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Interaction of BDNF with cytokines in chronic schizophrenia

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) interacts with cytokines. Although both BDNF and cytokines occur at abnormal levels in schizophrenia patients, their interactions have not yet been examined. We therefore compared serum BDNF, TNF-α, interleukin (IL)-2, IL-6, and IL-8 levels in 92 chronically medicated schizophrenia patients and 60 healthy controls. We correlated these serum levels within these subject groups with each other and with clinical symptoms assessed according to the Positive and Negative Syndrome Scale (PANSS). Compared to the control group, the schizophrenia patients had significantly lower BDNF and TNF-α levels, and higher IL-2, IL-6, and IL-8 levels. The patients also showed a significant positive correlation between BDNF and both IL-2 and IL-8 levels, and low BDNF and TNF-α levels together were associated with poor performance on the PANSS cognitive factor. Thus, an interaction between cytokines and neurotrophic factors may be implicated in the pathophysiology of chronic schizophrenia. In particular, the cytokine TNF-α may interact with BNDF causing cognitive impairment.

1. Introduction

The neurodevelopmental model of schizophrenia suggests a "2-hit" model (Keshavan, 1999; Rapoport et al., 2012), in which a first hit may be a prenatal viral or bacterial infection that activates microglia and immuno-inflammatory pathways (Canetta and Brown, 2012; Altamura et al., 2013), followed by secondary inflammatory hits during adolescence with consequent autoimmune responses (Anderson and Maes, 2013). These autoimmune responses in the brain can act through cytokines, and abnormal cytokine levels are associated with various neurological, neurodegenerative, and neurotoxic conditions, including schizophrenia (Altamura et al., 2013; Miller et al., 2013; Na et al., 2014; Müller, 2014; Upthegrove et al., 2014; Zakharyan and Boyajyan, 2014; Sperner-Unterweger and Fuchs, 2015). Two recent meta-analyses have shown cytokine alterations in schizophrenia patients. The first meta-analysis by Potvin et al. (2008) found increased levels of *in vivo* peripheral interleukin (IL)-1RA, sIL-2R, and IL-6 in schizophrenia patients. The second meta-analysis by Miller et al. (2011) found significant increases in macrophage-derived cytokines IL-1β, IL-6, and TNF-α, as well as the Th1-derived cytokines interferon-γ and IL-12 in first-episode psychosis.

Low levels of brain-derived neurotrophic factor (BDNF) are associated with schizophrenia (Buckley et al., 2011; Favalli et al., 2012; Nieto et al., 2013) in both chronic antipsychotic-treated patients and antipsychotic-free or naïve, first-episode patients with schizophrenia (Chen et al., 2009; Xiu et al., 2009; Pillai et al., 2010; Rizos et al., 2010; Nurjono et al., 2012). Although some authors have failed to replicate these findings in both medicated and antipsychotic-naïve patients (Green et al., 2011), a recent meta-analysis supports reduced peripheral BDNF levels in both medicated and drug-naïve patients with schizophrenia (Green et al., 2011). Furthermore, BDNF has been associated with positive symptoms (Buckley et al., 2007; Xiu et al., 2009), negative symptoms (Rizos et al., 2008; Chen et al., 2009), and tardive dyskinesia (TD) (Yang et al., 2011; Zhang et al., 2012a,b). Taken together, these findings demonstrate the relevance of BDNF to the pathophysiology of schizophrenia (Nurjono et al., 2012).

BDNF and cytokines are well-known to cross-regulate each other (Nawa et al., 2000; Calabrese et al., 2014). For example, IL-1β and transforming growth factor (TGF)-α suppress the normal expression of BDNF (Xiong et al., 1999), while IL-1β up-regulates the expression of nerve growth factor (NGF) (Heese et al., 1998). BDNF levels are also positively associated with IL-6 levels in major depressive disorder patients, but not in non-depressed controls

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(Patas et al., 2014). Among the sources of BDNF are human peripheral blood mononuclear cells (i.e. T-cells, B-cells, and monocytes), which upon stimulation release neurotrophins such as BDNF offering neuroprotection (Schulte-Herbrüggen et al., 2005).

Studies in humans and animals have explored the effects of antipsychotics on BDNF and cytokine levels (Nurjono et al., 2012). For example, some studies have found a differential regulation of BDNF mRNA expression in the rat hippocampus and neocortex by typical and atypical antipsychotic administration (Bai et al., 2003), with the atypical antipsychotics olanzapine and quetiapine enhancing BDNF expression (Rizos et al., 2008). Furthermore, serum BDNF levels were higher in chronic schizophrenia patients on clozapine or typical antipsychotics than risperidone (Xiu et al., 2009), and BDNF levels were positively associated with daily clozapine doses in patients with schizophrenia (Pedrini et al., 2011). However, some longitudinal studies have reported that lower serum BDNF levels did not increase after several weeks of antipsychotic treatment (Pirildar et al., 2004; Yoshimura et al., 2007). Alterations in cytokine levels have been repeatedly described in schizophrenia (Potvin et al., 2008; Miller et al., 2011), but the effect of antipsychotics on cytokine levels remains incompletely explored (Tourjman et al., 2013). Antipsychotics have anti-inflammatory effects in schizophrenia (Drzyzga et al., 2006; Tourjman et al., 2013) with significant increases in plasma levels of soluble IL-2 receptor and reductions in plasma levels of IL-1β and interferon-γ (Tourjman et al., 2013). Therefore, the effects of antipsychotics on BDNF or cytokine levels in schizophrenia deserve further examination.

