Progress in Neuropsychopharmacology & Biological Psychiatry 76 (2017) 163–168

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Cognitive impairment in first-episode drug-naïve patients with schizophrenia: Relationships with serum concentrations of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor

Wenhuan Xiao[a], Fei Ye[a], Chunlai Liu[b], Xiaowei Tang[a], Jin Li[a], Hui Dong[a], Weiwei Sha[a], Xiaobin Zhang[a,*]

[a] Department of Psychiatry, Affiliated WuTaiShan Hospital of Medical College of Yangzhou University, Yangzhou 225003, PR China
[b] Department of Psychiatry, Affiliated Kangren Hospital, Ili Kazak Autonomous Prefecture of Xinjiang 835000, PR China

ARTICLE INFO

Keywords:
Schizophrenia
Cognitive functions
Brain-derived neurotrophic factor
Glial cell line-derived neurotrophic factor
Neurotrophins

ABSTRACT

Objectives: Evidence suggests that brain-derived neurotrophic factor (BDNF) and glial cell line -derived neurotrophic factor (GDNF) are important in the regulation of synaptic plasticity, which plays a key role in the cognitive processes in psychiatric disorders. Our work aimed at exploring the associations between serum BDNF and GDNF levels and cognitive functions in first-episode drug-naïve (FEDN) patients with schizophrenia.
Methods: The BDNF and GDNF levels of 58 FEDN patients and 55 age- and sex-matched healthy controls were measured and test subjects were examined using several neurocognitive tests including the verbal fluency test (VFT), the trail making test (TMT), the digit span test (DST), and the Stroop test.
Results: Patients performed significantly worse than controls in nearly all neurocognitive performances except the forward subscale part of the DST. BDNF levels were inversely correlated to TMT-part B scores and positively correlated to VFT-action in the FEDN group. GDNF levels showed a positive correlation with VFT-action scores and a negative correlation with TMT-part B scores of these patients.
Conclusion: Current data suggests that cognitive dysfunction widely exists in the early stages of schizophrenia. BDNF and GDNF may be jointly contributed to the pathological mechanisms involved in cognitive impairment in FEDN patients with schizophrenia.

1. Introduction

Cognitive impairment is pervasive in first episode and drug-naïve (FEDN) patients with schizophrenia (Wu et al., 2016, Xiang et al., 2013) and fails to substantially improve after application of currently available antipsychotic medications (Goff, 2013). Cognitive deficits including decreased processing speed, verbal memory, executive function, and reduced learning and memory in patients with schizophrenia have all been reported, leading to disability in daily life and professional as well as social dysfunction (Barch and Sheffield, 2014, Gallagher and Varga, 2015, Harvey and Strassnig, 2012, Tobe et al., 2016, Wu et al., 2016). Yet, to date, the underlying pathophysiology involved in these cognitive impairments remains an open question.

Neurotrophic factors are important in regulating synaptic plasticity, which is known to play a key role in the cognitive processes. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), the most extensively investigated neurotrophins related to psychotic disorders (Hibi et al., 2009, Nieto et al., 2014, Souza et al., 2010), belong to two different families of neurotrophins. They have been recognized to facilitate synaptic plasticity by binding to their high-affinity receptors tyrosine kinase receptor B and GDNF family receptor α (Allen et al., 2015, Goodman et al., 2014, Wang, 2013), respectively. In addition, BDNF and GDNF stimulate and control the survival, development and maintenance of both dopaminergic (Kramer and Liss, 2015) and serotonergic neurons (Tsybko et al., 2014). Furthermore, both BDNF and GDNF elicit neuroprotective properties (Zhang et al., 2014a), particularly against oxidative and neuro-inflammatory damage (Martinez-Cengotitabengoa et al., 2016, Zhao et al., 2014), which may promote the recovery of cognitive function.

Additionally, BDNF Val66Met gene polymorphism has been shown to be associated with neurocognitive deficits (Lu et al., 2012, Lv and Zhang, 2014, Ward et al., 2015, Zhang et al., 2012a), which are modulated by the presence of Met66 allele on the BDNF gene. Postmortem studies indicated that altered BDNF biosynthesis was linked to smaller brain volume in schizophrenic patients (Ahmed,

* Corresponding author.
E-mail address: zhangxiaobim@163.com (X. Zhang).

http://dx.doi.org/10.1016/j.pnpbp.2017.03.013
Received 28 November 2016; Received in revised form 25 February 2017; Accepted 19 March 2017
Available online 22 March 2017

2014, Carlino et al., 2013, Suri et al., 2013), and BDNF was found to contribute to increased cognitive performance in animal models of schizophrenia (Elsworth et al., 2014, Gururajan et al., 2015, Yang et al., 2014), as well as in human patients (Ahmed et al., 2015, Forlenza et al., 2015, Wu et al., 2015, Zhang et al., 2014b). None the less, Hori, et al. stated that BDNF could not be regarded as a cognitive biomarker for schizophrenia, even if a small coefficient of correlation existed between BDNF and cognitive function (Hori et al., 2016). Furthermore, to date, less is known about the correlation between serum concentrations of BDNF and cognitive function in first episode psychosis patients.

