the participants that they will take part in a virtual game with two