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Altered serum levels of vascular endothelial growth factor in first-episode drug-naïve and chronic medicated schizophrenia

Fei Ye, Qiongqiong Zhan, Wenhuan Xiao, Xiaowei Tang, Jin Li, Hui Dong, Weiwei Sha, Xiaobin Zhang*

Department of Psychiatry, Affiliated WuTaiShan Hospital of Yangzhou University, Yangzhou 225003, PR China

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ABSTRACT

There is much evidence of a relationship between alterations in the brain's regional cellular energy metabolism and blood flow in schizophrenic. Vascular endothelial growth factor (VEGF) plays a role in the pathogenesis of neuropsychiatric illnesses. So, we compared serum VEGF levels in drug-naïve first-episode psychotic (FEP) and chronically medicated schizophrenic to examine if a correlation existed between VEGF and psychopathological symptoms. The serum VEGF levels were assessed in 46 FEP patients, 47 chronic medicated patients and 50 healthy controls. Symptoms of schizophrenia were evaluated with the Positive and Negative Syndrome Scale (PANSS) and sandwich enzyme-linked immunosorbent assay (ELISA) was used to measure serum VEGF levels. VEGF levels were significantly lower in FEP patients compared to both chronically medicated schizophrenic patients and healthy controls, while VEGF levels in chronically medicated patients were markedly higher than in healthy controls. Furthermore, a significant correlation was detected between the levels and the PANSS negative subscale among patient groups. However, no significant correlation was observed between VEGF and clinical variables in patients. This study suggested that imbalanced neurotrophic factors may be associated with the onset of schizophrenia, but subsequent increased VEGF may be related to medication or other factors in disease progression.

1. Introduction

Schizophrenia is a serious psychiatric illness that is responsible for substantial financial burden on healthcare systems worldwide and impairs social and occupational functions in affected individuals (Owen et al., 2016). Alarmingly, the prevalence of schizophrenia in China is increasing (Chan et al., 2015a,2015b), while the psychopathology of the disease remains obscure. Although there are various hypotheses regarding the origins of schizophrenia, there is evidence that it is a neurodevelopmental abnormality disorder featuring disrupted synaptogenesis and neuroplasticity (Kochunov and Hong, 2014; Stachowiak et al., 2013; Wheeler and Voineskos, 2014). This disruption results in abnormalities associated with neurotrophic factors which then play an important role in the disease's progression (Newton et al., 2013; Rao et al., 2015). These abnormalities in adults may result in altered connectivity of neural networks connectivity resulting in a reduced adaptability when external environmental factors are altered and thus, increased susceptibility to psychiatric and disorders (Martinez-Cengotitabengoa et al., 2016; Zakharyan et al., 2014).

Vascular endothelial growth factor (VEGF) is a potent angiogenetic factor that regulates vascular endothelial cell proliferation, migration, and vasopermeability in a variety of tissues (Ferrara and Davis-Smyth, 2013). Moreover, VEGF plays important roles in neurogenesis as well as neuronal protection, regeneration, growth, and axon outgrowth (Blumberg et al., 2008). Animal studies have indicated that adult neurogenesis occurs in an angiogenic niche of the hippocampus and that VEGF expression within this niche promotes the proliferation of neuronal progenitor cells both *in vitro* and *in vivo* (Palmer et al., 2000). In addition, a large body of evidence exists indicating that VEGF promotes axonal outgrowth (Khaibullina et al., 2004). Interestingly, there has been conflicting data regarding the role of VEGF in disease progression. Several studies suggested that VEGF expression was altered in the encephalon and peripheral regions of first-episode psychosis (FEP) patients(Balotsev et al., 2016; Lee et al., 2015; Pillai et al., 2016), whereas others found no significant difference in serum VEGF levels in these patients compared to healthy controls (Di Nicola et al., 2013; Lizano et al., 2016). However, to date, no studies have compared serum VEGF levels in drug-naïve FEP patients and chronically medicated schizophrenic patients as well as healthy control subjects. Therefore, a study was initiated to determine (1) whether serum VEGF levels

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

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Table 1
Demographics of participants.

