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Decreased BDNF in Patients with Antipsychotic Naïve First Episode Schizophrenia

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Abstract

OBJECTIVE—Brain-derived neurotrophic factor (BDNF) is a key factor known to mediate neuronal proliferation, differentiation, survival and response to stress. Decreases in BDNF levels have been reported in schizophrenia, but studies in treatment naïve patients are few. Herein we report on serum BDNF levels in a series of patients with first-episode treatment naïve psychoses in comparison to age matched healthy controls.

METHOD—Fasting serum BDNF levels were measured in 41 patients with treatment naïve first episode psychosis (24 with schizophrenia, schizoaffective disorder or schizophreniform disorder, and 17 with non-schizophrenia psychotic disorders) and 41 age-matched healthy controls.

RESULTS—A three group analyses of covariance (ANCOVA) showed a diagnosis effect ($p = .038$) in which patients with schizophrenia had lesser serum BDNF levels than patient with non-schizophrenia psychosis, who in turn had lesser BDNF levels than matched healthy controls. Planned two-group ANCOVAs suggested that patients with schizophrenia had lower serum BDNF level than matched controls ($p = .016$), whereas patients with non-schizophrenia psychosis did not differ from controls. There were no age effects on BDNF, but there was a trend ($p = .08$) for a gender by group interaction with greater reductions in female patients with schizophrenia. The BDNF levels did not correlate with magnitude of smoking, body mass index, severity of positive and negative symptoms or overall functioning.

CONCLUSIONS—Serum BDNF may be reduced at the onset of psychosis but its role in the pathogenesis of schizophrenia remains unclear. Elucidating the role of BDNF in schizophrenia and related psychotic may provide an important therapeutic target. Further studies are also needed to examine if patients with schizophrenia have more pronounced reductions in BDNF than those with affective psychosis.

Introduction

Brain-derived neurotrophic factor (BDNF) is one of several closely related polypeptides collectively referred to as neurotrophins, and is known to have a crucial role in the development, proliferation, regeneration, survival and maintenance of neuronal function of the central

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nervous system (Lewin and Barde 1996; Maisonpierre et al 1991). Apart from inducing the establishment of neuronal connections during development, BDNF continues to modulate the connections after their development (Poo 2001), and has been implicated in learning and memory (Hariri et al 2003; Mu et al 1999; Patterson et al 1996). It also interacts with other neurotransmitter systems that are implicated in schizophrenia, such as dopamine, glutamate, serotonin and GABA (Shoval and Weizman 2005). Of these, the interaction between BDNF signaling and dopaminergic pathways (Guillin et al 2001) is especially noteworthy in view of the quantum of evidence that implicates the dopaminergic pathway in schizophrenia (Egan and Weinberger 1997; Hall et al 2007). Among several types of neurons, BDNF facilitates the development of dopaminergic neurons (Thoenen 1995); this role seems especially prominent in the mesolimbic dopaminergic pathway (Altar et al 1997).

Given the level of support for glutamate in many contemporary models of schizophrenia and brain development (Keshavan 1999), interactions between BDNF and glutamatergic pathways (Carvalho et al 2008; Mattson 2008) also seem particularly relevant. Glutamate stimulates the production of BDNF (Mattson 2008), which, in turn, modulates glutamatergic synapses through pre- and postsynaptic targets (Carvalho et al 2008). At the presynaptic level, BDNF regulates glutamate release; its postsynaptic actions include changes in glutamate receptor phosphorylation and synthesis, changes in gene expression and local alterations in protein synthesis (Carvalho et al 2008).

There are a number of reasons to further explore the role of BDNF in schizophrenia. For example, cognitive deficits are increasingly seen as part of the core pathology of schizophrenia (Elvevag and Goldberg 2000). And two areas with well-documented roles in multiple domains of cognition, i.e. hippocampus and the prefrontal cortex, are noted to have reductions in BDNF mRNA expression and BDNF protein on post-mortem studies in schizophrenia (Durany et al 2001; Weickert et al 2003; Weickert et al 2005). Though BDNF is widely distributed throughout the central nervous system, hippocampus is also the site of high expression of BDNF and its TrkB receptor (Murer et al 2001). Unsurprisingly, BDNF expression in the hippocampus has become an attractive topic for schizophrenia research. In light of the evidence from animal studies that BDNF can cross the blood brain barrier (Pan et al 1998) and that the levels of BDNF in serum correlate with levels in the cortex (Karege et al 2002; Sartorius et al 2009), peripheral levels of BDNF are also attracting investigation.

