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The interplay between BDNF and oxidative stress in chronic schizophrenia

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Summary Neurodegenerative processes may be involved in the pathogenesis of schizophrenia. Brain-derived neurotrophic factor (BDNF), the most widely distributed neurotrophin and oxidative stress (OS) may be critical for several pathological manifestations of neurodegenerative disorders. Accumulating evidence suggests that both BDNF and OS may be involved in the pathophysiology of schizophrenia. However, the possible interaction between BDNF and OS has been under-investigated. Serum BDNF, plasma malondialdehyde (MDA) levels and superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities were analyzed using established procedures in 164 chronic medicated schizophrenia and 50 healthy controls. Schizophrenic symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) with cognitive and depressive factors derived from the five factor model of the PANSS. Compared to the control group, the patients exhibited a significant decrease in BDNF levels, in the activities of SOD and GSH-Px but a significant increase in MDA levels. In patients, but not in controls, we observed a significant negative correlation between BDNF and SOD. Furthermore, the interaction between BDNF and CAT was associated with the PANSS cognitive factor, and the interaction between BDNF and GSH-Px with the PANSS depressive factor. Both decreased BDNF levels and OS may be implicated in the pathophysiology of chronic schizophrenia. Their inverse association only in the schizophrenia group may reflect a pathological mechanism involving an interaction of oxidative damage and neurotrophin dysfunction. Moreover, OS may interact with

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the BDNF system to influence the clinical symptoms and cognitive impairment in schizophrenia, which is line with the neurodevelopmental hypothesis of schizophrenia.

1. Introduction

The neurodevelopment hypothesis of schizophrenia has postulated that interaction between genetics and environmental events during critical early periods in neuronal growth may negatively influence the way by which nerve cells are laid down, differentiated, and selectively culled by apoptosis (Nagahara and Tuszynski, 2011). Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, plays an important role in supporting neuronal survival and function during development and in adulthood (He and Katusic, 2012). Accumulating preclinical and clinical data indicate that dysfunctions of BDNF may contribute to impaired brain development, neuroplasticity and synaptic connectivity leading to schizophrenia (Buckley et al., 2011; Pillai and Buckley, 2012; Nieto et al., 2013). Numerous recent studies have shown decreased serum or plasma BDNF levels in chronic antipsychotic-treated, neuroleptic free or neuroleptic naive, first-episode patients with schizophrenia (Chen et al., 2009; Xiu et al., 2009; Pillai et al., 2010; Nurjono et al., 2012), although some authors failed to replicate these findings (Green et al., 2011). Further, several studies have reported that BDNF was found to be 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) (Zhang et al., 2012a,b). Taken together, these findings provide evidence that BDNF may be involved in psychopathology of schizophrenia.

Free radicals are highly reactive chemical species generated during normal metabolic processes, and, in excess, can damage lipids, proteins, and DNA, causing cellular dysfunction and even death (Lohr and Browning, 1995). Oxidative stress (OS) involves a disequilibrium between pro-oxidant processes and the antioxidant defense system in favor of the former (Lohr et al., 2003; Yao and Keshavan, 2011). An unbalanced accumulation of oxidized proteins in the brain potentiates neurodegeneration and impairs cognitive function (Radak et al., 2007). Numerous studies have confirmed that the accumulation of oxidative damage such as oxidized proteins and lipid peroxides in aged mammalian brains underlies the molecular basis of brain aging and neurodegenerative disorders like Parkinson's disease, Alzheimer's disease and Huntington's disease (Federico et al., 2012).

Increasing evidence suggests that OS may be involved in the pathophysiology of patients with schizophrenia (Ng et al., 2008; Yao and Reddy, 2011). For example, patients with schizophrenia have abnormal activities of critical antioxidant enzymes (Zhang et al., 2003), reduced levels of antioxidants (Raffa et al., 2009; Chittiprol et al., 2010), and increased levels of lipid peroxidation in plasma, red blood cells, and cerebrospinal fluid (Padurariu et al., 2010). Furthermore, antioxidant enzymes or lipid peroxidation are correlated with psychopathology in schizophrenia, including negative symptoms, positive symptoms and with TD (Zhang et al., 2003). In addition, some symptoms of schizophrenia improve with antioxidants, such as vitamins, extract of Ginkgo biloba or essential polyunsaturated fatty acids (Zhang et al., 2001; Yao and Keshavan, 2011). These findings provide further evidence that free radicals may be involved in the pathology of schizophrenia.

Recently, some preclinical and clinical studies have shown the complex and reciprocal interactions between neurotrophins, antioxidant enzymes and OS. For example, a previous rat study showed that regular exercise training improves memory, decreases the level of reactive oxygen species, and increase the production of BDNF and nerve growth factor (Radak et al., 2007). Wu et al. reported that a diet high in saturated fat (HF) induced increased oxidative stress, and HF-induced oxidative damage was associated with reduced expression of BDNF in rats. Furthermore, treatment with antioxidant vitamin E completely counteracted the HF-elicited reduction in levels of BDNF mRNA through its antioxidant effect (Wu et al., 2004). Interestingly, a negative correlation between serum BDNF and thiobarbituric acid reactive substances (TBARS — a measure of lipid peroxidation) was found in a bipolar disorder cohort during manic episodes (Kapczinski et al., 2008). Moreover, a positive correlation between serum BDNF and TBARS was found in chronically mediated patients with schizophrenia (Gama et al., 2008). Recently, He and Katusic (2012) reported that BDNF protects circulating angiogenic cells by increasing expression of manganese superoxide dismutase (MnSOD) thereby enhancing their antioxidant capacity. These findings suggest that oxidative stress can interact with the BDNF system, suggesting the need of further investigation with regards interactions of BDNF and oxidative markers in the mental disorders.

In view of the previously mentioned studies regarding BDNF and OS in schizophrenia and the potential interaction between OS and the BDNF system, we tested the hypothesis that decreased BDNF serum levels may be related to oxidative damage in schizophrenia. Also, we speculate that interaction of BDNF and OS might be associated with schizophrenia symptoms. Therefore, the purpose of the study was to investigate (1) whether decreased BDNF serum levels and altered antioxidant enzyme activities and lipid peroxidation occurred simultaneously in patients with schizophrenia; (2) an interaction between BDNF and OS parameters, or between symptom severity and BDNF and OS parameters; (3) a significant difference between typical and atypical antipsychotic drugs in the influence on the BDNF and OS parameters.

2. Methods

2.1. Subjects

One hundred and sixty four patients (male/female = 122/42) were recruited from among the inpatients of Beijing Hui-Long-Guan Hospital, a Beijing City owned psychiatric