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Decreased serum BDNF levels in chronic institutionalized schizophrenia on long-term treatment with typical and atypical antipsychotics

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ABSTRACT

Accumulating evidence showed that brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of schizophrenia. Decreased BDNF levels have been found in the serum of schizophrenic patients with mixed results. In the present study, we assessed serum BDNF levels in a large group of 364 schizophrenic patients (157 on clozapine, 89 on risperidone and 118 on typical antipsychotics), compared to 323 healthy control subjects matched for age and gender. The schizophrenia symptomatology was assessed by the Positive and Negative Syndrome Scale (PANSS), and serum BDNF levels were measured by sandwich ELISA. The results showed that BDNF levels were significantly lower in chronic patients with schizophrenia than in healthy control subjects (9.9 ± 2.0 ng/ml vs.11.9 ± 2.3 ng/ml, $p < 0.0001$). Lower BDNF levels were observed in patients treated with risperidone (9.3 ± 2.3 ng/ml) compared to those with clozapine (10.2 ± 2.0 ng/ml, $p < 0.001$) and typical antipsychotics (10.0 ± 2.1 ng/ml, $p < 0.01$). Furthermore, a stepwise multiple regression analysis identified types of antipsychotic drugs (beta $= -0.37$, $t = -3.15$, $p = 0.001$) and BDNF levels (beta $= -0.26$, $t = -2.51$, $p = 0.014$) as the influencing factor for the positive symptom subscore of PANSS. In addition, there was a sex difference in BDNF levels in patients with schizophrenia (9.7 ± 1.9 ng/ml for males vs.10.4 ± 2.1 ng/ml for female, $p < 0.005$), but not in normal controls. Our findings indicated decreased BDNF serum levels in chronic patients with schizophrenia, which may be related to clinical phenotypes, including gender, antipsychotic treatment and the severity of psychotic symptoms.

1. Introduction

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, plays an important role in the development, regeneration, survival and maintenance of function of neurons (Nawa et al., 2000; Karege et al., 2002). Recently, numerous studies have shown changes in BDNF levels in the blood of schizophrenic patients. For example, decreased serum or plasma BDNF levels have been reported in chronic antipsychotic-treated (Toyooka et al., 2002; Pirildar et al., 2004; Tan et al., 2005; Grillo et al., 2007; Ikeda et al., 2008), neuroleptic free (Palomino et al., 2006) or neuroleptic naive, first-episode schizophrenic patients (Buckley et al., 2007; Rizos et al., 2008). However, some authors failed to replicate these findings in both medicated and unmediated (Shimizu et al., 2003; Huang and Lee, 2006), or even found increased serum BDNF levels in treated schizophrenic patients (Gama et al., 2007; Reis et al., 2008) or in non-medicated schizophrenic patients with cannabis and multiple substance abuse (Jockers-Scherübl et al., 2004). Thus, the picture emerging is that BDNF levels deserve further examination in the peripheral blood of schizophrenia.

A few studies have examined the relationships between BDNF alteration and psychopathology in schizophrenia. For example, BDNF was found to be associated with positive symptoms (Buckley et al., 2007), negative symptoms (Zhang et al., 2007; Reis et al., 2008; Rizos et al., 2008), and TD (Tan et al., 2005). These findings provide evidence that BDNF may be involved in psychopathology of schizophrenia.

Some recent studies have found a differential regulation of BDNF mRNA expression in the rat hippocampus and neocortex by typical and

Abbreviations: ANOVA, analysis of variance; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BMI, body mass index; DA, dopamine; ELISA, enzyme-linked immunosorbent assay; PANSS, Positive and Negative Syndrome Scale; TD, tardive dyskinesia; 5-HT, serotonin.

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atypical antipsychotic administration (Bai et al., 2003), and atypical antipsychotics specifically olanzapine or quetiapine appear to favorably modulate BDNF expression (Pillai et al., 2006; Park et al., 2008; Rizos et al., 2008) . Our previous study showed that serum BDNF levels were higher in chronic schizophrenic patients on clozapine or typical antipsychotic than those on risperidone (Tan et al., 2005). A more recent study also showed a trend for a significantly higher BDNF levels in chronic schizophrenic patients on clozapine than those on typical antipsychotics (Grillo et al., 2007). However, some longitude studies reported that lower serum BDNF levels did not elevate after several week treatment with risperidone or antipsychotics (Pirildar et al., 2004; Yoshimura et al., 2007). In addition, alteration of serum BDNF levels has been influenced by the duration of the antipsychotic medication. It seems that alteration of serum BDNF is different in short-term period treatment than in long-term period treatment (Pillai et al., 2006; Gama et al., 2007). Thus, the effects of antipsychotic agents on the BDNF levels deserve further examination in cases of schizophrenia. The true alteration of BDNF levels induced by different typical or atypical medications is still unknown.

