



Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Schizophrenic Patients with Depressive Symptoms: A Preliminary Study

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ÖZET:

Depresif belirtileri olan şizofreni hastalarında beyin kaynaklı nörotrofik faktör (BDNF) düzeyleri: Bir ön çalışma

Amaç: Yapılan klinik ve hayvan çalışmalarından elde edilen sonuçlar şizofreninin nörogeleimsel, nörodegeneratif ve dopamin hipotezlerini desteklemektedir bu da beyin türevli nörotrofik faktörü (BDNF) şizofreninin patofizyolojisini açıklamada aday moleküllerden biri haline getirmiştir. Bu çalışmanın amacı depresyonu olan şizofreni hastalarında BDNF düzeylerini araştırmak ve bu değerleri major depresyonlu hastalar ve kontrol grubuyla karşılaştırarak şizofrenide görülen depresif belirtilerin doğasını anlamaktır.

Yöntem: Depresif belirtileri bulunan 8 şizofreni hastasının (ŞD) BDNF düzeyleri iki farklı kontrol grubuyla karşılaştırılmıştır. Birinci grup major depresyonlu (MD) hastadan (n=24), ikinci grup ise sağlıklı kontrollerden oluşmuştur (n=26).

Bulgular: ŞD grubunun BDNF düzeyleri kontrol grubuna benzer bulunurken MD grubunun BDNF düzeyleri her iki gruptan da istatistiksel olarak anlamlı düzeyde düşük bulunmuştur.

Sonuç: Depresif belirtileri olan şizofreni grubuyla major depresyon grubunun BDNF düzeyleri arasındaki farklılık bu iki bozukluğun farklı etiyolojileri olduğu hipotezini destekler niteliktedir.

Anahtar sözcükler: Beyin türevli nörotrofik faktör, depresif belirtiler, şizofreni

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ABSTRACT:

Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenic patients with depressive symptoms: a preliminary study

Objectives: Evidence from clinical, pharmacological and animal studies, have led to neurodevelopment, neurodegeneration, and dopamine hypotheses, and to the investigation of BDNF as a potential candidate molecule in the pathophysiology of schizophrenia. The aim of this study is to investigate the BDNF levels of schizophrenic patients with depression and compare them with major depression patients and controls in order to understand the nature of depressive symptoms seen in schizophrenia.

Methods: The BDNF levels of eight schizophrenic patients with depressive symptomatology (SD) were compared with two control groups. The first group consisted of major depressed patients (MDD) (n=24) and the second was the healthy control group (n=26).

Results: SD group had BDNF levels similar to control group and MDD group had significantly lower levels than the other two groups.

Conclusion: This difference of BDNF levels between schizophrenia with depression group and major depression group supports the hypothesis of distinct etiologies.

Key words: Brain-derived neurotrophic factor, depressive symptoms, schizophrenia

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INTRODUCTION

Schizophrenia is a common severe psychiatric disorder which affects approximately 1% of the world population (1). It's a neurodevelopmental disorder, characterized by disturbances in nearly every function of the brain: cognition, perception, affect, and thought (2). While attention was previously focused on the "positive signs" of the disorder (e.g. hallucinations, delusions), the importance of investigating the "negative signs" (e.g. apathy, anhedonia, flat affect, lack of motivation) is widely acknowledged to date (2). Although not recognized formally as part of the diagnostic criteria for schizophrenia, numerous studies subcategorize the symptoms of this illness into five dimensions: positive

symptoms, negative symptoms, cognitive symptoms, aggressive/hostile symptoms, and depressive/anxious symptoms (3). Descriptive and epidemiologic studies have documented a 25% modal occurrence rate of depressive-like syndromes during the longitudinal course of schizophrenia and depressive symptoms have been reported up to 81% in the same patient group (4).

Evidence from clinical, pharmacological and animal studies, have led to neurodevelopment, neurodegeneration, and dopamine hypotheses, and to the investigation of Brain-derived neurotrophic factor (BDNF) as a potential candidate molecule in the pathophysiology of schizophrenia (1). BDNF, the most abundant neurotrophin in the brain, supports the survival and differentiation of several types of neurons, such as dopaminergic and

GABAergic neurons, and has also been implicated in the types of synaptic plasticity associated with long-term potentiation and spatial memory. Postmortem studies on brains of schizophrenia patients have revealed changes in the BDNF protein or mRNA expression levels, although these observations remain controversial.

