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Decreased BDNF in serum of patients with chronic schizophrenia on long-term treatment with antipsychotics

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Abstract

Accumulating evidence suggests BDNF as a molecule involved in the pathophysiology of schizophrenia. To examine the BDNF levels and the relationship between BDNF levels and psychopathology in patients with schizophrenia, 81 physically healthy patients with schizophrenia were compared with 45 age-, sex- matched normal controls. The psychopathology of patients were assessed by the Positive and Negative Syndrome Scale (PANSS). Serum BDNF levels were measured by sandwich ELISA. The results showed that BDNF-like immunoreactivity were significantly lower in medicated patients with chronic schizophrenia than in healthy control subjects. A significant negative correlation between BDNF-like immunoreactivity and PANSS negative subscore was observed. As compared with normal controls, there was a significant decrease in BDNF-like immunoreactivity in patients treated with both atypical and typical antipsychotics. However, no correlation between standardized drug doses and BDNF-like immunoreactivity was found. These findings suggest that serum BDNF levels in chronic schizophrenia under antipsychotic medication may be decreased. However, long-term effects of antipsychotics remain to be characterized.

Keywords: Schizophrenia; Brain-derived neurotrophic factor; Psychopathology; Antipsychotics; Serum; Neurotrophin

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophic factor family and is widely expressed in the adult mammalian brain, playing a critical role in the development, regeneration, survival and maintenance of function of neurons [9]. It has also been demonstrated to modulate neurotransmitter synthesis, metabolism and release, postsynaptic ion channel fluxes, neuronal activity and long-term potentiation [1]. Recent studies have revealed a strong link between BDNF signals and dopaminergic function in the brain [4,6]. There is considerable in vitro and in vivo evidence that growth and functionality of DA neurons are regulated by BDNF [7]. Specifically, BDNF is involved in the neurodevelopment of dopaminergic-related systems [7,23], interacts with the mesolimbic DA systems [1], and involved in the therapeutic response to antipsychotic drugs [2]. In addition, BDNF from dopamine neurons was shown to be responsible for inducing normal expression of the dopamine D3 receptor in nucleus accumbens both during development and in adulthood [15]. More recently, it was reported that BDNF elicits long-lasting changes in cerebral neurotransmission. This process, through with BDNF influences dopamine responsiveness, might be an important determinant in the etiopathology and/or treatment of several conditions implicating dopamine [6]. In view of the interaction of BDNF and dopaminergic neurons, as shown above, it is of great interest to assess the potential role of BDNF in the pathogenesis of schizophrenia.

Indeed, recent postmortem studies have shown that BDNF mRNA is reduced in the hippocampus and prefrontal cortex of patients with schizophrenia [25]. However, other recent

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studies reported elevated levels of BDNF protein in the anterior cingulate cortex and hippocampus of schizophrenic patients [5,21]. Recently, two studies revealed decreased BDNF levels in the serum of chronic schizophrenic patients [16,24]. However, another study reported that there were no significant differences in serum BDNF levels among antipsychotic-naive and medicated patients and normal controls [18]. Thus, the picture emerging is that BDNF deserves further examination in the peripheral blood of schizophrenia.

Recently, some studies have reported that both atypical and typical antipsychotic drugs (such as haloperidol, clozapine and risperidone) decreased BDNF concentrations in frontal and occipital cortex and hippocampus [2] or reduced the expression of BDNF mRNA in the hippocampus in rats [11]. However, some studies have found that haloperidol down-regulates BDNF mRNA expression in the rat hippocampus compared with controls, while clozapine upregulates it [3]. These studies suggest a differential effect of atypical and typical antipsychotics on BDNF. To our knowledge, however, there is still no published study that has examined the effects of atypical and typical antipsychotics on BDNF levels in schizophrenia patients. The purpose of the present study, therefore, was to determine (1) whether serum BDNF levels were altered in chronic and medicated schizophrenic patients; (2) whether there was a difference in the effects of 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) [10].

