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Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia

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ABSTRACT

There is a growing body of evidence implicating the neurotrophin brain-derived neurotrophic factor (BDNF) in the pathogenesis of schizophrenia. As circulating BDNF levels may reflect the BDNF levels in the brain, we assessed serum BDNF in 40 institutionalized schizophrenic patients and 20 healthy controls. Serum BNDF levels were significantly increased in schizophrenic patients when compared to control subjects ($p < 0.001$). Interestingly, serum BDNF correlated positively with the clinical scores at the negative subscale of the positive and negative syndrome scale (PANSS) ($r = 0.41$; $p < 0.01$). Our results confirm the emergent literature on the involvement of BDNF in schizophrenia.

Schizophrenia is a chronic disabling psychotic mental disorder that is found in all societies and geographical areas, affecting approximately 1% of the general population [5]. Schizophrenia has a wide range of symptoms that generally begin in late adolescence or early adulthood and continue throughout life. Following Hughlings Jackon's approach to neurological symptoms, its symptoms are divided into positive and negative [2,5,17]. Positive symptoms include delusions and hallucinations, while negative symptoms comprise apathy, affective flattening, impoverishment of speech or alogia.

No single dysfunction or lesion in the brain appears to be responsible for causing schizophrenia. Rather, multiple genetic and environmental factors seem to play together to determine this complex disease [17]. A series of neuropathological and neuroimaging studies supports the hypothesis that schizophrenia may be a neurodevelopmental disorder associated with abnormal cell migration during the fetal and/or embryonic period [17,29]. Accordingly, molecules or mechanisms responsible for proper brain development may be implicated in the pathogenesis of schizophrenia [4,21].

Neurotrophins are a group of small highly basic proteins involved in cellular proliferation, migration and differentiation in the central nervous system during embryogenesis and organogenesis. In adult life, they are responsible for nerve regeneration and synaptic activity regulation, thus maintaining neural plasticity in the brain [4,21]. Brain-derived neurotrophic factor (BDNF) is the most widely distributed neutrophin in the central nervous system, including brain regions connected to schizophrenia [4,21]. Moreover BDNF was found to promote survive of a series of neuronal cells like the mesencephalum dopaminergic neurons which seem to be relevant to the pathophysiology of psychotic symptoms [11].

Indeed a large number of genetic studies has been carried out and demonstrated a possible correlation between BDNF gene polymorphisms and schizophrenia [7]. Several groups have also reported abnormal expression of BDNF and its receptor in cortical areas of schizophrenic patients [3,12,22,27,28].

As there is experimental evidence from animal model that circulating BDNF levels may reflect BDNF levels in the brain [26], some groups investigated serum and/or plasma levels of BDNF in schizophrenia. Most studies found decreased serum BDNF levels in treated and first-episode schizophrenic patients [1,8,18,23,25]. However, Gama et al. [6] found increased serum BDNF levels in treated schizophrenic patients while Jockers-Scherubl et al. [13]

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found increased levels in non-medicated patients with cannabis and multiple substance abuses. Others failed to find any difference in both medicated and unmedicated patients [10,20].

The reasons for these discrepant results are unclear but may be related to methodological issues and patient's features, including length of disease, subtype and treatment [26]. No previous study assessed chronic institutionalized patients. In this study, we investigated serum BDNF levels in institutionalized schizophrenic patients treated with typical antipsychotics. We also tried to establish correlations between serum BDNF content and psychopathology scores.

Forty institutionalized patients with schizophrenia were included in this study. All were men and their mean age (±S.D.) was 52.3 (9.8). The diagnosis of schizophrenia was performed according to DSM-IV criteria following the Mini International Neuropsychiatric Interview [19]. The clinical state of the patients was assessed using the brief psychiatric rating scale (BPRS) [16], the positive and negative syndrome scale (PANSS) [15] and the abnormal involuntary movement scale (AIMS) [9]. For comparison, 20 age-matched asymptomatic male subjects were recruited. The controls were also assessed for the presence of major psychiatric disorders or any significant clinical symptoms.

