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Atypical antipsychotic treatment increases glial cell line-derived neurotrophic factor serum levels in drug-free schizophrenic patients along with improvement of psychotic symptoms and therapeutic effects

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ABSTRACT

Glial cell line-derived neurotrophic factor (GDNF) plays an increasingly vital role in the pathogenesis of neuropsychiatric illnesses. Antipsychotic medications were shown to stimulate GDNF secretion from C6 glioma cells. The aims of this study were to investigate the serum concentration of GDNF, to monitor the therapeutic effect of atypical antipsychotics related to GDNF levels in drug-free schizophrenia patients, and to examine these levels in relation to psychotic symptoms. We recruited 138 drug-free schizophrenic patients and compared them with 77 matched healthy subjects. All patients were treated with atypical antipsychotic monotherapy. GDNF serum levels and psychiatric symptoms were assessed at baseline and after 2, 4, 6 and 8 weeks. GDNF levels gradually increased accompanied by a reduction in psychiatric symptoms during antipsychotic therapy. The levels of GDNF in responders were significantly increased after 8 weeks of treatment, however, no significant change was found in non-responders. Furthermore, a negative association between GDNF levels following pharmacotherapy and disease duration in schizophrenic subjects could be observed. The present study suggests that GDNF may be involved in the etiology of schizophrenia and pharmacological treatment.

1. Introduction

Schizophrenia is a serious mental illness that constitutes a substantial burden on healthcare and impairs social and occupational functioning in affected individuals (van Os and Kapur, 2009). Alarmingly, the population of schizophrenic patients in China is increasing (Chan et al., 2015a, 2015b), while the psychopathology of the disease remains obscure. One hypothesis is that schizophrenia is a neurodevelopmental abnormality disorder featuring disrupted synaptogenesis and neuroplasticity (Kochunov and Hong, 2014; Stachowiak et al., 2013; Wheeler and Voineskos, 2014), which is related to a malfunction of neurotrophic factors playing an important role in the disease process (Rao et al., 2015). Abnormal neurotrophic support in adult individuals may result in altered connectivity of neural networks and may reduce the brain's adaptability to changes. Furthermore, it may lead to increased susceptibility to psychiatric disorders (Martinez-Cengotitabengoa et al., 2016; Zakharyan et al., 2014). However, antipsychotic treatment was shown to alter the expression of neurotrophic factors, which may contribute to decreasing neurotoxic damage in schizophrenia (Fernandes et al., 2015).

Glial cell line-derived neurotrophic factor (GDNF), a member of the transforming growth factor-β superfamily, is a mediator involved in neuronal development, regeneration, survival and maintenance of dopaminergic, cholinergic and serotonergic neurons in the nervous system (Barroso-Chinea et al., 2016; Kumar et al., 2015; Tsybko et al., 2014). GDNF plays a critical role in the regulation of noradrenergic function (Koelsch et al., 2010; Salvatore et al., 2009) and is involved in protecting neurons and glial cells from oxidative stress (Chao and Lee, 1999).

There is growing evidence that neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), are related to pathophysiological mechanisms of antipsychotics (Martinez-Cengotitabengoa et al., 2016; Song et al., 2015; Zakharyan et al., 2014; Zugman et al., 2015). According to a meta-analysis, schizophrenia is associated with lower expression of BDNF, and decreased production of plasma BDNF can be reversed by antipsychotic drug treatment (Fernandes et al., 2015). Previous studies illustrated that atypical antipsychotic agents may aid cortical neuroprotection and hippocampal neurogenesis (Kusumi et al., 2015). Antipsychotic medications could counteract the disturbance in neuronal transmission and plasticity in schizophrenia by normalizing BDNF. Thus, we proposed that atypical antipsychotics may produce similar effects on GDNF

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serum levels in schizophrenic individuals.

To the best of our knowledge, there are two reports that monitored concentrations of serum GDNF in schizophrenic subjects. One report showed no difference between serum GDNF levels in medicated schizophrenia patients and healthy controls (Niitsu et al., 2014), However, Tunca et al. (2015) observed a significant reduction dependent of drug treatment. Nevertheless, some studies have documented that antidepressants (Liu et al., 2012), antipsychotics (Shao et al., 2006) and mood stabilizers (Varela et al., 2015) could elevate GDNF mRNA and protein levels. However, the effect of atypical antipsychotic drugs on GDNF serum levels and the relationship between concentrations of serum GDNF and therapeutic effects in acute episodes of schizophrenia has not been determined.

The aims of this study were to measure the serum concentration of GDNF and to monitor the therapeutic effect of atypical antipsychotics on GDNF levels in drug-free schizophrenic patients. Moreover, we explored whether GDNF variations were correlated with clinical improvement.

2. Materials and methods

2.1. Subjects

In total, 138 drug-free, acute-episode, hospitalized schizophrenia patients were collected from August 2013 to January 2014 at Yangzhou Wu Tai Shan Hospital, China in this study. A total of 67 of 138 patients (48.6%) were never treated while 71 of 138 patients (51.4%) were medication free for at least 2 weeks before enrollment. The diagnoses of schizophrenic disorder were evaluated by a trained psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria. Psychotic symptoms were assessed using the positive and negative symptom scale (PANSS) and the clinical global impressions scale (CGI) at the baseline and after 2,4,6,8 weeks of treatment. All participants neither had psychiatric disorders such as bipolar disorder, substance use disorder nor any medical diseases, including heart, liver, kidney and diabetes mellitus.