So far, most, but not all studies of patients with schizophrenia have shown decreased serum levels of BDNF [for a review see (Buckley et al 2007a)]. The discrepancy in the results of the previous studies could plausibly be attributed to small sample sizes and confounds such as duration of illness, use of antipsychotic medication and life style factors associated with chronic severe mental illness. Among these confounds, antipsychotic agents are known to differentially affect BDNF levels (Angelucci et al 2005; Angelucci et al 2000; Bai et al 2003; Grillo et al 2007). These confounds can be addressed by investigating first episode treatment naïve patients with schizophrenia, but only a few studies have examined BDNF in this population. Except for a recent study from China (Chen et al 2009), sample sizes have been small (Buckley et al 2007b; Rzos et al 2008). The study from China (Chen et al 2009) detected reduced serum BDNF levels in 88 treatment naïve patients with schizophrenia, however the correlation between serum BDNF levels and the severity of positive symptoms was counter-intuitively positive. The investigators speculated if the inter-ethnic differences in the allelic frequencies of the BDNF gene polymorphisms between eastern and western population are a factor in the discrepancies between the results of available studies.

Recently, we examined serum levels of 41 patients with first episode treatment naïve psychosis with matched healthy controls. We hypothesized that patients with first episode treatment naïve schizophrenia would have lesser serum levels of BDNF than matched controls, whereas those

with non-schizophrenia psychoses will have comparable BDNF levels to those of matched controls. In view of the well-documented involvement of BDNF in developmental plasticity (Wong et al 2009) and the known effects of gender (Ozan et al 2009) and body mass index (Shugart et al 2009), we examined the effect of these parameters on BDNF.

Methods

The study participants, patients as well as healthy controls, were recruited from Western Psychiatric Institute and Clinic, Pittsburgh, PA. Forty one patients with first episode psychosis were enrolled. Among these, 24 patients (age 22.4 ± 5.47 ; 17 males) met DSM-IV diagnostic criteria for schizophrenia related psychoses (17 schizophrenia, 6 schizoaffective disorder, and 1 for schizophreniform disorder) (Table 1). The remaining 17 patients (age 20.76 ± 4.4 ; 10 males) had a diagnosis of non-schizophrenia psychoses (3: depression with psychotic features, 14: Psychosis Not Otherwise Specified). None of them previously had received any antipsychotic medication. In order to generate a relatively homogenous sample, enrollment was limited to those between the ages of 14 and 50. Forty one age and gender-matched healthy control subjects (age 22.31 ± 5.67 ; 25 males), recruited from the same neighborhoods as the patients, were also included in the study. Diagnosis was confirmed with the use of Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (First et al 1995) and consensus discussions using all clinical data including at least a six month follow up. The exclusion criteria specified that anyone with mental retardation, significant neurological or major medical disorder and current substance abuse disorder or substance dependence within the past 6 months had to be excluded. All participants signed an informed consent after receiving full explanation of the study. The study was approved by the University of Pittsburgh Institutional Review Board.

The severity of psychotic symptoms was rated by the Scale for Assessment of Positive Symptoms (Andreasen 1984), Scale for Assessment of Negative Symptoms (Andreasen 1983) and Global Assessment Scale (American Psychiatric Association 1994).

Samples were drawn for BDNF before beginning antipsychotic treatment. After an overnight fast of at least 8 hours, subjects were asked to come for blood draws. Blood samples were collected between 8am and 10am with the participants in a supine position. After collection and centrifugation, serum was stored at -70°C . Subsequently, the samples were examined in a batch.