The ability of BDNF to cross the blood–brain barrier suggests that blood serum BDNF levels may reflect BDNF levels in the brain. However, reports about BDNF levels in the serum of schizophrenic patients have been somewhat inconsistent. Thus, an increase, no change, or a reduction in the concentration of BDNF in the blood of schizophrenics has been reported. Nevertheless, these findings suggest that BDNF is likely to be related to the pathogenesis of schizophrenia. Abnormal BDNF signaling can influence neuronal differentiation and synaptic function leading to altered brain development and functioning (5,6).

On the other hand the role of BDNF in depression is much clear. There are studies determining structural changes in response to stress, especially in patients with depression. The oversecretion of glucocorticoids in the hypothalamic-pituitary-adrenal (HPA) axis causes decrease of BDNF m-RNA and neurogenesis due to stress exposure leading to the atrophy and possible apoptosis of vulnerable neurons in the hippocampus when their BDNF is cut off (7). This, in turn, leads to depression and to the consequences of repeated depressive episodes, namely, more and more episodes and less and less responsiveness to treatment. A corollary to this hypothesis is that antidepressants act to reverse this by causing the genes for neurotrophic factors to be activated (7). Some findings demonstrate an antidepressant-like property of BDNF in the animal models of depression, which may be mediated by increased activity in monoaminergic systems (8). Antidepressants increase BDNF mRNA in the brain, via 5-HT_{2A} and beta-adrenoceptor subtypes and prevent the stress-induced decreases in BDNF mRNA (9-14).

In schizophrenic patients depressive symptoms can emerge during the acute phase of disorder as a dimension of schizophrenia. In this study it is hypothesized that the depression seen in schizophrenic patients has a distinct biological nature from major depression. In order to test this hypothesis the BDNF levels of schizophrenic patients with depression are compared with the BDNF levels of major depression patients and controls.

METHODS

Subjects

Eight schizophrenic patients with depressive symptomatology and a score over 12 in the Calgary Depression Scale for Schizophrenia who were followed at the outpatient psychosis unit of Celal Bayar University Hospital, between June 2003 and October 2004 were recruited. Two control groups were established for this study. The first group consisted of major depressive disorder patients (n=24) and the healthy control group (n=26) consisted of randomly selected healthy individuals with regular health screenings. In schizophrenia with depression group (SD) all of the patients were on antipsychotic medication but not on antidepressants, and the major depressive disorder (MDD) group patients have not received any psychopharmacological treatment for at least one year. All subjects provided their written informed consent for the study

BDNF Assessment

Venous blood samples (5 ml) from the patients were collected in anticoagulant-free tubes between 11:00-12:00 A.M. They were kept at room temperature for 1 hour followed by another hour at 4°C before serum was isolated. Samples were centrifuged at 4°C (3000 rpm, for 15 min. using a refrigerated centrifuge) and the sera were transferred to a new set of polypropylene tubes. The sera were stored at -70°C for batch assessments. Serum BDNF levels were measured by a solid-phase sandwich, two-site, enzyme-linked immunoassay (ELISA), using the BDNF Emax Immunosay System reagents (Promega, Madison, WI, USA) according to the manufacturer's instructions. In this procedure flat bottom 96 well plates were coated with Anti-BDNF monoclonal antibody to bind soluble BDNF and the plates were incubated overnight at 4°C. After washing the plates with wash buffer (Tris-HCl, pH 7.6) and blocking for nonspecific binding, the plates were incubated at 25°C for 1 hour without shaking and later washed once. BDNF standards and samples, in duplicate, were added to the appropriate wells and the plates incubated for 2 hours at 25°C. The second specific BDNF polyclonal antibody was added and incubated 2 hours at 25°C so that the captured BDNF binds the polyclonal antibody. After washing the amount of specifically bound polyclonal antibody is then detected using species-

specific anti-IgY antibody conjugated to horseradish peroxidase as a tertiary reactant. Unbound conjugate is removed by washing and following incubation with a chromogenic substrate and stopping the reaction with 1N hydrochloric acid the absorbencies were measured at 450 nm using an automatic ELISA microplate reader. Intra-assay precision (coefficient of variation CV) was 8.8% at 28.6 pg/ml; 2.9% at 53.3 pg/ml.

