



Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology

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Abstract

Brain-derived neurotrophic factor (BDNF), which plays an important role in neurodevelopmental plasticity and cognitive performance, has been implicated in neuropsychopathology of schizophrenia. We examined the levels of both cerebrospinal fluid (CSF) and plasma BDNF concomitantly in drug-naive first-episode psychotic (FEP) subjects with ELISA to determine if these levels were different from control values and if any correlation exists between CSF and plasma BDNF levels. A significant reduction in BDNF protein levels was observed in both plasma and CSF of FEP subjects compared to controls. BDNF levels showed significant negative correlation with the scores of baseline PANSS positive symptom subscales. In addition, there was a significant positive correlation between plasma and CSF BDNF levels in FEP subjects. The parallel changes in BDNF levels in plasma and CSF indicate that plasma BDNF levels reflect the brain changes in BDNF levels in schizophrenia.

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Introduction

Brain-derived neurotrophic factor (BDNF) has emerged as a key contributor to brain plasticity and cognition, and it has become a focus of intense research on the psychopathophysiology of schizophrenia (Pillai, 2008). Altered BDNF expression in schizophrenia has been shown in post-mortem and in clinical studies, including recent studies of functional polymorphisms (specifically Val66Met) of the *BDNF* gene and its clinical as well as functional associations in schizophrenia (Lu & Martinowich, 2008). Most of the reports published so far on BDNF levels in

schizophrenia are from studies performed on blood (Buckley *et al.* 2007b; Grillo *et al.* 2007; Ikeda *et al.* 2008) or post-mortem brain regions (Hashimoto *et al.* 2005; Weickert *et al.* 2003). However, data on correlation between the changes in BDNF levels in blood and brain of drug-naive first-episode psychotic (FEP) patients is lacking, this could be vital to understanding its role in neuropathology and clinical treatment outcome. Cerebrospinal fluid (CSF) is probably the most promising body fluid for detection of brain-specific molecular alterations and pathological abnormalities (Schwarz & Bahn, 2008). However, there are no previous reports demonstrating the BDNF profile in CSF of schizophrenia subjects. In this study, we examined levels of both CSF and plasma BDNF concomitantly in drug-naive FEP subjects to determine if these levels are different from control values and if any correlation exists between changes in CSF and plasma BDNF levels.

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Table 1. Demographic and clinical characteristic of the study subjects

	Control males (n = 13)	Control females (n = 23)	FEP males (n = 15)	FEP females (n = 19)
Age (yr)	39.38 ± 10.02	37.21 ± 10.49	34.8 ± 9.19	29.57 ± 8.28 n.s.
DUP (months)	n.a.	n.a.	3.71 ± 2.13	4.10 ± 1.82 n.s.
PANSS-Total	n.a.	n.a.	104.13 ± 20.59	104.84 ± 18.93 n.s.
PANSS-P	n.a.	n.a.	29.86 ± 6.08	28.21 ± 4.21 n.s.
PANSS-N	n.a.	n.a.	22.46 ± 5.59	23.78 ± 7.73 n.s.
PANSS-G	n.a.	n.a.	51.8 ± 10.87	52.84 ± 9.67 n.s.

FEP, First episode of psychosis; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; PANSS – Total, PANSS total score; PANSS-P, PANSS positive symptom factor score; PANSS-N, PANSS negative symptom factor score; PANSS-G, PANSS general psychopathology cluster score; n.a., not applicable; n.s., non-significant comparison between FEP males and FEP females.

Values are mean ± s.d.

Methods and materials

Study subjects

The patients enrolled were from consecutive admissions to the outpatient treatment unit of the Department of Psychiatry, Bharati Vidyapeeth Medical College, Pune, India. Control subjects consisted of healthy volunteers from the general population and were assessed using Structured Clinical Interview for DSM-IV Disorders, Non-Patient Version (SCID-NP).

Inclusion criteria

Healthy controls and patients were male or female, aged 18–40 yr. Drug-naïve FEP subjects carried a diagnosis of schizophrenia or schizophreniform disorder at the 6-month follow-up evaluation. None of the subjects were diagnosed as schizoaffective. All diagnoses were derived from the Structured Clinical Interview for DSM-IV (SCID; APA, 1994).