Eighty-one physically healthy Chinese patients who met DSM-III-R criteria for schizophrenia, using the Structured Clinical Interview for DSM-III-R (SCID) [20], were compared with 45 Chinese normal controls. All schizophrenic patients were of the chronic type, and were recruited from among the inpatients of Beijing Hui-Long-Guan Hospital, a Beijing City owned psychiatric hospital. All patients had been receiving stable dose of oral neuroleptic medications for at least 6 months. The medications that patients had been taking were either clozapine ($n = 38$), risperidone ($n = 19$), haloperidol ($n = 12$), chlorpromazine ($n = 5$), perphenazine ($n = 5$) or others ($n = 2$).

The patients were considered resistant to treatment according to these criteria: no response to at least two antipsychotics treated 3 months or over at full dose, equivalent to chlorpromazine 800 mg/day. The additional criteria consisted of the following: clinically stable patients with duration of illness for at least 5 years, age between 25 and 60 years, with the Clinical Global Impression (CGI) scale ratings of a score of 4 or higher. Normal controls were recruited from the community, and matched for age and gender. All subjects were Han Chinese being recruited at the same period from Beijing area. Both patients and matched normal subjects had the similar socioeconomic status and dietary patterns. Demographic data for patients and normal controls are summarized in Table 1.

A complete medical history and physical examination, laboratory tests, and electrocardiogram were obtained from patients and control subjects. All were in excellent physical health and any subjects with abnormalities were excluded. Neither the schizophrenic patients nor the control subjects suffered from substance abuse/dependence. Psychiatric disorders were ruled out among controls by psychiatric review evaluation conducted by a psychiatrist. They also had a negative history of psychiatric disorder in their first-degree relatives. All subjects gave signed, informed consent to participate in the study, which was approved by the Institutional Review Board, the Institute of Mental Health, Peking University.

Table 1
Demographics of patients and normal control subjects

	Schizophrenia ($n = 81$)	Control subjects ($n = 45$)
Sex (M/F)	63/18	34/11
Age (years)	48.1 ± 5.8	45.6 ± 4.5
Duration of illness (years)	22.6 ± 7.7 (range, 5–33)	NA
Age of onset (years)	25.2 ± 6.9	NA
The numbers of hospitalization	3.8 ± 2.7	NA
Years of hospitalization	9.4 ± 5.9	NA
Subtypes of schizophrenia		
Paranoid type	23	
Disorganized type	10	
Undifferentiated type	10	
Residual type	38	
CGI-severity	5.9 ± 1.4	NA

Ten milliliters of blood was drawn from healthy controls and patients with schizophrenia by simple venapuncture between 7.00 and 9.00 a.m. after overnight fasting at the same period of one week. After clotting, the samples were subsequently centrifuged for 15 min at 3500 rpm at room temperature. Serum was then separated, aliquoted and stored at −70 °C until analysis.

Serum BDNF levels were measured within 1 month by sandwich ELISA using a commercially available kit (BanDing Biomedical, Inc., Chinese Academy of Sciences, Beijing, China). A full description of the assays has been given in our previous report [22]. Briefly, standard 96-well plates were coated with the mouse monoclonal anti-BDNF immunoglobulin and incubated overnight at 4 °C. After three washes, coating buffer containing 1% BSA was added to each well and the plates were incubated at room temperature for 1 h. The samples and standards (concentration 0.1–256 ng/well) were applied in duplicate and triplicate, respectively, and incubated overnight at 4 °C. The plates were then washed three times, followed by incubation with chick anti-BDNF IgY overnight at 4 °C. After three washes, a 1:1000 dilution of peroxidase labeled anti-chick IgY antibody were added per well, and the plates were incubated for 6 h at 4 °C. After further washing, the reaction was developed at room temperature and then stopped. Absorbencies were measured by a microtiter plate reader (absorbency at 450 nm). The standard curve was linear from 0.1 to 256 ng/ml BDNF. As regards ELISA, the question of cross reactions with similar compounds occurring in