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Original Article

Serum nerve growth factor beta, brain- and glial-derived neurotrophic factor levels and psychopathology in unmedicated patients with schizophrenia

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Abstract

Background: There is accumulating evidence that neurotrophic factors may be involved in the pathophysiology of patients with schizophrenia. This study aimed to explore the relationship between serum nerve growth factor beta (NGF-beta), brain-derived neurotrophic factor (BDNF), and glial-derived neurotrophic factor (GDNF) levels and psychopathology in unmedicated patients with schizophrenia.
Methods: Serum NGF-beta, BDNF, and GDNF levels were determined using enzyme-linked-immunosorbent assay (ELISA) in the serum of 30 unmedicated patients with schizophrenia. Symptomatology was assessed with the expanded version of the 24-items brief psychiatric rating scale (BPRS-E), which was divided into four conceptual domains: manic excitement/disorganization, depression/anxiety, negative symptoms, and positive symptoms. Kolmogorov−Smirnov one sample test was performed to test non-parametric variables. Spearman's correlation was performed to examine the correlations between the cytokines of interest and psychopathology. Benjamini-Hochberg procedure was applied for multiple corrections.
Results: Serum GDNF levels correlated negatively with the BPRS-total ($r = -0.533$, corrected $p = 0.002$) and BPRS-manic ($r = -0.456$, corrected $p = 0.011$) subtests. BDNF levels showed a positive correlation with BPRS-total ($r = 0.480$, corrected $p = 0.007$). In addition, NGF-beta did not associate with psychopathology measured by BPRS scores.
Conclusion: Neurotrophic factors play a vital role in the regulation of neuroplasticity and neurogenesis in humans. This study suggests that BDNF and GDNF may be contributing to the pathological mechanisms involved in unmedicated patients with schizophrenia.

Keywords: Cytokines; Neurotrophic factors; Psychopathology; Schizophrenia

1. Introduction

Schizophrenia (SZ) is a severe psychiatric disorder and the median incidence of schizophrenia was 15.2 per 100,000 persons.[1] Due to its chronic relapsing course, SZ poses considerable burden on caregivers and society.[2] Disturbances of the dopaminergic system have been considered as one of the hypotheses for schizophrenia pathogenesis.[3] Elevated presynaptic striatal dopaminergic function is most highly correlated with positive symptoms (psychosis), while low prefrontal cortex dopaminergic function is associated with negative symptoms (blunted affect, anhedonia, and avolition).[3] Another hypothesis proposes that schizophrenia is a neurodevelopmental disorder involving disturbances in neuronal migration, connections, and neuroplasticity.[4,5]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Nerve growth factor (NGF) is a neurotrophic factor and neuropeptide essential for the regulation of differentiation, maintenance, and survival of innervating neurons.[6] Previous studies have indicated that lower serum levels of NGF such as brain-derived neurotrophic factor (BDNF),[6−11] glial cell-derived neurotrophic factor (GDNF),[8,9,12] and beta nerve growth factor (β-NGF)[13−15] were found in patients with SZ. However, other studies showed no significant differences between patients with SZ and healthy controls in GDNF,[16] BDNF[13,17,18] and NGF-beta.[18−20] Nevertheless, two recent meta-analysis studies discussed these inconsistent findings and concluded that serum levels of BDNF and NGF were moderately lower in patients with SZ than in controls.[21,22] These studies support the possible role of neurotrophic factors in the development of SZ.

Serum cytokine alteration correlates with the severity of psychopathology in schizophrenia. Some studies have reported that BDNF serum levels are positively correlated with positive symptoms, as measured with the Positive and Negative Syndrome Scale (PANSS),[4] while others have shown negative correlations.[7,23] So far, few studies have investigated the association between GDNF and psychopathology.[8,16] One study[16] reported that higher GDNF serum levels were associated with greater severity of attention deficits on the scale for the assessment of negative symptoms (SANS) in SZ but another more recent study reported contrary results.[8] The contradictory results of these studies may be further explained by characteristics of disease severity and length of untreated psychosis, and diverse usage of antipsychotic agents among studies.[8,16] Therefore, the association between GDNF and psychopathology remains unknown.

No previous study has simultaneously examined the association between serum BDNF, GDNF and NGF-beta levels and psychopathology in patients with SZ. Moreover, psychotropic drugs may alter BDNF, GDNF, and NGF-beta serum levels.[12,16] To further contribute to this issue, the aim of this study was to examine the association between serum BDNF, GDNF, and NGF-beta levels and psychopathology in unmedicated patients with SZ.

2. Methods

2.1. Participants

Thirty patients from a medical center located in Southern Taiwan admitted from August 2014 to August 2015 were enrolled in the present study. All patients met the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorder, 5th edition (DSM-5).[24] Patients were unmedicated for a minimum of three months before enrollment. We excluded those (1) with mental retardation, neurocognitive disorders, major depressive disorder, bipolar I or II disorder, and substance dependence; (2) who could not provide informed consent. This study was approved by the Ethics Committee of Kaohsiung Veterans General Hospital (VGHKS13-CT5-08).

2.2. Instruments

The Brief Psychiatric Rating Scale (BPRS) is one of the most frequently used screening tools allowing clinicians to quickly assess psychopathology in various psychiatric disorders. The original BPRS consists of 16-items and was developed in 1962,[25] it was later extended to 18 items.[26] More recently, the expanded version of 24-items BPRS (BPRS-E) was developed to increase the instrument's sensitivity to psychotic and affective disorders.[27] The BPRS-E was administered to 30 patients by a psychiatrist (CLL).[27] Four conceptual domains (manic excitement/disorganization, depression/anxiety, negative symptoms, and positive symptoms) were considered for sub-analysis in the present study.[28] The presence and severity of psychiatric symptoms were rated from 1 (not present) to 7 (extremely severe). The total scores varied from 24 to 168, with higher scores denoting more severe psychopathology.

2.3. Bioassay

Venous blood (5 mL) was collected between 7:00 and 8:00 AM to avoid circadian fluctuation of the measured cytokines. After centrifugation at 3000 rpm for 10 min, the serum was separated from the blood and was stored at −70 °C prior to assay.

Serum levels of NGF-beta (Cat. No. DY256), GDNF (Cat. No. DY212), and BDNF (Cat. No. DBD00) were measured using a sandwich enzyme-linked-immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA), according to the protocols provided by the manufacturer. Serum samples were diluted 2-, 2-, and 10-fold with PBS for detection of NGF-beta, GDNF, and BDNF, respectively. All the experiments were performed in duplicate. The intra- and inter-assay levels of variation were less than 10%. The detection limits for NGF-beta, GDNF, and BDNF were 31.3, 31.3, and 62.5 pg/mL, respectively.

2.4. Statistical analysis

Patient demographics and clinical characteristics are presented as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Kolmogorov-Smirnov one sample test (K-S test) was performed to test non-parametric variables. We used the median of the BPRS total and sub-domain scores to separate patients into high and low scoring groups, as like in previous studies.[29,30] Mann-Whitney U test was used to examine group differences between the high and low groups in NGF-beta, GDNF, and BDNF. In addition, Spearman's correlation was performed to examine the correlations among NGF-beta, GDNF, and BDNF and BPRS and sub-domain scores, as cytokines of interest (NGF-beta, GDNF, BDNF) were non-normally distributed (K-S test; all $p < 0.05$). Given that we conducted multiple correlations across items, it is vital to account for the risk of Type I errors. Therefore, we applied the Benjamini-Hochberg procedure because it has been shown to demonstrate greater power than Bonferroni correction.[31,32] All

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