Exclusion criteria

Exclusion criteria were the same for both control subjects and patients, as published in our recent reports (Kale *et al.* 2008, 2009). Thirty-four drug-naïve FEP patients (15 males, 19 females), were recruited according to the following exclusion criteria: full-scale IQ < 80, history of major atherosclerotic risk factors (e.g. hypertension, hypercholesterolaemia, or diabetes mellitus), history of atherosclerotic, neurological or psychiatric illness, chronic alcoholism, smoking, and obesity with a body mass index above 27. For the evaluation of past and current psychological conditions, the SCID was used. The 36 controls (13 males,

23 females) were subjects who had no past history of psychosis (or major mood disorder) and were not using any medication for other medical problems.

Clinical assessments

Demographic details and clinical characteristics of study subjects (healthy controls and FEP subjects) are shown in Table 1. The clinical state of the patients was evaluated independently by two of the authors at baseline and the findings were recorded on the Positive and Negative Syndrome Scale (PANSS) – positive and negative symptom scores (Kay *et al.* 1987). The assessments were carried out within 1 wk of enrolment by trained psychologists. Schizophrenia diagnosis was confirmed by repeated ratings at 6-month follow-up. Ratings were done by two clinicians (inter-rater reliability of >0.94 over the study period), one rater was part of the study and the other not associated with the study. The research protocols and consent forms were approved by the institutional review board (IRB) of Bharati Vidyapeeth Medical College, Pune, India. The Indian IRB protocol was also approved by the IRB of the Medical College of Georgia, Augusta and is in line with the Declaration of Helsinki. All subjects participating in the study signed written consent forms.

Collection of blood and CSF samples

Collection of blood, preparation of plasma and collection of CSF were done according to well established and documented procedures. Briefly, fasting venous blood was collected immediately on enrolment into tubes containing EDTA. The plasma samples were

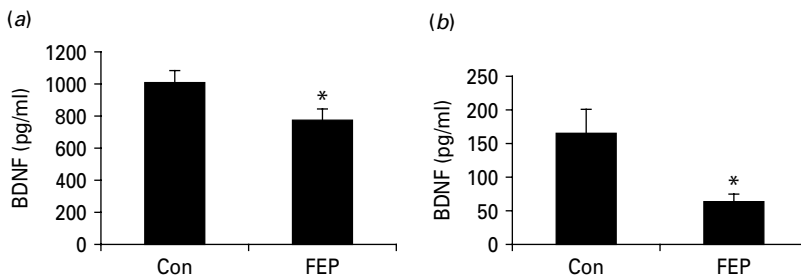


Fig. 1. Brain-derived neurotrophic factor (BDNF) protein levels in first-episode psychosis (FEP) subjects and healthy controls (Con). BDNF protein levels were measured by ELISA in (a) plasma and (b) CSF of FEP subjects and controls. Values are expressed as mean \pm S.E.M. $p=0.031$ and $p=0.003$ for plasma and CSF, respectively.

separated by centrifugation, coded, and stored at -80°C until further analysis (Kale *et al.* 2008, 2009). CSF was collected by spinal taps which were performed in the lateral decubitus position. Clear CSF (1 ml) was collected on the same day as blood collection in vials containing *para*-methylsulfonyl fluoride (PMSF, prevents protein degradation), placed in ice, then coded, and stored at -80°C until further analysis.

BDNF immunoassay

BDNF protein was measured as previously described (Buckley *et al.* 2007b) with a conventional sandwich ELISA using the BDNF E_{max} immunoassay system (Promega, USA) according to the manufacturer's instructions.

Results

We found a significant decrease in BDNF protein levels in plasma ($p=0.031$) and CSF ($p=0.003$) of drug-naive FEP subjects compared to controls (Fig. 1). To determine the association between plasma and CSF BDNF levels we performed the correlation analysis between plasma and CSF BDNF levels in FEP subjects. A significant positive correlation was found between the plasma and CSF BDNF protein levels in FEP subjects ($n=18$, $r=0.509$, $p=0.03$). Correlations were also examined between plasma and CSF contents of BDNF and psychopathology scores. A highly significant negative correlation was found for scores of the baseline PANSS positive symptom subscales with plasma ($n=23$, $r=-0.438$, $p=0.036$) and CSF ($n=24$, $r=-0.414$, $p=0.04$) BDNF levels. However, no correlations were found with other PANSS symptom scores. A stepwise multiple regression analysis showed that plasma BDNF ($\beta=-0.465$, $t=-2.52$,

$p=0.019$) and CSF BDNF ($\beta=-0.485$, $t=-2.48$, $p=0.022$) levels influence PANSS positive symptom scores. In addition, stepwise regression showed a strong correlation between plasma and CSF BDNF levels ($\beta=0.511$, $t=2.30$, $p=0.036$).

