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Age-associated decrease in serum glial cell line-derived neurotrophic factor levels in patients with major depressive disorder

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ABSTRACT

Background: Many studies have supported the role of neurotrophic hypothesis in the pathophysiology of mood disorders. This study examined serum levels of glial cell line-derived neurotrophic factor (GDNF), one of the neurotrophic factors, in patients with major depressive disorder (MDD) at different disease states.
Methods: The serum GDNF levels were measured in 55 patients with MDD (29 severe patients and 26 remitted patients) and 35 healthy controls by ELISA method. Severity of depressive symptoms was assessed using the 17-item Hamilton Rating Scale of Depression (HAM-D) (HAM-D ≧19 for severe MDD, HAM-D ≦7 for remitted MDD).
Results: MDD patients were found to have significantly lower serum GDNF levels than healthy controls ($p<0.001$). This decrease was significant in older-aged ($p=0.003$) and middle-aged ($p=0.026$) groups, but not in the younger-aged group. We found no difference in GDNF level between severe and remitted MDD patients.
Conclusions: In spite of some limitations, our results indicate an age-associated reduction in serum GDNF levels in patients with MDD, further supporting the role of the neurotrophic factor as a disease marker and a new target for developing antidepressant treatment.

1. Introduction

Depression is one of the most serious brain disorders in the world, associated with high social and occupational disability, disease burden, and risk of suicide (Greden, 2001). However, the etiologies of depression are still unclear. The pathogenesis of depression and the mechanisms underlying antidepressant effects may relate to regulation of multiple neurotrophic factors (Castren et al., 2007; Duman and Monteggia, 2006), including brain-derived neurotrophic factor (BDNF) (Guilloux et al., 2012; Martinowich et al., 2007; Sen et al., 2008), vascular endothelial growth factor (VEGF) (Nowacka and Obuchowicz, 2012; Warner-Schmidt and Duman, 2008), neurotrophin-3 (Otsuki et al., 2008; Reus et al., 2011), and insulin-like growth factor-1 (IGF-1) (Park et al., 2011; Weber-Hamann et al., 2009).

GDNF, a neurotrophic factor extensively distributed in mammalian brains (Golden et al., 1998), first binds to the GDNF-family receptor α1 (GFRα1) and then forms a complex with receptor tyrosine kinase (RET) receptor, resulting in the activation of intracellular tyrosine kinase domain and downstream signaling pathway (Airaksinen and Saarma, 2002). GDNF influences the development, survival, and differentiation of dopaminergic neurons (Lin et al., 1993) and is able to increase the density and neurite length of γ-aminobutyric acid (GABA)-immunoreactive neurons (Ducray et al., 2006). GDNF has also been shown to prevent both neurons and glial cells from oxidative stress (Chao and Lee, 1999; Cheng et al., 2004). Considered together, these findings suggest that GDNF may play a role in the pathogenesis of neuropsychiatric diseases through its neuroprotective effects in the brain (Pascual et al., 2008).

The change of GDNF levels in patients with psychiatric disorders has been examined. It has been found that blood GDNF protein levels were significantly lower in patients with mood disorders than in normal subjects (Takebayashi et al., 2006; Zhang et al., 2008, 2010). In addition, GDNF messenger ribonucleic acid (mRNA) expression was reported to be reduced in peripheral blood in patients with major depressive disorder (MDD) (Otsuki et al., 2008). Similarly, circulating serum GDNF level was found to be decreased in patients with

Abbreviations: ANOVA, analysis of variance; ANCOVA, analysis of covariance; MDD, major depressive disorder; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1; GDNF, glial cell line-derived neurotrophic factor; GFRα1, GDNF-family receptor α1; RET, receptor tyrosine kinase; GABA, γ-aminobutyric acid; mRNA, messenger ribonucleic acid; HAM-D, Hamilton Rating Scale for Depression; ELISA, enzyme-linked immunosorbent assay; SPSS, Statistical Package for the Social Sciences; BMI, body mass index; ROS, reactive oxygen species; RNS, reactive nitrogen species; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; CNS, central nervous system.

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late-life depression and the level was negatively correlated to the severity of disease (Diniz et al., 2012). However, some other studies showed inconsistent findings. For example, Michel et al. examined the post-mortem cortical regions, limbic area, basal ganglia, thalamus, and cingulate gyrus in patients with depressive disorders, and reported significantly higher GDNF concentrations in parietal cortex in depressed patients than in control subjects (Michel et al., 2008). It was also found that plasma GDNF levels were higher in euthymic patients with bipolar disorder (Barbosa et al., 2011), and in patients with late-onset depression (Wang et al., 2011). The inconsistency may be related to the confounding effects of severity of depressive symptoms, age, gender, or concomitant physical illnesses. In this study, we compared serum GDNF levels in MDD patients, in both severe and remitted states, with healthy controls, and also examined whether there is any moderating effect of age and gender.