Recently, research has begun to focus on the role of GDNF in the pathophysiology of cognitive function (Pelleymounter et al., 1999, Voikar et al., 2004). For instance, preclinical trials have shown that cultured rat astrocytes secrete GDNF following cognitive enhancement (Koyama et al., 2004) and furthermore, GDNF has been associated with enhanced memory and learning (Bakshi et al., 2006, Shim et al., 2015). Indeed, expression and subsequent secretion of GDNF was found to improve cognitive deficits in mice (Pertusa et al., 2008, Zhang et al., 2014a), but to date it has only been one clinical report describing the relationship between serum concentrations of GDNF and cognitive impairments in chronically medicated schizophrenia subjects (Niitsu et al., 2014).

The present study was, therefore, to determine if lower serum concentrations of BDNF and GDNF in FEDN patients with schizophrenia were directly correlated with cognitive impairment. We hypothesized that individuals with schizophrenia, compared to healthy individuals, would exhibit lower levels of neurotrophins and concurrently poorer cognitive function, as well as a close relationship exists between them. To the best of our knowledge, no study has simultaneously examined the associations between serum BDNF and GDNF levels and cognitive performance in first-episode patients with schizophrenia.

2. Methods

2.1. Subjects

Fifty-eight patients from the WuTaiShan Hospital of Yangzhou University, Yangzhou, China, admitted between December 2014 and November 2015 were used for the current study. All patients met the diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (Association AP, 2013). Patients were first episode and medication naïve before enrollment, Psychotic symptoms were assessed using the positive and negative symptom scale (PANSS) and the scores of test at least 60. Patients with mental retardation, dementia, affective disorders, substance abuse/dependence, neurological disease (including epilepsy), diabetes mellitus, heart, liver and kidney diseases, as well as those who were impulsively noisy or who had an educational level below primary or secondary level were excluded. In addition, none of the patients were illiterate or suffered from audio–visual diseases. After serum concentrations of BDNF and GDNF were found, and cognitive assessment was administrated, each patient was started on a suitable course of psychotropic medication, typically no later than a week after admission.

At the same period, a total of 55 healthy subjects were recruited from the community in Yangzhou. Healthy volunteers were in good physical health, competent at the cognitive tests, and had no personal or familial psychiatric history with DSM-V Axis I psychiatric diagnosis. Age and education were matched between patients and control subjects. This study was approved by the Ethics Committee of Yangzhou WuTaiShan Hospital. Each subject gave written informed consent after receiving a full explanation of the study purpose and procedures. This study was designed as exploratory, cross-sectional and case-control trials.

2.2. Cognitive assessment

A battery of cognitive tests were administered to all subjects to measure cognitive performance as follows: verbal fluency tests (VFT-animals and VFT-actions), trail making tests (TMT-part A and TMT-part B), digit span tests (DST-Forward and DST-Backward), and Stroop tests (words, colors and interference). The selected tests were oriented towards verbal fluency, attention and processing speed, attention distribution, working memory, motor speed, and executive function. The process of cognitive measurements have previously been given in detail elsewhere (Niitsu et al., 2011, Oral et al., 2012). The administration of cognitive functions took approximately two hours and were performed by an experienced psychiatric specialist in the test laboratory. The higher the test scores, the better the cognitive function, except in regards to the TMT. Not all patients were able to complete all cognitive tests.

2.3. BDNF and GDNF assessment

Venous blood from subjects fasted overnight was drawn into tubes without anticoagulant between 07:30 and 08:30 and centrifuged at 3000*g* for 15 min after sampling and serum was separated, aliquoted, and stored at − 70 °C prior to use. Concentrations of BDNF and GDNF were measured using a sandwich enzyme-linked immunosorbent assay according to the manufacturer's instructions (Promega, Madison, WI, USA). All samples were performed in triplicate by investigators who were blind to the experimental groups. BDNF serum concentrations were expressed as ng/mL while GDNF were expressed as pg/mL. The intra-assay and inter-assay variations both neurotrophins less were than 5%.

2.4. Data analysis

Data was analyzed using SPSS 16.0 software (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess normal distribution and chi-squared analysis was performed on dichotomous variables. For normally distributed continuous variables, data are presented as means ± standard deviation (SD) and analyses were carried out using independent sample t-tests. Differences between non-homogenously distributed variables were evaluated with the Mann-Whitney *U* test. The impact of diagnosis and gender on BDNF and GDNF levels were analyzed using two-way analysis of variance (ANOVA). The relationships among BDNF and GDNF serum levels, and clinical and cognitive variables were assessed with Spearman's correlation coefficients. Stepwise regression analysis was employed to explore the potential influence of confounding variables on cognitive performance. Differences of $P < 0.05$ were considered significant.

3. Results

3.1. Demographic data and cognitive functions

Table 1 presents demographics, clinical characteristics and cognitive performance of the sample cohort. There were no significant differences between patients and healthy controls with respect to age, gender, education, BMI and smoking status ($P > 0.05$). Moreover, FEDN patients performed significantly worse than controls in nearly all neurocognitive performance tests ($P < 0.05$), except for the DST-Forward subscale ($t = -1.104$, $df = 111$, $P = 0.270$).

In addition, we examined the correlations between scores of neuropsychological tests and the PANSS total and its subscale scores in patients with acute phase of schizophrenia. Interestingly, we found the scores of PANSS negative symptom negatively correlated with actions subscale of the VFT ($r = -0.302$, $df = 58$, $P = 0.021$), and Stroop words ($r = -0.326$, $df = 58$, $P = 0.013$) in patients.