BRAIN-DERIVED NEUROTROPHIC FACTOR AND ITS SERUM LEVELS
IN SCHIZOPHRENIC PATIENTS

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ABSTRACT
INTRODUCTION: Neurotrophins have an important role in regulating the development and maintenance of the peripheral and central nervous systems' function. Thus, the neurotrophin hypothesis of schizophrenia has postulated that the changes in the brain of schizophrenic patients are the result of disturbances of developing processes involving these molecules. AIM: We analyse in the present study the changes in the serum levels of brain-derived neurotrophic factor (BDNF) in schizophrenic patients as possible epiphenomena of underlying alterations of the neurotrophic factor in central nervous system, reflecting its role in the pathophysiology of schizophrenia. PATIENTS AND METHODS: Twenty-one schizophrenic patients satisfying the DSM-IV criteria for diagnosis of schizophrenia were enrolled in the study. The control group consisted of 28 age-matched mentally healthy subjects. Serum BDNF levels were determined in patients and normal controls using ELISA (Chemicon International, USA & Canada). The data were analyzed statistically with Student’s t-test in SPSS 9.0. RESULTS: The serum BDNF levels were lower in the schizophrenic patients than in the control subjects, reaching statistically significant difference (t = 2.72, p = 0.009). Female patients had lower serum BDNF levels than the male patients but the difference fell short of statistical significance (t = 0.1, p = 0.9). CONCLUSIONS: The BDNF reduction in serum indicates a potential deficit in neurotrophic factor release in patients with schizophrenia and support the concept that BDNF might be associated with schizophrenia.

Key words: BDNF, serum, schizophrenia

СЫВОРОТЧНЫЕ УРОВНИ BDNF У ПАЦИЕНТОВ С ШИЗОФРЕНИЕЙ
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РЕЗЮМЕ
ВВЕДЕНИЕ: Нейротрофины играют важную роль в процессе развития и в поддержке функций периферической и центральной нервной систем. Согласно нейротрофической гипотезе шизофрении изменения в мозгу пациентов с шизофренией являются результатом нарушений в процессе развития, в которые включены эти молекулы. ЦЕЛЬ: В настоящем исследовании авторы анализируют изменения в сывороточных уровнях BDNF у пациентов с шизофренией как вероятный эпифеномен предшествующих нарушений этого нейротрофического фактора в ЦНС, отражающего его роль в патофизиологии заболевания. ПАЦИЕНТЫ И МЕТОДЫ: 21 пациент (покрыты DSM-IV критерии диагноза „шизофрения”) включено в настоящее исследование. Контрольная группа состоит из 28 психически здоровых индивидов. Пациенты и здоровые индивиды одного и того же возраста. Сывороточные уровни BDNF определены иммунометрически с помощью ELISA анализа. Полученные данные анализированы Student’s t-test-ом в SPSS 9.0. РЕЗУЛЬТАТЫ: Сывороточные уровни BDNF у больных шизофренией более низкие по сравнению с уровнями у здоровых индивидов, достигая статистически значимой разницы (t = 2.72, p = 0.009). Пациенты женского пола показывают более низкие уровни BDNF по сравнению с мужчинами, но разница не достигает статистической значимости (t = 0.1, p = 0.9). ЗАКЛЮЧЕНИЕ: Редукция в сывороточных уровнях BDNF предполагает возможный дефицит в продукции этого нейротрофического фактора и подкрепляет идею, что BDNF можно связать с шизофренией.

Ключевые слова: BDNF, сыворотка, шизофрения
Brain-Derived Neurotrophic Factor and its Serum Levels in Schizophrenic Patients

INTRODUCTION

The etiology and pathophysiology of schizophrenia have not been elucidated so far. It is conceivable that a variety of changes in the central nervous system can lead to clinical manifestation of the disease. There is strong evidence suggesting that nonheritable factors in the pathogenesis of schizophrenia are associated with abnormalities during prenatal development.1,2 Neurotrophins have an important role in regulating the development and maintenance of the peripheral and central nervous systems’ function.3 Thus, the neurotrophin hypothesis of schizophrenia has postulated that the changes in the brain of schizophrenic patients are the result of disturbances of developing processes involving these molecules.3,4 Neurotransmitter deficits are thereby considered as epiphenomena of underlying neurotrophin disorganization. This hypothesis is supported by studies showing that some neurotrophins like brain-derived neurotrophic factor (BDNF) are abnormally regulated in the central nervous system (CNS) of animal models of schizophrenia5-7 and by the findings that schizophrenic patients have reduced number of BDNF-positive neurons.8

It has been reported that BDNF is anterogradely transported in the CNS, a fact that considerably expands the concept of neuronal-derived trophic action and lends some support for the hypothesis that BDNF, similarly to neurotransmitters, can act at the synaptic level9 and might thus have broader functions than assumed previously. Also, numerous central neurons coexpress BDNF and its specific receptor TrkB. Thus, BDNF has the potential to function via different mechanisms such as: (1) a neurotransmitter-like axodendritic communication, (2) in autocrine loops and paracrine interactions between neighbouring cells; and (3) in trophic mechanisms, as retrograde communication from axon terminals to the cell body.10

The multitude of BDNF actions on different types of neurons supports the view that malfunctioning of this neurotrophin may be a contributing factor in the development of psychiatric disorders, while effects of antipsychotic and antidepressive treatments on BDNF will lead to long-term adaptive changes in brain function.11-13 The aim of the present study was to analyse the changes in the serum level of BDNF in schizophrenic patients as possible epiphenomena of underlying alterations of the neurotrophic factor in CNS by schizophrenia.