Earlier studies featured comparatively small sample size, which often leads to false positive results. We recruited a larger sample of patients ($n=364$) in the present study, which might provide us an enough power to elucidate the following questions: (1) whether serum BDNF levels were altered in chronic and medicated schizophrenic patients; (2) whether there was a differential effects of long-term treatment with typical and atypical antipsychotics on BDNF levels; and (3) whether there was a relationship between BDNF levels and psychopathological parameters, using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2. Methods

2.1. Subjects

Three hundred and sixty four physically healthy patients (male/female = 281/83) who met DSM-IV for schizophrenia were compared with 323 Chinese normal controls. All schizophrenic patients were recruited from among the inpatients of Beijing Hui-Long-Guan Hospital, a Beijing City owned psychiatric hospital. Diagnoses were made for each patient by two independent experienced psychiatrists. All schizophrenic patients were of the chronic type, with duration of illness for at least 5 years, age between 25 and 70 years (mean 51.3 ± 9.2 years). All patients had been receiving stable dose of oral neuroleptic medications for at least 12 months prior to entry into the study. Antipsychotic treatment consisted mainly of monotherapy with clozapine ($n=157$), risperidone ($n=89$), and other typical antipsychotics ($n=118$) including haloperidol ($n=31$), chlorpromazine ($n=21$), perphenazine ($n=26$), sulpiride ($n=27$) or others ($n=13$). The mean dose of each antipsychotic drug used in the study were 243 ± 119 mg/day for clozapine, 4.2 ± 3.4 mg/day for risperidone, 21 ± 16 mg/day for haloperidol, 373 ± 167 mg/day for chlorpromazine, 26 ± 19 mg/day for perphenazine, and 544 ± 287 mg/day for sulpiride. Mean antipsychotic dose (as chlorpromazine equivalents) was 446 ± 341 mg/day. The mean duration of each antipsychotic drug was 5.9 ± 3.8 years for clozapine, 2.8 ± 2.0 for risperidone, 5.3 ± 5.1 for haloperidol, 6.1 ± 6.3 for chlorpromazine, 4.6 ± 3.3 for perphenazine and 4.8 ± 3.8 years for sulpiride. The average duration of the current antipsychotic treatment was 5.5 ± 4.9 years at the time of the investigation.

Normal controls (male/female = 228/95) were recruited from the local community, and matched for age and gender. Current mental status and personal or family history of any mental disorder was assessed by a clinical psychiatrist. None of the healthy control subjects presented a personal or family history of psychiatric disorder. All subjects were Han Chinese being recruited at the same period from Beijing area.

A complete medical history and physical examination were obtained from all subjects. Any subjects with physical abnormalities were excluded. Neither the schizophrenic patients nor the control subjects suffered from drug or alcohol abuse/dependence. All subjects gave signed, informed consent to participate in the study, which was approved by the Institutional Review Board, Beijing HuiLongGuan hospital.

2.2. Clinical assessment

The patient's psychopathology was assessed on the day of the blood sampling by four psychiatrists who were blind to the clinical status with the PANSS. To ensure consistency and reliability of rating across the study, these four psychiatrists who had worked at least 5 years in clinical practice simultaneously attended a training session in the use of the PANSS before the start of the study. After training, a correlation coefficient greater than 0.8 was maintained for the PANSS total score by repeated assessments during the course of the study.

2.3. BDNF measurement

Ten ml of blood samples were collected into sterile empty tube without anticoagulant and allowed to clot at room temperature. Serum was separated by centrifugation at 3000 rpm for 10 min and then stored at −70 °C until use.

Serum BDNF levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (BanDing Biomedical, Chinese Academy of Sciences, Beijing, China). A full description of the assays has been given in our previous report (Tan et al., 2005). Briefly, standard 96-well plates were coated with the mouse monoclonal anti-BDNF immunoglobulin and incubated overnight. After washing, the samples and standards (concentration 0.1–256 ng/well) were incubated overnight. The plates were then washed three times with washing buffer, followed by incubation with chick anti-BDNF overnight. After three washes, a 1:1000 dilution of peroxidase labeled anti-chick antibody were added. After further washing, the reaction was developed at room temperature with tetramethylbenzidine (TMB) and stopped with phosphoric acid. Absorbencies were measured by a microtiter plate reader (absorbency at 450 nm).

All samples were assayed by a technician blind to the clinical situation. The identity of all subjects was indicated by a code number maintained by the principal investigator until all biochemical analyses were completed. Inter- and intra-assay variation coefficients were 7 and 5%, respectively.

2.4. Statistical analysis

Initial analysis included all subjects. BDNF data was analyzed with a 2×2 ANOVA representing the between-subject group factors (patients vs. healthy controls) and sex (male vs. female). Secondary analyses consisted of 4×3 analysis of covariance (ANCOVA) with the between-factors of subtype (4 levels: paranoid, disorganized, undifferentiated, or residual) and antipsychotic drugs (3 levels: clozapine, risperidone or typicals). For the main models, ANCOVAs were constructed with subtype or antipsychotic drug as the independent variables, and BDNF as dependent variables, with sex, age, education, smoking, body mass index (BMI), illness course, age of onset, dose of drug (equivalent to chlorpromazine) and duration of antipsychotic treatment as the covariates. Post hoc comparisons between subtypes or antipsychotic drugs were made using the Fisher's least significant difference (LSD) procedure. In addition, *t*-tests were used to compare the differences between male and female groups. Finally, correlation between variables was studied using Pearson product moment correlations. Bonferroni corrections were applied to each test to adjust for multiple testing. Stepwise multiple regression analysis was performed to investigate the relationships between psychotic symptoms and clinical variables and BDNF levels. Two-tailed significance values were used and significance levels were set at 0.05.