Statistical analysis

To compare the serum BDNF levels among the three study groups, the data were subjected to Kruskal-Wallis Test for independent variables for non-parametric analysis of variance.

RESULTS

Age-Gender

The median values for ages of the patients in SD group, MDD group, and the control group were 34 (25-58), 28 (18-78), and 32.5 (23-41) respectively, and there was no statistically significant difference among the three groups ($p=0.437$). Sixtytwoandahalf percent ($n=5$) of SD group was male, 70.8% ($n=17$) of MDD group was female, and 76.9% ($n=19$) of control group was female. Although the ratio of male patients in the SD group was higher than the other two groups and this difference was not statistically significant ($p=0.172$) (Table 1).

significantly lower than the other two groups ($p= 0.009$) (Table 1).

DISCUSSION

In this study BDNF levels of schizophrenic patients with depression found to be significantly higher than those of major depression patients and they were similar to those of the control group.

Not having low BDNF levels in schizophrenic group is not surprising when inconsistent results in the literature about schizophrenic patients are considered. An increase, no change, or a reduction in the concentration of BDNF in the serum of schizophrenics have been reported (5,6). On the other hand low serum BDNF levels in patients with major depressive disorder compared to control subjects have been demonstrated in many studies (14,15). It can be speculated that having depressive symptoms don't lower the serum BDNF levels in schizophrenic patients.

Another reason for finding BDNF levels in schizophrenic patients similar to levels of healthy controls may be due to treatment with antipsychotic medication. All of the patients in the schizophrenia group were on atypical antipsychotic medication. In one study it was shown that antipsychotic drugs reduce BDNF mRNA expression in the hippocampus of healthy rats treated with clozapine and haloperidol, but do not significantly lower BDNF expression in the prefrontal cortex. In another study it was

Table 1: Demographic features and serum BDNF levels of the groups

| | Schizophrenia with depression group | Major depressive disorder control group | Healthy controls group | p |
|--------------|-------------------------------------|---|------------------------|--------|
| Age | | | | |
| median | 34 | 28.0 | 32.5 | 0.437 |
| min-max | 25-58 | 18-78 | 23-41 | |
| Gender | | | | |
| Male | 5 (62.5%) | 7 (29.2%) | 6 (23.1%) | 0.172 |
| Female | 3 (37.5%) | 17 (70.8%) | 19 (76.9%) | |
| BDNF (ng/ml) | | | | |
| median | 31.8 | 18.8 | 28.8 | 0.009* |
| min-max | 9.35-38.55 | 8.36-41.93 | 22.25-50.97 | |

*Statistically significant

Serum BDNF Levels

The median values for serum BDNF levels were 31.8 ng/ml (9.35-38.55) in the SD group, 18.8 ng/ml (8.36-41.93) in MDD group and 28.8 ng/ml (22.25-50.97) in the control group. The median value of MDD group was

found that clozapine reduces BDNF expression in rat hippocampus but does not significantly lower its expression in prefrontal cortex. Haloperidol and risperidone significantly affect brain NGF levels, suggesting that these drugs influence the turnover of endogenous growth factors.

Chronic administration of these drugs decreases BDNF concentration in rat's frontal cortex, occipital cortex, and hippocampus. Short-term administration of haloperidol decreases BDNF immunoreactivity in the rat's ventral pallidum. These observations demonstrate that medication can alter the levels of neurotrophic factors (16). Furthermore, it is shown in more than one study that antipsychotic medication does not lower BDNF expression in the prefrontal cortex. The schizophrenia patients in our study had depressive symptoms and they didn't have severe positive symptoms. Negative, cognitive, and depressive symptoms seen in schizophrenia may arise from a deficit of dopamine in mesocortical projection areas, such as dorsolateral prefrontal cortex. It can be assumed that, because the depressive symptoms in schizophrenia are related to dysfunction of prefrontal cortex and antipsychotics do not effect the BDNF expression in the prefrontal cortex, similarity of BDNF levels of schizophrenic group to those of the healthy control group is not surprising.