Schizophrenic patients were treated with monotherapy of atypical antipsychotic drugs. The instructions in the study population were as follows: risperidone (N=17, 3–6 mg/d), Quetiapine (N=18, 0.3–0.6 g/d), Olanzapine (N=20, 10–20 mg/d), Aripiprazole (N=15, 10–20 mg/d) or Ziprasidone (n=10, 20–60 mg/d). The doses of antipsychotics were based on psychiatric symptoms. We converted antipsychotic drug doses to 100 mg/day equivalent doses of chlorpromazine. There were no significant differences among five different types of chlorpromazine equivalent dosage. Other concomitant drugs were allowed except for other antipsychotics, The agent and dosage of concomitant medications was unchanged throughout the study. Subjects would discontinue the procedure if they had experienced any symptoms or problems during the trial. Patients were subdivided into responders and non-responders according to a 50% reduction in the initial PANSS total and subscale scores after 8 weeks of treatment (Leucht et al., 2007; Suzuki et al., 2012).

A total of 77 healthy subjects were recruited as control subjects through local advertisements. The inclusion criteria for control subjects were good physical health and no personal or familial psychiatric history. Age and gender were matched between patients and control subjects. This study was approved by the Ethics Committee of Yangzhou University. Both the patient and a parent or legal guardian gave written informed consent after receiving a full explanation of the study purpose and procedures.

2.2. Laboratory data

Blood was collected in all patients at baseline and after 2, 4, 6 and 8 weeks of antipsychotic treatment. Blood collection in healthy controls was conducted at the same time. Venous blood from fasted subjects was drawn into tubes without anticoagulant between 07:30 and 08:30 h and centrifuged at 3000*g* for 15 min after sampling. Serum was then aliquoted and stored at −70 °C prior to use. GDNF partially exists in blood and tissues in the form of binding proteins, and the acid treatment procedure can disturb process of the ligand and receptor interaction to increase the detectable amount of GDNF (Okragly and Haak-Frendscho, 1997). Concentrations of GDNF were detected in sandwich enzyme-linked immunosorbent assay according to the manufacturer's instructions (Promega, Madison, WI, USA), using an acid treatment procedure - the diluted samples were acid-treated to approximately pH 2.6 and subsequently neutralize them to pH 7.6. All samples were performed in triplicate and are expressed as pg/mL. The intra-assay and inter-assay variations were less than 5%. Sample collection and analysis was performed by investigators who were blind to the participants' groups.

2.3. Statistical analysis

Data were analyzed with SPSS 16.0 (Chicago, IL, USA). Chi-squared analysis was performed on categorical data. For continuous variables, data are presented as means ± standard deviation (SD) and analyses were performed using independent sample t-tests and analysis of variance (ANOVA). Body mass index (BMI) was used as a covariate for further comparison of GDNF in patient and control groups. Changes of serum GDNF levels from baseline to endpoint for each treatment group were assessed using a repeated measures ANOVA. The relationships between GDNF levels and clinical variables were assessed using Pearson's correlation coefficients and line regression analysis. Differences of $P < 0.05$ were considered to be significant.

3. Results

3.1. Demographic data

A total of 138 schizophrenic patients were recruited in the study. During the trial, 58 patients discontinued medication prematurely because of protocol violation (n=11), withdrawal of consent (n=11), lack of effectiveness (n=4), loss of follow-up (n=27) or adverse events (n=5). The most common study-related adverse events were weight gain (n=1), dizziness (n=1), rigidity (n=1), akathisia (n=1) and nausea (n=1). A total of 80 patients and 77 matched healthy volunteers completed the whole procedure. The drop-out rate in the patient group was 42.0%, There was no difference serum GDNF level at baseline between the shedding and non-shedding patients (391.0 ± 115.9 vs. 390.2 ± 131.2 pg/mL; t=-0.039, P=0.969). However, the baseline GDNF in schizophrenia patients (n=138) different than controls (390.6 ± 124.5 vs. 572.9 ± 261.5 pg/mL; t=-5.764, P=0.000).

The study's primary findings are summarized in Table 1. There was a significant difference in BMI between patient and control groups (t=2.430, P=0.016). No other significant difference in demographic data was noted between the two groups. There were no significant correlations between serum GDNF levels and gender, age, smoking status, education or BMI in any subjects ($P > 0.05$).

3.2. GDNF levels

GDNF levels detected in the study population were as follows: M_0 (390.2 ± 131.2 pg/mL), M_1 (416.3 ± 117.3 pg/mL), M_2 (478.4 ± 137.7 pg/mL), M_3 (537.9 ± 217.6 pg/mL) and M_4 (556.5 ± 213.2 pg/mL). During the study period, an ANOVA test showed that GDNF levels gradually increased over the assessment time points (F(4,395)=14.885, $P < 0.001$), while CGI severity and PANSS total and subscale scores all improved significantly from M_0 to M_4 ($P < 0.001$; Table 2; Fig. 1A). A total of 65 of 80 patients (81.3%) were responders while 15 of 80 patients (18.8%) were non-responders by the end of the trial. It is worth noting that responders showed a significant difference in GDNF