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Effect of treatment on serum glial cell line-derived neurotrophic factor in depressed patients

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Abstract

Post-mortem studies have demonstrated a decreased number of glia, reduced glial density, and a decreased glia/neuron ratio in different brain areas of patients diagnosed with a major depressive disorder (MDD). Researchers have therefore suggested that neurotrophic growth factor systems might be involved in the aetiology of MDD. This study aimed to test whether glial cell line-derived neurotrophic factor (GDNF), a member of the transforming growth factor β family, in serum was associated with MDD. Serum concentrations were measured in MDD patients before treatment ($n=76$), after 8 weeks of antidepressant treatment ($n=39$), and in control subjects ($n=50$) using a sandwich ELISA method. Serum GDNF was significantly lower in MDD patients before treatment than in control subjects ($P<0.001$). From baseline to remission after 8 weeks of treatment, the increase in serum GDNF was statistically significant ($P<0.001$). The present study suggests that lower serum GDNF might be involved in the pathophysiology of MDD and antidepressant treatment increases the GDNF in MDD.

Keywords: Antidepressants; GDNF; MDD

1. Introduction

Major depressive disorder (MDD) is a common major psychiatric disorder of uncertain aetiology. Post-mortem studies have demonstrated a decreased number of glia in the frontal cortex, and reduced glial density and a decreased glia/neuron ratio in the amygdala in MDD patients (Hamidi et al., 2004; Cotter et al., 2002). Moreover, previous studies have shown that brain-derived neurotrophic factor (BDNF), neurotrophin-3, and fibroblast growth factor (FGF) systems are altered in different tissue samples, including post-mortem brain tissue, cerebrospinal fluid, and blood from patients with mood disorders (Shimizu et al., 2003; Hock et al., 2000; Evans et al., 2004). Neurotrophic factors are potent regulators of neuronal plasticity, survival, and development, and their reduced availability can result in increased cellular vulnerability or even cell death (Huang and Reichardt, 2001). It has been postulated that the enhanced and prolonged secretion of neurotrophic factors in response to antidepressant treatment could promote neuronal survival and protect neurons from the damaging effects of stress. A recent study showed that glial cell line-derived neurotrophic factor (GDNF) is decreased in the whole blood of bipolar and unipolar subjects during "partial or full remission state" (Takebayashi et al., 2006). Further, preclinical studies found that the mood stabilizers, lithium and valproate, increase GDNF levels *in vivo* and *in vitro* (Castro et al., 2005; Angelucci et al., 2003).

Abbreviations: ELISA, enzyme linked immunosorbent assay; GDNF, glial cell line-derived neurotrophic factor; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; SPSS, Statistical Package for Social Sciences; SD, Standard deviation.

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GDNF is a neurotrophic factor belonging to the transforming growth factor β family, and was initially discovered as one of the most potent survival factors for dopaminergic neurons (Airaksinen and Saarma, 2002). Subsequent studies have shown that GDNF is widely expressed throughout the brain (Pochon et al., 1997), and has pronounced effects on other central and peripheral neuronal populations (Airaksinen and Saarma, 2002). For instance, GDNF plays important roles in higher-order brain function and dysfunction, such as cognitive abilities and drug addiction (Messer et al., 2000; Gerlai et al., 2001), and GDNF+/− mutant mice show abnormal hippocampal synaptic transmission (Nanobashvili et al., 2000). A recent report demonstrated that serum GDNF immunoreactivity is increased in bipolar patients during acute manic and depressive episodes (Rosa et al., 2006). Here, we examined whether the serum GDNF in patients with MDD is altered from healthy control subjects prior to antidepressant drug treatment and whether antidepressant drug treatment can change the serum concentration of GDNF in MDD patients.

