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Decreased serum fibroblast growth factor - 2 levels in pre- and post-treatment patients with major depressive disorder

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HIGHLIGHTS

- Serum FGF-2 levels were determined in patients with MDD and healthy controls, using ELISA.
- Serum FGF-2 levels in patients with MDD were significantly lower compared with those in healthy controls.
- Serum FGF-2 levels decreased significantly but marginally in patients after 8-week antidepressant treatment.

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ABSTRACT

Increasing evidence indicates that neurotrophic factor dysfunction might be involved in the pathophysiology and treatment of major depressive disorder (MDD). Fibroblast growth factor (FGF)-2, one of the major neurotrophins, plays an important role in the central nervous system (CNS). The aim of this study was to explore whether the FGF-2 in serum was associated with MDD and to evaluate the effects of antidepressant treatment on serum FGF-2 levels. Serum FGF-2 levels were determined in 28 pre- and post-treatment MDD patients and 30 healthy controls using ELISA. The results of the current study revealed that serum FGF-2 levels in MDD patients were significantly lower than those in healthy controls ($p = 0.005$), and the serum FGF-2 levels decreased significantly but marginally following treatment for 8 weeks ($p = 0.005$). These findings demonstrate that the lower serum FGF-2 levels contribute to the pathophysiology of MDD and that FGF-2 may be used as a peripheral biological marker for MDD.

1. Introduction

Major depressive disorder (MDD) is a debilitating mental illness with enormous personal and social burdens, affecting approximately 350 million people worldwide [15]. Though the etiology and pathophysiology of MDD remain unclear, in recent years, the neurotrophic hypothesis of depression has attracted the attention of researchers. According to this hypothesis, it is suggested that depression results at least in part from the depletion of neurotrophic factor support and/or the decreased neurogenesis, which may eventually lead to structural and functional abnormalities of neural networks in the brain [4]. Thus, the pathogenesis of depression and the mechanisms underlying antidepressant effects may relate to the regulation of multiple neurotrophic factors.

Fibroblast growth factor (FGF)-2, one of the major neurotrophins, is widely expressed throughout the central nervous system (CNS). This neurotrophin plays a key role in early brain development, neuroprotection, adult neurogenesis and neuroplasticity [18]. Taken together, this neurotrophic hypothesis of depression leads to the assumption that low concentrations of FGF-2 may be associated with MDD.

In recent years, it has been demonstrated that the FGF-2 may be involved in both the pathophysiology and treatment of MDD [7,22]. Reduced FGF-2 expression levels in frontal cortical areas

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and the hippocampus have been demonstrated in animal models of depression and postmortem studies in MDD [7,9,19]. Moreover, electroconvulsive therapy and different classes of antidepressants have been found to increase FGF-2 expression levels [1,3,13,14]. In addition, FGF-2 infusion into the brain of rats and mice has been demonstrated to produce antidepressant-like effects in animal models of depression [6,11,20].

However, up to now, few clinical studies have reported on the peripheral FGF-2 levels in MDD patients. Moreover, the findings thus far have been controversial. Recently, in contrast to the hypothesis above, an increase in serum FGF-2 levels was reported in depressed patients with borderline personality disorder (BPD) [12]. However, another study found there was no difference in the plasma FGF-2 levels between MDD patients and healthy controls [21]. In addition, although antidepressants increase BDNF levels in rat and human brains, there are no existing available data yet pertaining to the effect of antidepressants on serum FGF-2 levels in MDD patients.

In this context, we combined a cross-sectional and longitudinal, uncontrolled observational design to explore whether serum FGF-2 levels in MDD patients prior to drug treatment are lower than those in healthy controls and whether drug treatment can change the serum concentration of FGF-2 in MDD patients.

2. Materials and methods

2.1. Participants

Twenty-eight in- and out-patients with MDD were recruited for this study from the Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine. All diagnoses were made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). The inclusion criteria were as follows: (1) age 18–65 years, (2) Han ethnicity, (3) either medication-naive or medication-free for at least 6 weeks before the recruitment, and (4) HDRS-24 $\geq$ 20.

