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Differential neuroendocrine and immune responses to acute psychosocial stress in women with type 1 bipolar disorder

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ABSTRACT

Bipolar disorder (BD) has been associated with immune imbalance, including lymphocyte activation and increased pro-inflammatory cytokines. Immune activation is part of stress response, and psychosocial stress has been implicated in the pathogenesis of psychiatric disorders. Here, we investigated the neuroendocrine and immune responses to acute psychosocial stress challenge in BD. Thirteen euthymic participants with type 1 BD and 15 healthy controls underwent the Trier Social Stress Test protocol (TSST). Blood samples were collected before and after TSST. Lymphocytes were isolated and stimulated *in vitro* to assess lymphocyte activation profile, lymphocyte sensitivity to dexamethasone, mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) signaling by flow cytometry. Heart rate and salivary cortisol levels were monitored across the task. BD participants exhibited blunted stress responses as shown by reduced heart rate and salivary cortisol levels in comparison to healthy controls. BD was also associated with reduction in the percentage of regulatory T cells, but with expansion of activated T cells. When compared to controls, patients showed increased lymphocyte MAPK p-ERK and p-NF-κB signaling after the stress challenge, but exhibited a relative lymphocyte resistance to dexamethasone. In conclusion, stress-related neuroendocrine responses are blunted, associated with increased immune activation and lower sensitivity to glucocorticoids in BD. An inability in reducing NF-κB and MAPK signaling following TSST could be underlying the immune imbalance observed in BD.
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1. Introduction

Psychosocial stress is a well-known risk factor for several psychiatric disorders and it has been shown to affect both the onset and course of Bipolar Disorder (BD) (Kapczinski et al., 2008; Post and Leverich, 2006). Consistent with stress-related physiological changes, mood disorders have been associated with dysregulation of the neuroendocrine and immune systems (Kim et al., 2004; O'Brien et al., 2006). Although previous work demonstrated that hypothalamic-pituitary-adrenal (HPA) axis is deregulated in mood disorders (Ahrens et al., 2008; Spiliotaki et al., 2006; Stetler and Miller, 2011), the great majority of studies did not investigate stress reactivity.

Laboratory stress studies provide a unique opportunity to address the underlying mechanisms involved in stress reactivity. The Trier Social Stress Test (TSST), a validated laboratory psychosocial stress task, is commonly used to analyze biological changes due to controlled stress exposure (Kirschbaum et al., 1993). Social evaluative stressors, such as TSST, are capable of eliciting cortisol secretion, which can be used as an objective measure of HPA axis function (Dickerson et al., 2009; Kapczinski et al., 2008). Immune activation is also part of the stress response leading to exacerbation of several chronic inflammatory conditions (Buske-Kirschbaum et al., 2010, 2002, 2007; Ritz et al., 2011). Higher immune responses have been associated with lower cortisol responses to acute psychosocial stress in healthy subjects (Edwards et al., 2010; Kunz-Ebrecht et al., 2003; Wolf et al., 2009). However, stress reactivity is largely unknown in BD, and failure to mount adequate neuroendocrine responses following stress could be associated with detrimental overshooting immune responses.

A growing body of evidence suggests an immunological imbalance in BD, associated with a pro-inflammatory profile. Higher

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plasma levels of pro-inflammatory cytokines and soluble receptors have been described during manic (Barbosa et al., 2011; Brietzke et al., 2009; Kim et al., 2010, 2004; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007) or depressive episodes (Kim et al., 2004; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007) in BD. Altered proportions of activated/regulatory lymphocyte subsets and differential intracellular signaling have been implicated in the immunological imbalance in BD (do Prado et al., 2013). Nuclear factor kappa B (NF-κB) is a pleiotropic transcription factor readily activated following different stimuli (Hayden and Ghosh, 2004), and the phosphorylation of the p65 subunit (p-p65) results in its translocation to the nucleus and consequent transcription of different pro-inflammatory genes. Bierhaus et al. (2003) reported increased NF-κB signaling after TSST as a mechanism converting social stress into immune activation in healthy individuals (Bierhaus et al., 2003). In this line, Pace et al. (2006) found increased p65 DNA binding major depression after TSST and a consequent increase in IL-6 plasma levels (Pace et al., 2006). Mitogen-activated protein kinase (MAPK) proteins are involved in many cellular processes such as differentiation, proliferation, activation and apoptosis, and may contribute to the immune alterations observed in BD (Johnson and Lapadat, 2002; Raman et al., 2007). Three major MAPK cascades are known, including the extracellular signal-regulated protein kinase (ERK), c-jun amino-terminal protein kinase/stress-activated protein kinase (JNK) and p38 (Raman et al., 2007). While phosphorylation of ERK1/2 is involved in cellular proliferation, differentiation, activation and survival, phosphorylated p38 is related to cellular energy and pro-apoptotic fate (Johnson and Lapadat, 2002; Raman et al., 2007; Strniskova et al., 2002). Although changes in intracellular signaling events are likely to be involved with immune imbalance, there is no information regarding the role of acute psychosocial stress upon these molecules in BD.