Discussion

The key findings from the present study are as follows: (1) BDNF protein levels are low in plasma and CSF of FEP subjects; (2) plasma and CSF BDNF protein levels show a significant negative correlation with scores of the baseline PANSS positive symptom subscales and (3) a strong positive correlation exists between plasma and CSF BDNF protein levels in FEP subjects. The data from the present study supports previous reports of decreased plasma levels of BDNF in schizophrenia (Buckley *et al.* 2007b; Palomino *et al.* 2006; Tan *et al.* 2005). In addition, the present study extends the findings in blood samples by measuring CSF levels of BDNF in FEP subjects and controls. The correlation of plasma BDNF levels to CSF BDNF indicates that plasma BDNF levels can be useful for understanding the parallel changes in brain BDNF. Furthermore, both plasma and CSF BDNF levels show significant correlation with the baseline PANSS positive symptom scores. Our data on the correlation between plasma BDNF levels and positive symptoms scores are in accord with a previous report by Buckley *et al.* (2007b). Changes in BDNF levels have also been reported in psychiatric diseases other than schizophrenia. Reduced serum BDNF levels have been reported in drug-free patients with major depression (Karege *et al.* 2002) and healthy subjects with depressive personality traits (Lang *et al.* 2004). Increasing evidence also indicates that suicidal behaviour is associated with lower expression of BDNF (Deveci *et al.* 2007).

The notion of aberrant neurodevelopment as a pathogenic mechanism for schizophrenia has been supported by extensive neuroimaging and neurobehavioural studies in young, first-episode drug-naïve psychotic patients (Keshavan *et al.* 2004; Wright *et al.* 2000). In addition, post-mortem studies have provided evidence for neuropathological abnormalities that appear to have a neurodevelopmental origin (Heckers, 1997; Jarskog, 2006; Selemon *et al.* 1995). These studies indicated altered neural plasticity (i.e. altered neural proliferation and migration), delayed myelination, reduced neuropil and synapse, and possibly enhanced cell vulnerability. BDNF has been found to play vital role in neural development, survival and repair in the central nervous system (Linnarsson *et al.* 2000; Zigova *et al.* 1998) and has been implicated in plasticity and neuroprotection in schizophrenia (Buckley *et al.* 2007a). Thus, the lower levels of BDNF in plasma and CSF reported in the present study in drug-naïve FEP patients may have significant implications for the neurodevelopmental abnormalities prior to emergence of early functional deficits (both cognitive performance and negative symptoms) at the onset of psychosis (Akbarian *et al.* 1993; Arnold *et al.* 1991).

The change in BDNF levels found in schizophrenia subjects could be part of the disease pathology or due to changes in brain plasticity. BDNF levels have also been shown to be altered due to many other factors (such as genetic, prenatal and environmental factors) which have possible roles in the pathophysiology of schizophrenia (Angelucci *et al.* 2005). Since the data from the above clinical studies have shown mixed results, further studies are required to establish the mechanism of change in BDNF levels in schizophrenia. However, the present study indicates a positive association in the change in BDNF levels between plasma and CSF, irrespective of the cause-effect mechanism. We found a higher BDNF concentration in plasma compared to CSF. The major potential sources of BDNF in plasma are smooth muscle cells, endothelial cells, and activated macrophages or lymphocytes. In addition, BDNF can cross the blood-brain barrier. The low BDNF levels in CSF found in the present study could be due to a higher metabolic rate in CSF compared to plasma (Laske *et al.* 2007).

In conclusion, the findings of this study indicate that subjects with first-episode psychosis have decreased BDNF levels in plasma and CSF, and these levels show a significant correlation with positive symptom scores. Therefore, developing therapeutic strategies that can activate BDNF signalling may prove beneficial for improved clinical outcome of schizophrenia.

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None.

Statement of Interest

None.

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