Serum levels of BDNF were determined with an enzyme-linked immunosorbent assay (ELISA) method (BDNF Emax Immunoassay System, Promega, USA), according to the manufacturer's instructions. Briefly, 96-well flat bottom immunoplates were coated with Anti-BDNF monoclonal antibody and incubated at 4°C overnight. After blocking by non-specific binding with Block & Sample Buffer, standards and samples were added to the plates and incubated and shaken for 2 h at room temperature. Subsequently, after washing with TBST wash buffer, plates were incubated for 2 h with Anti-Human BDNF polyclonal antibody. The last incubation required the addition of Anti-immunoglobulin Y-horse-radish peroxidase conjugate. In the last step of the assay, TMB One solution was added in order to develop the color. After stopping the reaction with HCl 1 N, the absorbance was read at 450 nm on a microplate reader and BDNF concentrations were determined automatically according to the BDNF standard curve (ranging from 7.8 to 500 pg ml⁻¹ purified BDNF). The sensitivity of the assay was 4 pg/ml. All the samples were analyzed in duplicate in one session by an investigator blind to experimental set up.

Statistical Analysis

Serum BDNF levels were normally distributed in the patients with schizophrenia and in patients with non-schizophrenia psychosis. A three-group comparison was first carried out by an analysis of covariance (ANCOVA) with gender and diagnosis as grouping variables and age as a covariate. Where significant at $p < .05$, this was followed by planned two group ANCOVAs. Spearman correlation coefficients (Rho) were used for examining correlations. Data are presented as means $\pm$ standard deviations (s.d.).

Results

The groups were comparable in terms of age ($F(2, 78) = .58$; $p = .56$), gender (Mann Whitney $U = 602$; $p = .60$), race (Mann Whitney $U = 728$; $p = .70$), and BMI ($F(2, 65) = 1.44$; $p = .24$) (Table 1). BDNF levels in the patients with schizophrenia, patients with non-schizophrenia psychosis and healthy controls were 97.58 ± 31.41 ; 107.76 ± 26.06 and 116.78 ± 38.42 respectively. A three-group ANCOVA showed a significant diagnosis effect ($F(2, 75) = 3.4$, $p = .038$) in which the group of patients with schizophrenia had the lowest serum BDNF levels, followed by the group with non-schizophrenia psychosis, and then the group with matched healthy controls (Figure 1). The two-group comparisons showed that patients with schizophrenia had lower BDNF level than matched controls ($F(1.60) = 6.19$; $p = .016$), whereas patients with non-schizophrenia psychosis did not differ from controls ($F(1, 53) = .66$; $p = .42$). The difference in BDNF levels between schizophrenia and control groups remained significant even when the one outlier (one control with very high BDNF value) was excluded ($F(1, 59) = 8.1$; $p = .006$). There was a trend towards lower BDNF levels in females ($F(1, 79) = 3.52$; $p = .06$). There was also a trend for a gender by group interaction ($F(2, 74) = 2.6$; $p = .08$) with greater reductions in BDNF in female patients with schizophrenia.

BDNF levels did not correlate with age, BMI or magnitude of smoking in healthy controls (Spearman Rho ranging from 0.12 to -0.23 ; $p > .1$), in non-schizophrenia psychotic patients (Rho = -0.02 to -0.29 ; $p > .1$) and in schizophrenia patients (Rho = -0.13 to 0.31 ; $p > .1$). The severity of positive symptoms (SANS), negative symptoms (SAPS) or overall functional status (as measured by GAS) also did not correlate with BDNF in non-schizophrenia psychotic patients (Rho = 0.06 to -0.16 ; $p > .1$) and in schizophrenia patients (Rho = 0.14 to -0.31 ; $p > .1$).

Discussion

Our results suggest that patients with schizophrenia have decreased serum BDNF levels as compared to the matched controls before they received antipsychotic treatment. The results replicate the evidence for decreased BDNF levels in earlier studies of psychosis (Buckley et al 2007b; Chen et al 2009; Rizo et al 2008). However, we did not find evidence of a correlation between the severity of psychotic symptoms and BDNF levels. This may mean that decreased BDNF is not a state-related feature of acute symptomatology. Further studies are needed to examine whether these alterations are stable over time.