	FEP (n = 46)	Chronic patients (n = 47)	Controls (n = 50)	$F/t/\chi^2$	p-value
Age (years)	25.3 ± 6.2	37.4 ± 7.4	36.2 ± 6.4	46.673[a]	0.000
Sex (Males)	27/19	27/20	23/27	1.919[c]	0.383
Education (years)	9.5 ± 2.9	10.3 ± 3.4	11.9 ± 2.9	8.019[a]	0.001
Age of onset (years)	24.9 ± 6.2	22.1 ± 4.0		2.595[b]	0.011
PANSS positive subscale	24.2 ± 5.6	23.2 ± 5.9		0.795[b]	0.429
PANSS negative subscale	19.3 ± 5.3	22.2 ± 5.7		2.548[b]	0.012
PANSS general subscale	31.3 ± 5.6	29.5 ± 5.5		1.560[b]	0.122
PANSS total score	74.9 ± 7.0	75.0 ± 6.9		0.104[b]	0.918

FEP = first episode and drug-naïve patients with schizophrenia; BMI = body mass index; PANSS = Positive and Negative Syndrome Scale.
[a] F test.
[b] t test.
[c] χ^2 test.

differed among FEP patients at the onset of psychosis compared to chronically medicated schizophrenic patients and healthy control subjects; and (2) whether a strong correlation existed between serum VEGF levels and psychotic symptoms in schizophrenic individuals.

2. Methods

2.1. Subjects

Forty-six patients from the WuTaiShan Hospital of Yangzhou University, Yangzhou, China, admitted between December 2014 and November 2015, were enrolled in the current study. All patients met the diagnostic criterion of schizophrenia in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Patients were first-episode and drug-naïve before the enrollment. Psychotic symptoms were measured by means of the positive and negative syndrome scale (PANSS) and the corresponding scores of each patient needed to reach a threshold of 60 at least in order to be part of the study. In parallel, 47 chronically medicated patients with schizophrenia were also enrolled from the same hospital. Chronically medicated patients were diagnosed by four independent and experienced clinical psychiatrists and schizophrenia was confirmed using the Structured Clinical Interview of Axis I DSM-IV Disorders. Exclusion criteria included patients with; mental retardation, dementia, affective disorders, substance abuse/dependence, neurological disease (including epilepsy), as well those suffering with diabetes mellitus or heart, liver or kidney diseases.

Healthy controls (50) were recruited from the wider community in Yangzhou. All controls were in good physical health and had no personal or familial history of mental illness, as assessed by DSM-V Axis I psychiatric diagnosis. This study has been given sanction by the Ethics Committee of Yangzhou WuTaiShan Hospital. Each subject submitted an informed consent after being given a detailed explanation of the study.

2.2. Serum VEGF measurements

Venous blood from subjects who fasted overnight was drawn into tubes without anticoagulant between 07:30 and 08:30 h and centrifuged at 3000 × g for 15 min in order to separate the serum, which was subsequently aliquoted and stored at −70 °C until further use. Concentrations of VEGF were tested using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (DVE00; R&D Systems, Minneapolis, IN, USA). All assays were performed in triplicate by investigators who were blinded to the experimental groups. Serum VEGF concentrations were expressed as pg/ml. The intra-assay and inter-assay variations were less than 5%.

2.3. Clinical measures

Four psychiatrists who were blinded to the ELISA results assessed patient psychopathology on the day of blood sampling using the PANSS. All psychiatrists participating in the study had over five years of experience in clinical practice and had received a specialized course regarding assessment of the PANSS prior to the study. To guarantee consistency and reliability of the PANSS ratings after training, paired ratings from two psychiatrists for the same patient assessment were compared for each of the repeated appraisals during the study. Those comparisons that had a correlation coefficient > 0.8 on the PANSS total score were included.

2.4. Statistical analysis

Data were analyzed using SPSS 16.0 (Chicago, IL, USA). Chi-squared analysis was performed on categorical data. For continuous variables, data were presented by means ± standard deviation and analyses were achieved using independent sample t-tests and analysis of variance or univariate analysis of covariance. Owing to the abnormal distribution of the raw VEGF, patients group and healthy controls VEGF values were normalized through logarithmic transformation. Mean log VEGF values were compared among patients and healthy controls using an independent sample t-test. Pearson's correlations and Spearman's correlations were performed separately in controls and patients among log VEGF and age, antipsychotic dosage, treatment duration, as appropriate. The correlation between log VEGF levels and clinical variables were appraised using Pearson's correlation coefficients and line regression analysis. $p < 0.05$ was considered significant.

3. Results

3.1. Demographic data

The primary findings are summarized in Table 1. There were significant differences among the three groups with regard to age (F = 46.673, df = 2, 140, $p < 0.001$) and education (F = 8.019, df = 2, 140, p = 0.001). Further, important differences were noted between two experimental cohorts in age of schizophrenic onset (t = 2.595, df = 93, p = 0.011) and PANSS negative subscale (t = 2.548, df = 93, p = 0.012). The correlation between serum VEGF levels and age was significant across all groups (r = 0.192, df = 143, p = 0.022). Neither sex nor education was associated with VEGF levels among the three groups.

3.2. Serum VEGF levels

Log VEGF levels were significantly different among FEP patients (2.5 ± 0.2 pg/ml), chronically medicated patients (2.7 ± 0.2 pg/ml)