Following written informed consent, blood was collected aseptically and serum prepared and stored at −70 °C for up to 4 months until BNDF analysis. This study was approved by the local ethics committee and it was conducted according to the tenets of the Declaration of Helsinki.

The concentration of BDNF in serum of patients and controls was measured according to the procedure supplied by the manufacturer and using sandwich ELISA kits for BDNF (DuoSet, R&D Systems, Minneapolis, MN, USA). All samples were assayed on duplicate. The detection limits for these assays were 10 pg/ml. In brief, the capture antibody (concentration provided by the manufacturer) was diluted in phosphate-buffered saline (PBS), added to each well and left overnight at 4 °C. The plate was washed four times in PBS with 0.05% Tween 20 (Sigma, St. Louis, MO, USA). The plate was blocked with 1% bovine serum albumin and incubated for 2 h at room temperature before washing four times with PBS and 0.05% Tween 20. The samples and standards were added and the plate incubated overnight at 4 °C. After washing the plate, detection antibody (concentration provided by the manufacturer) diluted in PBS was added. The plate was incubated for 2 h at room temperature. After washing the plate, streptavidin (DuoSet R&D Systems, Minneapolis, MN, USA) was added and the plate incubated for 30 min. At last, color reagent *o*-phenylenediamine (Sigma, St. Louis, MO, USA) was added to each well and the reaction was allowed to develop in the dark for 15 min. The reaction was stopped with the addition of 1 M H_2SO_4 to each well. The absorbance was read on a plate reader at 492 nm wavelengths (Emax, Molecular Devices, Minneapolis, MN, USA).

Differences between two groups were evaluated using the Mann–Whitney *U*-test as data did not show normal distribution. Correlation analyses between cytokine levels and clinical parameters were also performed using Spearman's correlation coefficient. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences, SPSS 12.0 software (SPSS Inc., Chicago, IL, USA).

All patients were hospitalized over a 10-year period and were under typical antipsychotic treatment. The mean (±S.D.) duration of illness and hospitalization were, respectively, 32.4 (±9.2) and 18.9 (±6.3) years. Most patients were taking haloperidol (28; dose range: 5–25 mg/day), while remaining patients were taking chlorpromazine (3; dose range: 300–500 mg/day), levomepromazine (3; dose range: 100–300 mg/day) or trifluorperazine (6; dose range: 5–15 mg/day). The mean (±S.D.) BPRS, PANSS-positive, PANSS-negative and AIMS scores were, respectively, 42.8 (±9.2), 17.1 (±7.5), 24.1 (±4.4) and 11.3 ± (7.1).

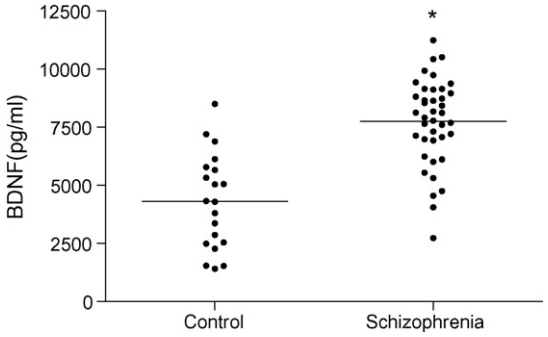

Fig. 1. Serum levels of brain-derived neurotrophic factor (BDNF) in chronic institutionalized schizophrenic patients ($n = 40$) and control subjects ($n = 20$). Bars represent median values. *$p < 0.001$, Mann–Whitney test.

Patients with schizophrenia had significantly higher serum concentration of BDNF (median [range], mean ± S.D. pg/ml; 8016 [2739–11,244], 7751 ± 1847 pg/ml) in comparison to control subjects (median [range], mean ± S.D. pg/ml; 4315 [1415–8503], 4305 ± 2046 pg/ml) ($p < 0.001$) (Fig. 1).

Correlation analyses did not show significant association between the serum levels of BDNF and the severity of symptoms as assessed by BPRS, PANSS-positive and AIMS, the duration of illness, antipsychotic treatment or hospitalization. A significant positive correlation was found between serum BDNF and scores of the PANSS-negative (Fig. 2).