Our finding of an association does not necessarily imply causation; it is also possible that the reductions in BDNF may be a consequence of another pathophysiological process such as alterations in glutamatergic pathway. Nevertheless, there are reasons to think that our finding is not an epiphenomenon. BDNF is critically involved in modulating activity-dependent neuronal structure and function, and thereby in neuronal plasticity (Bramham and Messaoudi 2005). For instance, serum BDNF levels has been shown to correlate with cortical levels of n-acetyl aspartate (NAA), a marker of neuronal integrity (Lang et al 2007). Moreover, a genetic variation at a single BDNF locus, the BDNF Val66Met polymorphism is associated with reduced hippocampal NAA, episodic memory and hippocampal volume (Bueller et al 2006;

Hariri et al 2003; Stern et al 2008),. It is possible that reduced BDNF levels lead to impaired neurotrophic support during brain development causing either diminished proliferation or excessive pruning of synapses; this may lead to reduction of synapse-rich neuropil reported to underlie the pathophysiology of schizophrenia (Glantz and Lewis 2000; Selemon et al 1995). This intriguing possibility needs to be examined further by investigating the relation between BDNF levels and other indices of developmental brain pathology such as cortical gray matter loss, as well as by studies of relevant animal models such as BDNF knockout mice (Hill et al 2005). Since other neurotrophic factors such as NGF are also altered in schizophrenia (Parikh et al 2003), the relation between BDNF and other neurotrophic factors in producing the observed synaptic abnormalities in schizophrenia also needs to be investigated.

Since decreases in BDNF has also been detected in the studies of depression (Sen et al 2008), bipolar disorder (Kapczinski et al 2008), and childhood neglect (Grassi-Oliveira et al 2008), it is possible that reduced BDNF cuts across diagnostic boundaries and reflects impaired neuroplasticity in major psychiatric disorders. Recent literature suggests contemporary pharmacological treatments of psychiatric disorders may be limited by impairments in neuroplasticity, which may also underlie the failure of available antipsychotic agents to yield any more than modest improvement in cognition (Fisher et al 2009; Krystal et al 2009). Thus, a recent study (Vinogradov et al 2009) that demonstrated that BDNF could be “normalized” with neuroplasticity-based cognitive training seems very promising. It was especially heartening to see that the increase in BDNF was associated with improved quality of life.

One of the strengths of our study was the use of previously untreated first episode psychosis patients, which helps avoid confounds of medications and illness chronicity. While reduced BDNF has recently been reported in two other studies (Chen et al 2009; Rizos et al 2008), ours is the first study to utilize a non-schizophrenia psychosis sample as a control group. Another strength was the fact that we controlled for the time of the day since there is some evidence of diurnal variation in BDNF levels (Piccinni et al 2008).

A significant limitation of this line of research area is that serum BDNF levels may be derived from central as well as peripheral sources such as the platelets. The generalizability of our findings could also be limited by the heterogeneity of our study sample. Furthermore, since sleep deprivation impacts BDNF levels (Guzman-Marin et al 2006), lack of control for quality of sleep on the night before the data collection could also have affected our results.

Despite these limitations, our study is an important step in understanding the pathophysiology of schizophrenia. Further studies will be needed to document the effect of individual antipsychotic medications on BDNF. Continued work will hopefully lead to the development of interventions that address the core pathology of schizophrenia better than the available treatments.

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Figure 1. Scatterplot showing serum BDNF levels (pg/mL) in first episode schizophrenia, healthy controls and non-schizophrenia psychosis patients. Boxes represent standard deviations.

Table 1

Clinical and demographic characteristics.

	Healthy controls (n = 41)	Non- schizophrenia psychotic disorder (n = 17)	Schizophrenia (n = 24)	Statistic	Significance
Age (years)	22.31 ± 5.67	20.76 ± 4.4	22.4 ± 5.47	F = .58	P = .56
Sex (males)	25	10	17	Mann Whitney U = 602	P = .6
BMI (sq root transformed)	4.85 ± .48	4.89 ± .42	5.08 ± .5	F = 1.48	P = .23
SAPS (total score)		12.81 ± 10.3	24.29 ± 10.57	F = 11.62	P = .001
SANS (total score)		31.5 ± 7.08	41.7 ± 10.41	F = 11.72	P = .001
GAS		33.37 ± 10.42	45.31 ± 11.51	F = 11.59	P < .002