Patients with any other psychiatric axis-I or axis-II disorders other than MDD, any physical diseases (i.e., organic brain diseases, hypertension, diabetes mellitus, tumor, and thyroid disease), or history of familial psychiatric disorders were excluded from this study. In addition, pregnant or lactating patients were excluded.

Thirty age- and sex-matched healthy volunteers of Han ethnicity were recruited as controls. Healthy controls with a history of personal or familial psychiatric disorders, with any physical diseases, or who were pregnant or lactating were excluded from the study. All participants received a complete physical evaluation and a formal psychiatric evaluation by two senior psychiatrists independently. In addition, the medical records of all participants were reviewed. The Institutional Review Board of Shanghai Mental Health Center approved the research protocol, and all participants provided written informed consent.

2.2. Naturalistic follow-up and clinical assessment

The recruited MDD patients received individually tailored pharmacotherapy according to the currently accepted therapeutic guidelines. The severity of the depressive symptoms in patients was evaluated using the 24-item Hamilton Depression Rating Scale (HDRS-24) at baseline (w0) and after 8 weeks of treatment (w8). The reduction rate of the total HDRS score was calculated to evaluate the efficacy of antidepressant treatment, and responders were defined as those with a reduction rate of total HDRS score $\geq$ 50%.

2.3. Blood sample collection and serum FGF-2 measurement

Following an overnight fast, 5 ml of venous blood from both patients and healthy controls was collected between 7 and 9 a.m. in anticoagulant-free tubes at w0. After collection, the blood samples were kept at room temperature for 1 h before separation of the serum by centrifugation at 3000 rpm for 20 min at 4 °C. Serum samples were aliquoted and stored at −80 °C until further analysis. The FGF-2 levels were measured using a human bFGF ELISA kit (Anogen, Mississauga, Ontario, Canada) according to manufacturer's instructions. The intra-assay coefficients of variation were less than 7%. All samples were performed by an operator who was blind to the clinical status of the participants. The same blood collection and laboratory procedures were performed again at w8 for all patients. The concentration of FGF-2 was expressed as pg/ml.

2.4. Statistical analysis

Data were analyzed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA), and figures were prepared using GraphPad Prism 6.0 (GraphPad Prism Software Inc., San Diego, CA, USA). Categorical variables were assessed using Chi-square tests, such as for gender. The age of patients and controls was compared using an independent-samples *t*-test. Serum FGF-2 levels all followed the asymmetrical distribution in controls (w0) and patients (both w0 and w8) based on the Shapiro–Wilk test; however, for patients, the differences between FGF-2 levels at w0 and w8 were normally distributed. Therefore, the difference between serum FGF-2 levels in patients before treatment and controls was evaluated using the Mann–Whitney *U*-test. In addition, the paired *t*-test was used for analyzing serum FGF-2 levels in the pre- and post-treatment MDD groups. In addition, the Wilcoxon test for paired samples was used for analyzing HDRS scores in the pre- and post-treatment MDD groups. The relationship between serum FGF-2 and clinical variables was assessed using Spearman's correlation coefficient. All results are presented as the mean ± standard deviation (SD). Statistical significance was defined as $p < 0.05$ (two-tailed).

3. Results

3.1. Naturalistic follow-up

The demographic and clinical data of the participants are listed in Table 1. After 8 weeks, all of the 28 patients completed the follow-up evaluation and sample collection. The following antidepressants were administered including venlafaxine ($N = 10$), paroxetine ($N = 4$), fluoxetine ($N = 3$), escitalopram ($N = 6$), dulox-

Table 1
Demographics and clinical characteristics of participants.

	MDD ($n = 28$)	HC ($n = 30$)	χ^2 or F	p value
Sex (M/F)	10/18	13/17	0.351	0.553[a]
Age (years)	46.25 ± 12.44	42.80 ± 9.24	3.252	0.234[b]
Age of onset (years)	39.82 ± 12.27			
Length of disease (years)	6.18 ± 7.86			
Patients				
With first episode	10			
With recurrent episode	18			
Patients				
With psychotic symptoms	3			
Without psychotic symptoms	25			
Patients				
With familial history	2			
Without familial history	26			

MDD, major depressive disorder; HC, healthy controls.
[a] Chi-square test.
[b] Independent samples *t*-test.