Here, we investigated a comprehensive set of neuroendocrine and immune responses, including activation/regulatory cell profiles, lymphocyte sensitivity to glucocorticoids and intracellular cell signaling (MAPK and NF-B), of euthymic women with BD type 1 and healthy controls to an acute psychosocial stress challenge. It was hypothesized that blunted neuroendocrine responses to stress could be associated with immune activation in BD.

2. Methods

2.1. Subjects

Thirteen euthymic female participants with BD type I were recruited by convenience sampling at mental health facility in Porto Alegre, Brazil. Age- and sex-matched healthy controls ($n = 15$) were also recruited to the study. All participants provided their written informed consent before inclusion in the study approved by the Ethical Committee of PUCRS. The BD type 1 diagnosis was based on a psychiatric clinical interview and confirmed with the *Structured Clinical Interview for DSM-IV-Axis I Disorder* (SCID-I) administered by a well-trained clinical psychologist and discussed with an expert psychiatrist. Severity of depressive and manic symptoms was assessed by the *Hamilton Depression Rating Scale* (HDRS) and the *Young Mania Rating Scale* (YMRS), respectively. All individuals were euthymic at the time of procedures. Euthymia was defined by YMRS and HDRS scores <8 in the last 30 days (Clark et al., 2002). Exclusion criteria to both BD subjects and controls included: (a) presence of major axis I psychiatric disorder such as psychotic disorder, mood disorder (for control group), anxiety disorder or substance related disorder according to SCID-I; (b) history of a severe medical illness; (c) history of brain injury; (d) presence of systemic diseases or neurological disorder, (e) pregnancy and (f) use of any substance that may induce immune or endocrine changes (except psychopharmacotherapy for BD participants).

2.2. Trier social stress test (TSST)

The TSST is a standardized psychosocial stress protocol that elicit acute stress responses (cortisol and HR) and involves the delivery of a free speech (5 min) concerning their suitability for employment in a mock job interview and mental arithmetic tasks (5 min) in front of a panel of judges and fake camera and video recorder (Kirschbaum et al., 1993). All recruited participants completed the protocol.

2.3. Heart rate

In order to assess the arousal response to TSST the heart rate (HR) was continuously assessed and recorded in 5 min intervals throughout the stress protocol using a wireless chest heart rate transmitter (Polar, New York, USA).

2.4. Cortisol analyses

Salivary cortisol levels were assessed in order to been used as an objective marker of stress-induced activation of the HPA axis (Kirschbaum et al., 1993). Saliva samples were collected with cotton rolls immediately before (5 min) and after (20 min) TSST. In addition, three different samples were collected (30, 15 and 5 min before task) during preparation phase as baseline values. During recovery phase salivary cortisol were assessed in two different points (30 and 60 min after task). After the protocol all samples were centrifuged and stored in −80 °C until analysis. Samples were analyzed in duplicates by radioimmunoassays (Coat-A-Count® Cortisol Kit – Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The sensitivity of this assay was estimated in 0.1 nM. The intra- and inter-assay coefficients of variation were less than 10%. Results from each of the sampling times were expressed in nmol/L. In addition, integrated salivary cortisol levels were estimated by the trapezoidal rule to calculate the area under the curve (AUC) and data were expressed as nM per liter per hour.

2.5. Blood collection and cell isolation

Twenty milliliters of peripheral blood were collected by venipuncture pre- and post-TSST in the same arm and stored in EDTA tubes prior to analyses. The first sample was taken 30 min before the task, during preparation period. The second sample was taken at the end of recovery phase (40 min after stress). Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation for 30 min at 900*g*. Cells were counted by means of microscopy (100×) and viability always exceeded 95%, as judged from their ability to exclude Trypan Blue (Sigma, St. Louis, MO). PBMCs were resuspended in complete culture medium (RPMI-1640, supplemented with 0.5% gentamicine, 1% glutamine, 1% hepes, 0.1% fungizone, and 10% fetal calf serum; all from Sigma) and adjusted to yield a final concentration of 2×10^5 cells/well.

2.6. Immunophenotyping of lymphocytes

A large panel of lymphocyte subpopulations was identified by multi-color flow cytometry. In order to evaluate specific lymphocyte subsets, cells were stained for 30 min with combinations of the following monoclonal antibodies: anti-CD3 FITC and PECy5 (T cells), anti-CD4 PE and FITC (Th cells), anti-CD8 PE (Tc cells), anti-CD19 PE (B cells), anti-CD56 FITC (NK cells), anti-CD25 FITC (activated T cells), anti-CD45RO FITC (memory T cells), anti-CD69 FITC (early activated cells), anti-FOXP3 PECy5 (regulatory T cells),

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