Nawa et al. (2000) have suggested that the interaction between cytokines and neurotrophic factors may contribute to the etiology of schizophrenia, but this association has not been directly examined. We therefore tested this hypothesis by investigating whether: (1) serum BDNF and cytokine levels differ from healthy controls; (2) BDNF and cytokine levels are correlated in schizophrenia patients or healthy controls; (3) BDNF and cytokine levels are independently or interactively associated with the psychopathology of schizophrenia; and (4) BDNF and cytokine levels differ in patients taking typical versus atypical antipsychotic medications.

2. Methods

2.1. Subjects

Ninety-two physically healthy patients (male/female = 75/17) were recruited from the inpatients of Beijing Hui-Long-Guan Hospital, a Beijing City owned psychiatric hospital. No subjects in the present sample were included in previous reports (Zhang et al., 2002). The current study was conducted from December 2006 to May 2008. All patients met the DSM-IV diagnosis of schizophrenia, which was confirmed by two independent experienced psychiatrists based on the Structured Clinical Interview for DSM-IV (SCID). No patients with schizophrenia had comorbid psychiatric disorders. Their clinical subtypes were: 35 paranoid (38.0%); 11 disorganized (12.0%), 11 undifferentiated (12.0%), and 35 residual (38.0%). Patients were aged 35–75 years with mean illness duration of 23.2 ± 7.3 years. All patients had been receiving stable doses of oral antipsychotic drugs for at least 12 months before entering this study. Antipsychotic treatment consisted of monotherapy with either an atypical antipsychotic, including clozapine (n = 49) or risperidone (n = 12), or a typical antipsychotic (n = 31), including haloperidol (n = 11), perphenazine (n = 9), chlorpromazine (n = 6), or sulpiride (n = 5). The mean antipsychotic dose (as chlorpromazine equivalents) was 434.1 ± 369.0 mg/day.

For comparison, healthy controls were recruited from the local community. We drew a random sample from the resident registration files among those aged 35–75 years who lived in the Haidian District of Beijing, and sent each subject a letter explaining the purpose of the study. Local officials and health centers arranged for the interviews and measurements to take place at the center office at times convenient to the participants. All participants were interviewed by trained investigators. A clinical interview was used to exclude potential controls with Axis I disorders by a research psychiatrist. This psychiatrist used the standardized SCID diagnostic assessment to exclude participants with mental disorders such as common anxiety disorders and mood disorders.

All subjects provided signed, informed consent to participate in this study, which was approved by the Institutional Review Board, Beijing Hui-Long-Guan Hospital. They were Han Chinese recruited at the same time from the Beijing area. The inclusion of Han Chinese alone was an *a priori* criterion. The patients and the healthy controls had a similar socioeconomic status and dietary patterns. We obtained a complete medical history and physical examination from all subjects. We excluded pregnant or breast-feeding females and subjects with medical abnormalities, including central nervous system diseases, acute, unstable or significant medical illnesses (e.g. cancer, infection, lung disease, diabetes, hypertension, or cerebrovascular disease), and a history of severe allergies. Neither the patients nor the healthy controls had any history of alcohol or substance dependence (aside from tobacco). In addition, the use of alcohol or other recreational drugs in the week prior to the current study was an additional exclusion criterion. Finally, we also excluded any control subjects taking psychotropic medications (e.g. antidepressant, anti-anxiety, antipsychotic, or mood stabilizing drugs), hormonal agents, anti-inflammatory agents, antihypertensives, anti-hyperlipidemics, and anti-diabetics. Apart from the antipsychotic medications, these same medication exclusions were applied to the patients.

In summary, we had initially planned to recruit 220 people (110 patients vs 110 controls). After screening, 68 subjects (18 patients and 50 controls) were excluded due to documented medical abnormalities (8 patients and 6 controls), substance dependence other than tobacco (2 patients and 11 controls), taking non-psychotic medications (2 patients and 12 controls), comorbid other psychiatric disorders (3 patients and 8 controls), and refusal to participate in the study/inability to provide consent (3 patients and 13 controls).

2.2. Clinical assessment

Four psychiatrists who had simultaneously attended a training session in the use of the Positive and Negative Syndrome Scale (PANSS) rated patients on this scale. After training, repeated assessment showed that the inter-observer correlation coefficient was maintained at >0.8 for the PANSS total score.

The PANSS introduced by Kay et al. (1987) has been separated into five-factor components labeled as 'positive', 'negative', 'cognitive', 'depression', and 'excitement' (Wallwork et al., 2012; Rodriguez-Jimenez et al., 2013). The cognitive factor (sometimes called 'disorganization') refers to the patient's cognitive function, and consists of three PANSS items: 'Conceptual disorganization' (P2), 'Difficulty in abstract thinking' (N5), and 'Poor attention' (G11) (Wallwork et al., 2012). This cognitive factor was later confirmed in the clinical assessment of patients with schizophrenia (Rodriguez-Jimenez et al., 2013), suggesting that the cognitive component of the PANSS is a valid measure of cognitive deficits in schizophrenia.

2.3. Blood sampling

We obtained blood samples to assess BDNF and cytokine parameters at the time of the PANSS ratings. Venous blood from