2. Methods

2.1. Sample

From the cohort of psychiatric inpatients admitted to the Department of Psychiatry of Yangzhou Wu Tai Shan Hospital in China between January 2006 and March 2007, 76 Chinese Han depressive patients between 20 and 65 years of age were recruited. The subjects were diagnosed with MDD according to DSM-IV criteria (American Psychiatric Association, 1994) using a Structured Clinical Interview for DSM-IV (First et al., 1998); they had no history of other psychiatric disorders or physical/neurological diseases. None of the patients had a history of a manic or hypomanic episodes or a first-degree relative with bipolar disorder. The diagnosis was reached independently by at least two senior psychiatrists. All patients scored 18 or higher on the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). They were either medication-naive or medication-free for at least 4 weeks. They signed a written informed consent form, which was approved by the local Institutional Review Board. After an initial assessment with the HDRS, antidepressant treatment was started. For patients, GDNF values obtained from the serum samples collected on the day before antidepressant initiation and at the end of 8 weeks of treatment were designated as baseline and follow-up values, respectively. Thirty-nine MDD patients completed the HDRS assessments and the serum samples collection after 8 weeks of treatment. Antidepressants were chosen according to current clinical practice in the light of patients' tolerances and responses in previous episodes. The following antidepressant drugs were administered to the 39 MDD patients who completed the HDRS assessments and the serum sample collections after 8 weeks of treatment: 8 of the patients received venlafaxine (mean dose, 190 mg/day) while 31 patients received SSRI antidepressants (5 of the patients received sertraline at a mean dose of 100 mg/day, 13 patients received fluoxetine at a mean dose of 32 mg/day, 4 patients received paroxetine at a mean dose of 35 mg/day, and 9 patients received 40 mg/day of citalopram). Three of these patients also received mood stabilizer treatment.

Fifty healthy subjects (22 males and 28 females) were studied as control subjects. The inclusion criteria for control subjects were good physical health and no history of mental disorders, neurologic diseases, or drug abuse. Age and gender were matched between the MDD patients and the normal controls. Written informed consent was obtained after a full written and verbal explanation of the study.

2.2. Assessment

Following an overnight fast, serum samples from the patients and healthy controls were collected between 8:00 and 9:00 a.m and stored at −80 °C until used for assay. The concentrations of GDNF were measured by using the enzyme linked immunosorbent assay (ELISA; Emax Immunoassay System kit; Promega, Madison, WI, USA) according to the manufacturer's instructions. All samples were tested in triplicate and the mean was calculated. The intra- and inter-assay coefficients of variation were <4% and <5%, respectively.

2.3. Data analysis

For statistical analysis, the data were expressed as the means ± S.D. and were analyzed with the statistical analysis software, SPSS, version 10.0 (SPSS, Inc., Chicago, IL, USA). Chi-squared analysis was performed on categorical data, such as gender, and study groups were compared for continuous variables by a two-tailed *t*-test and ANOVA. The relationship between the serum GDNF and clinical variables was examined using Pearson's correlation coefficient. Statistical significance is indicated by *P* values less than 0.05.

3. Results

Table 1 shows the demographic and clinical characteristics of both the MDD and control groups. At baseline, the mean serum GDNF concentration was 343.2±201.3 pg/ml and the mean HDRS score was 28.6±7.9 (n=76) in the MDD patients. The concentrations of serum GDNF were significantly lower in the patients with MDD (mean=343.2±201.3 pg/ml, $P<0.001$) compared with the control subjects (mean=749.9±300.4 pg/ml). No significant correlation was found between serum GDNF

Table 1
Demographic features, HDRS scores and GDNF serum concentrations of the groups

	Major depression (n=76)	Control (n=50)	*P*
Age (years)	45.1±14.7	43.4±13.4	0.519
Gender			
Male	34 (44.7%)	22 (44.0%)	0.935
Female	42 (55.3%)	28 (56.0%)	
Age of onset (years)	36.6±13.1		
Duration of illness (years)	8.3±9.3		
HDRS	28.6±7.9		
GDNF (pg/ml)	343.2±201.3	749.9±300.4	0.0001