PATIENTS AND METHODS

The study included 21 chronic schizophrenia patients consecutively admitted to the Clinic of Psychiatry at St. Georgi University Hospital in Plovdiv. The patients satisfied DSM-IV criteria for diagnosis of schizophrenia based on case records review, a semi-structured interview based on a checklist of items from DSM-IV and information obtained from relatives in order to enhance the validity of the diagnosis. Potential subjects were excluded from the study if they had any signs of mental retardation, history of alcohol or drug abuse, neurological disorder or somatic disorder with neurological components.

The control group consisted of 28 age-matched mentally healthy volunteers. Potential control subjects were excluded from the study if they had first-degree relatives with mental disease.

The study was approved by the local Ethics Committee and all subjects gave written informed consent to participate.

BDNF ELISA

Blood (5 ml) from the patients and normal controls was sampled and serum isolated by centrifugation at 1500 x g x 10 min. Serum was kept at -20°C before testing. Serum BDNF levels were determined using ELISA (Chemicon International, USA & Canada). Briefly, BDNF of the sample was bound specifically to a polyclonal antibody and incubated with a second monoclonal antibody. Horseradish peroxidase and tetramethylbenzidine solution were added to produce a color reaction.

STATISTICAL ANALYSIS

The Student’s t-test was used to analyze data with SPSS 9.0. The level of significance was set at p < 0.05.

Figure 1. Boxplots of BDNF values in schizophrenic patients and control subjects.
RESULTS

The findings showed that BDNF levels were significantly reduced in the serum of schizophrenic patients compared with the controls (10.14 ± 3.08 vs. 12.32 ± 2.41, p = 0.009). There were gender differences: female patients had lower serum BDNF levels than the male patients (10.11 ± 3.63 and 10.33 ± 1.94, respectively) but the difference fell short of statistical significance (t = 0.1, p = 0.9). There was no effect of the duration of the disease on the serum levels of BDNF but the sample size was rather small for definitive conclusions.

Boxplot graph presents the median, 25 and 75 percentiles and values that are significantly distant from the rest. The size of the cell corresponds to the interquartile distance or span between 25 and 75 percentile. Fifty percent of cases fell within the cell. Extreme values were 3 cell, and the final 1.5 to 3 cell lengths from the top and bottom of the cage. The smallest and largest values that did not fall within the terminal are also presented (Fig. 1).

There was greater variability in the values of BDNF in the schizophrenic patients than in the controls. Individual values of BDNF in the schizophrenic group of patients ranged from 4.1 to 16.02, while in the control group the lowest value was 7.46 and the highest - 16.22. The median in the schizophrenic patients group was significantly lower than in the control group. In the schizophrenic patients a relatively well defined negative trend of the median was seen and in the controls there was a pronounced positive deviation in the values of BDNF.

DISCUSSION

The findings in the current study suggest that an alteration in the neurotrophic factor system is one of the factors which have been considered in the pathological cascade of schizophrenic psychoses. The BDNF reduction in serum indicates a potential deficit in neurotrophic factor release in patients with schizophrenia. Our results support the view that BDNF would be associated with schizophrenia.\[^{14,15}\] However, we could not conclude that treatment with antipsychotics alters serum BDNF levels in patients with schizophrenia.

The theory that alterations of the neurotrophic factor metabolism is a pathophysiological event in schizophrenia may be related to maldevelopmental phenomena which have been postulated for this group of psychotic disorders and is supported by studies describing alterations in the level of neurotrophic factors and their receptors in schizophrenia.\[^{3}\] Our findings are strongly consistent with previously reported human studies showing altered BDNF levels in schizophrenic patients, both in plasma and the CNS\[^{8,16}\] and suggest that changes in the expression of BDNF might contribute to the disease pathophysiology, one aspect of which is a disturbed capacity for functional plasticity in these individuals.

Results from studies on human post-mortem tissues from schizophrenic patients show a significant decrease in the expression levels of BDNF and its receptor TrkB in the corticolimbic system.\[^{8,17}\] Lastly, findings that BDNF is decreased by factors correlated with first episode onset such as stress and estrogens withdrawal are also consistent with the putative BDNF role in schizophrenia. Interestingly, these stress-induced decreases in BDNF are blocked by 5-HT2 receptor antagonists, a receptor binding property of many neuroleptics.\[^{18,19}\] Electroconvulsive treatment which is effective in treatment-resistant schizophrenia in combination with neuroleptics upregulates the expression of BDNF.\[^{15,20,21}\] For these reasons, in addition to providing a link between neurodevelopment and neurodegenerative phenomena, BDNF is an attractive candidate target molecule in the treatment of schizophrenia.

CONCLUSIONS

The observed reduction in BDNF serum level indicates potential deficit in neurotrophic factor release in patients with schizophrenia. The changes in the serum level of BDNF in the schizophrenic patients are discussed as possible epiphenomena of underlying alterations of the neurotrophic factor in CNS, reflecting its role in the disease pathogenesis.

REFERENCES

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