It should also be pointed out that many more growth factors, other than BDNF, should be taken into account for their likely involvement in the neuropathological processes. Among them are nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), neurotrophin 6 (NT-6), neurotrophin 7 (NT-7), fibroblast growth factors (FGFs), transforming growth factors (TGF- α and TGF- β), glial derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), Insulin-like growth factor (IGF-1 and IGF-2), Interleukin 1, 3 and 6 (IL-1, IL-

3, IL-6), interferone γ (IFN- γ), bone morphogenetic protein (BMP), platelet-derived growth factor (PDGF), and tumor necrosis factor- α (TNF α). Theoretically, any of the neurotrophins mentioned above may contribute to the pathophysiology of schizophrenia. Multiple mechanisms may be plausible: either decreased or increased levels of neurotrophins, imbalance between different neurotrophins, abnormalities in the control and timing of their production, secretion, and signaling pathways (Shoval & Weizman 2005). The neurotrophins suggested to be most relevant to the pathophysiology of schizophrenia other than BDNF are NGF, NT-3 and FGFs (2,17,18).

Depressive symptoms are frequently associated with schizophrenia, but this does not necessarily mean that they fulfill the diagnostic criteria for a comorbid major depressive disorder. These symptoms can emerge as a dimension of schizophrenia. Thus, the biochemical etiologies of depressive symptoms seen in schizophrenia and major depressive disorder may differ. In this present study, finding a statistically significantly difference between BDNF levels of schizophrenia with depression group and major depression disorder group supports the hypothesis of distinct etiologies. However, because the patient group is not big enough this may remain as a speculation. So further studies with greater number of subjects are needed.

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References:

1. Qian L, Zhao J, Shi Y, Zhao X, Feng G, Xu F, Zhu S, He L Brain-derived neurotrophic factor and risk of schizophrenia: An association study and meta-analysis. *Biochem Biophys Res Commun.*2007; 353:738-743.
2. Shoval G, Weizman A. The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. *Eur Neuropsychopharmacol.* 2005; 15:319-329.
3. Stahl SM. Psychosis and Schizophrenia. In *Essential Psychopharmacology* second edition (Stahl SM ed). Cambridge University Press 2000, pp 365-399.
4. Siris SG. Suicide and schizophrenia. *J Psychopharmacol* 2001; 15:127-135.
5. Watanabe Y, Muratake T, Kaneko N, Nunokawa A, Someya T. No association between the brain-derived neurotrophic factor gene and schizophrenia in a Japanese population. *Schizophr Res.* 20006; 84:29-35.
6. Palomino A, Vallejo-Illarramendi A, González-Pinto A, Aldama A, González-Gómez C, Mosquera F, González-García G, Matute C. Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients. *Schizophr Res.* 2006; 86:321-322.
7. Stahl SM. Depression and bipolar disorders. In *Essential Psychopharmacology* second edition (Stahl SM ed). Cambridge University Press 2000, pp 135-197.
8. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol Biochem Behav.* 1997; 56:131-137.
9. Altar CA. Neurotrophins and depression. *Trends Pharmacol Sci* 1999; 20:59-61.
10. Vaidya VA, Siuciak JA, Du F, Duman RS. Hippocampal mossy fiber sprouting induced by chronic electroconvulsive seizures. *Neuroscience* 1999; 89:157-166.

11. Scaccianoce S, Del Bianco P, Caricasole A, Nicoletti F, Catalani A. Relationship between learning, stress and hippocampal brain-derived neurotrophic factor. *Neuroscience* 2003; 121:825-828.
12. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry* 2003; 54:70-75.
13. Chen B, Dowlathshaki D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry* 2001, 50:260-265.
14. Aydemir O, A. Deveci, F. Taneli. The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; 29:261-265.
15. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res.*2002; 15;109:143-148.
16. Durany N, Thome J. Neurotrophic factors and the pathophysiology of schizophrenic psychoses *Eur Psychiatr* 2004; 19:326-337.
17. Gaughran F, Payne J, Sedgwick PM, Cotter D, Berry M. Hippocampal FGF-2 and FGFR1 mRNA expression in major depression, schizophrenia and bipolar disorder. *Brain Res Bull.* 2006; 70: 221-227.
18. Klejbor I, Myers JM, Hausknecht K, Corso TD, Gambino AS, Morys J, Maher PA, Hard R, Richards J, Stachowiak EK, Stachowiak MK. Fibroblast growth factor receptor signaling affects development and functioning of dopamine neurons- inhibition results in a schizophrenia-like syndrome in transgenic mice. *J Neurochem.* 2006; 97:1243-1258.