To the best of our knowledge, this is the first study to assess serum BDNF levels in institutionalized schizophrenic patients who were on long-term treatment with typical antipsychotics. In this sample, serum BDNF levels were increased and correlated with the severity of negative symptoms.

Our results are in line with some studies that found increased serum levels of BDNF in schizophrenic patients [6,13], but contrast with others [1,8,18,23,25]. There may be several reasons for the inconsistency of results, including genetic background of the populations studied, effect of drug treatment, clinical heterogeneity and duration of schizophrenia. Of note, our study and the study performed by Gama et al. [6] investigated Brazilian patients with longer illness duration (respectively, 32.4 ± 9.2 and 15.5 ± 8.7 years). We hypothesize that higher levels of BDNF in schizophrenia described in both studies could be related to the genetic background of these Brazilian patients and the longer duration of the disease. However we have found no association between BDNF levels

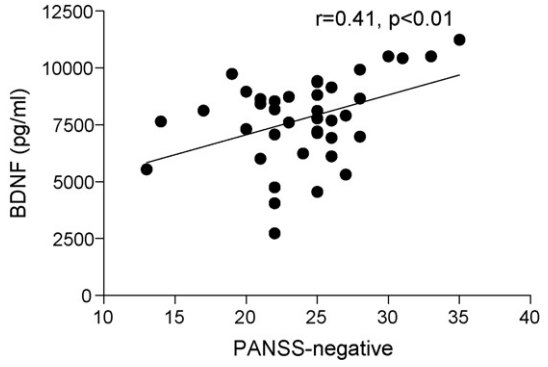

Fig. 2. Positive correlation between serum levels of brain-derived neurotrophic factor (BDNF) and negative symptoms assessed by the positive and negative syndrome scale (PANSS) in institutionalized schizophrenic patients ($n = 40$).

and duration of schizophrenia. One alternative hypothesis would involve the effect of antipsychotic treatment. Long-term antipsychotic treatment could interfere on BDNF levels. Although there is experimental evidence supporting this assumption, data on human subjects is lacking [21]. For instance, Pirildar et al. [18] found that antipsychotic treatment for weeks did not influence serum BDNF levels when compared to drug-free levels in schizophrenic patients. Moreover neuropathological studies did not observe significant difference in cerebral BDNF levels between neuroleptic-treated and neuroleptic-withdrawn patients, indicating that increase in BDNF is likely to represent a molecular pathological feature of the disease itself, rather than an effect of antipsychotics [22].

Considering that serum BDNF levels may reflect BDNF levels in brain [14], our results are also concordant with neuropathological studies that demonstrated higher BDNF levels in cortical areas, specifically in cingulate cortex, of schizophrenic patients [3,22]. Thus, in long-term schizophrenia, it is possible that high levels of BDNF represent a reaction to the cerebral damage that occurred in the early years of the disease when neurodegenerative process seem to be more intense and BDNF levels would be decreased [1,6]. This hypothesis would also explain the positive correlation between BDNF levels and negative symptoms in our study. Higher levels of BDNF in the course of schizophrenia would indicate a more severe neuronal damage in its onset. As a consequence, BDNF would be associated with markers of schizophrenia severity, such as negative symptoms.

Huang and Lee [10] did not find differences in serum BDNF levels between schizophrenic patients and controls, but rather reported higher BDNF levels in patients with residual schizophrenia, a chronic form of the disease in which negative symptoms are more prominent. Interestingly we found a significant positive correlation between BDNF and negative symptoms. This has not been previously reported. Tan et al. [24] found that plasma BDNF levels was inversely correlated with AIMS total score in patients with tardive dyskinesia. More recently Buckley et al. [1] described a negative correlation between BDNF and positive symptoms in first-episode schizophrenia patients who were not medicated. They even proposed that BDNF could be a neurobiological marker for change in psychopathology scores, indicating remission or exacerbation.

In conclusion, we found altered serum BDNF levels in institutionalized schizophrenic patients what is consistent with the emergent literature that points to the abnormality in the physiology of BDNF in schizophrenia. Further studies assessing institutionalized patients are necessary to confirm our results.

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