2. Methods

2.1. Subjects

The subject inclusion process is described in Fig. 1. Briefly, 229 inpatients and outpatients meeting the DSM-IV-TR criteria of MDD were recruited. The diagnosis was conducted by a well-trained psychiatrist (Dr. Y. Lee or P.-Y. Lin) using Structured Clinical Interview for DSM-IV (SCID-IV). After recruitment, patients were screened by the criteria described in Fig. 1, to exclude major systemic or neurological diseases, or substance abuse. Especially, only the MDD patients with Hamilton Rating Scale for Depression (HAM-D) equal or higher than 19 (severe patients) or equal or lower than 7 for over 6 months (remitted patients) were included. Finally, there were 29 severe MDD patients and 26 remitted MDD patients that were included into current study. Control subjects were initially recruited from a general health examination center. Initially, 176 subjects were recruited and screened by the criteria described in Fig. 1. In addition to exclude major systemic or neurological diseases, they were screened by the 12-item Chinese Health Questionnaire (CHQ) (Cheng et al., 1990) to exclude psychiatric morbidity. The CHQ was originally developed to identify minor psychiatric disorders in both community and hospital subjects, with sensitivity and specificity as 0.78 and 0.77, respectively (Chong and Wilkinson, 1989). The optimal cutoff point with the best compromise between high sensitivity and a low false–positive rate is 3/4. In our protocol, the control subjects with CHQ score higher than 3 were excluded. This study was conducted by using a case–control design. Finally, 35 control subjects were chosen to match age and gender of included patients. Both the patients and controls were of Han Chinese origin and from Kaohsiung metropolitan area in Taiwan. This study was approved by the institutional review board and informed consent was obtained from each participant.

In our sub-classification of patients, we defined drug-free patients as ones without receiving any psychotropic agents for at least 3 months. Also, treatment-resistant depression (TRD) was defined by the criteria proposed by Souery et al., where MDD patients had poor response to two adequate trials of different classes of antidepressants (Souery et al., 1999). For patients under treatment with psychotropic agents, we transformed their antidepressant dosage into imipramine equivalent and antipsychotics dosage into chlorpromazine equivalent according to previous reports (Bollini et al., 1999; Shen, 1999; Woods, 2003).

In our later analysis, to examine the moderating effect of age on the GDNF level, we divided all the patients according to their age, and coded them as younger-age patient subgroup with below 40 years (YPS), middle-aged patient subgroup with 40–49 years (MPS), and older patient subgroup with over 50 years (OPS). Also, we divided all the healthy control subjects into three subgroups in the similar way and coded them as young healthy control subgroup (YHS), middle-aged healthy control subgroup (MHS), and older healthy control subgroups (OHS).

Besides, we also subdivided all the patients merged from the two patient groups into another three subgroups according to their age of first episode, and coded them as younger age of onset patient subgroup with age of onset below 55 years (YOPS), and older age of onset patient subgroup with age of onset over 55 years (OOPS).

2.2. Blood sample preparation and serum GDNF analysis

From each participant, 10 ml of venous blood was drawn between 7 am and 10 am. Samples were centrifuged 3000 *g* for 10 min, and stored at −80 °C until assay was performed. The GDNF level in serum was detected using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Promega GDNF Emax® Immunoassay system, Madison, WI, USA), according to manufacturer's instructions. The GDNF level was adjusted by the protein levels in our serum samples as suggested in the manufacturer. Assay for each participant was performed in duplicate.

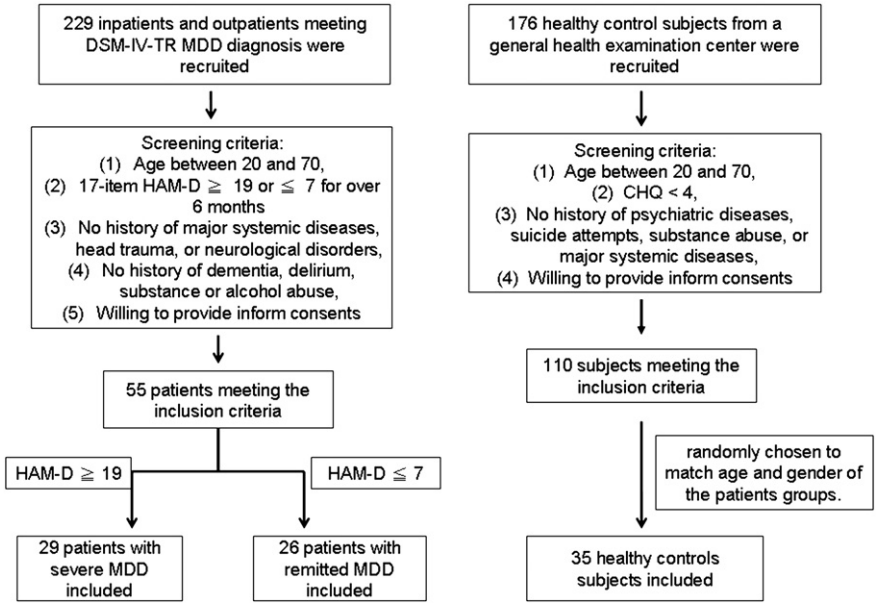

Fig. 1. The subject selection procedure. Abbreviations: CHQ, Chinese Health Questionnaire; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision; HAM-D, Hamilton Rating Scale for Depression; MDD, major depressive disorder.