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Decreased glial cell line-derived neurotrophic factor levels in patients with depression: A meta-analytic study

Pao-Yen Lin [a, b, *], Ping-Tao Tseng [c]

[a] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[b] Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[c] Department of Psychiatry, Tsyr-Huey Mental Hospital, Kaohsiung Jen-Ai's Home, Taiwan

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ABSTRACT

Glial cell-line derived neurotrophic factor (GDNF) has been shown to promote development, differentiation, and protection of CNS neurons and was thought to play an important role in various neuropsychiatric disorders. Several studies have examined the GDNF levels in patients with depression but shown inconsistent results. In this study, we compared blood GDNF levels between depressive patients and control subjects through meta-analytic method. The effect sizes (ESs) from all eligible studies were synthesized by using a random effect model. In this meta-analysis, we included 526 patients and 502 control subjects from 12 original articles. Compared to control subjects, blood GDNF levels are significantly decreased in patients with depression (ES = −0.62, $p = 0.0011$). However, significant heterogeneity was found among included studies. Through subgroup analysis, we found that GDNF was still decreased in studies with major depressive disorder (ES = −0.73, $p = 0.0001$); in studies with non-old-age depression (ES = −1.25, $p = 0.0001$), but not with old-age depression; and in studies using serum samples (ES = −0.86, $p < 0.0001$), but not in studies using plasma sample. Meta-regression did not show moderating effects of mean age of subjects, gender distribution, and age of onset of depression. Our findings support blood GDNF levels as a biomarker of depression as a whole, but the results were modulated by psychiatric diagnosis, age of included subjects, and sampling sources. With these results, future studies are required to examine whether effective antidepressant treatment is associated with an increase in serum GDNF levels.

1. Introduction

Depression is one of the most serious mental disorders in the world, and is associated with social and occupational disability, heavy financial burden, and high risk of suicide (Greden, 2001). Although the etiologies of depression are still unclear, evidence has supported that neurotrophic dysregulation plays an important role in the pathogenesis of depression (Duman and Li, 2012). Altered expression of multiple types of neurotrophic factors has been found in patients with depression, including brain-derived neurotrophic factor (BDNF) (Bocchio-Chiavetto et al., 2010; Molendijk et al., 2014), nerve growth factor (de Azevedo Cardoso et al., 2014; Pallavi et al., 2013), neurotrophin-3 (Otsuki et al., 2008; Pallavi et al., 2013), vascular endothelial growth factor (Berent et al., 2014; Fornaro et al., 2013), and insulin-like growth factor-1 (Sievers et al., 2014; Weber-Hamann et al., 2009).

Glial cell line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor-β superfamily and is extensively distributed in mammalian brains, including hypothalamus, substantia nigra, and thalamus (Golden et al., 1998). It first binds to the GDNF-family receptor α1 (GFRα1) and then forms a complex with receptor tyrosine kinase receptor, activating intracellular tyrosine kinase domain and downstream signaling protein cascade (Airaksinen and Saarma, 2002). GDNF promotes the differentiation of dopaminergic neurons (Christophersen et al., 2007; Lin et al., 1993) and serotonergic neurons (Ducray et al., 2006), and can increase neurite growth in various neuronal types (Ducray et al., 2006; Takaku et al., 2013; Wakeman et al., 2014). In addition, GDNF has been shown to protect mesencephalic neuron-derived cells (Ortiz–Ortiz et al., 2011), serotonergic neurons from dorsal

* Corresponding author. Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, 123, Dapi Road, Niaosong District, Kaohsiung City 833, Taiwan. Tel.: +886 7 7317123x8751; fax: +886 7 7326817.
E-mail address: py1029@adm.cgmh.org.tw (P.-Y. Lin).

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raphe nucleus (Hochstrasser et al., 2011), and mesencephalic dopaminergic neurons (Jaumotte and Zigmond, 2014), and glial cells (Uzdensky et al., 2013) from oxidative or neuro-inflammatory injury. 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).

In past few years, changes in GDNF activity have been examined in patients with depression. Takebayashi et al. (2006) first found that whole blood GDNF levels were significantly decreased in remitted patients with major depressive disorder (MDD). And the findings were replicated in some other studies (de Azevedo Cardoso et al., 2014; Diniz et al., 2012; Pallavi et al., 2013; Tseng et al., 2013; Zhang et al., 2014, 2008). On the contrary, Rosa et al. (2006) found an increase in GDNF immunocontent in patients with bipolar depression. In addition, Wang et al. (2011) reported a significant increase in plasma GDNF concentrations in patients with late-onset depression. The inconsistency of these results may be related to the psychiatric diagnosis of the patients, age of subjects, gender distribution, severity of depression, sample sources (plasma, serum, or whole blood), or concomitant physical or psychiatric illnesses. The goals of current meta-analysis are (1) to determine the difference in blood GDNF levels between patients with depression and control subjects, and (2) to examine potential variables that can modulate the difference.

2. Methods

2.1. Literature search and screening

Eligible articles were searched in the database of PubMed at the National Library of Medicine by two independent reviewers (P.-Y. Lin and P.-T. Tseng). The search was performed by using the search terms "(depression OR MDD) AND GDNF", for articles available by August 2014, and without special limitation in language. The titles and abstracts of articles obtained by this search strategy were screened by the reviewers to determine if they were potentially eligible for inclusion in this meta-analysis, and to exclude articles that were apparently non-eligible, such as review articles, non-human studies, articles not mentioning GDNF, and case reports. In case of disagreement in eligibility, we reached agreement through consensus.

2.2. Inclusion criteria of studies in the meta-analysis

The included articles passing initial screening were examined based on the inclusion criteria used in selecting studies into this meta-analysis, including articles that: (1) measured blood GDNF protein level, (2) included patients diagnosed with depression, (3) presented cross-sectional comparison in GDNF levels between the patients and control, and (4) dataset were not overlapping with other articles. When dataset of subjects from two articles were overlapping, we only included the article with larger sample size.

2.3. Meta-analytic methods

The primary outcome was to compare blood GDNF levels between patients with depression and controls. For each identified study, the effect sizes (ESs) expressing the difference in GDNF level between patients and controls were described as the standardized mean difference (SMD) based on Hedges's adjusted g, where values greater than 0 indicated that the GDNF level was higher in patients than controls. The means and standard deviations of the GDNF levels of both patients and controls were used to derive the ES for each individual study. When these data could not be available from these articles, we contacted the authors to acquire the original data or we derived the ES from other statistical parameters, such as t value or p value. The ESs of individual studies were synthesized by the random effects model (Shadish and Haddock, 1994). The significance of the pooled ES was determined by the z-test. When the pooled ES showed significant result, sensitivity analyses were performed to determine if any individual study was responsible for the significant finding. In this analysis, each study was individually removed and the significance was re-tested.

Heterogeneity among included studies was examined based on the null hypothesis that the group of ESs came from a homogeneous source. It was assessed by Q statistics, their related p-value, and the I^2 statistic, which is the percentage of the variability in the estimate of the effect that is due to heterogeneity rather than random error. Larger value of I^2 statistic indicates higher heterogeneity. A rejection of homogeneity suggests that there may be systemic differences existing among the included studies. To examine possible source of heterogeneity among studies, both meta-regression and subgroup analysis were conducted. We performed meta-regression by using unrestricted maximum likelihood method, to examine whether mean age and gender distribution (proportion of females) of both patients and controls, or age of onset of depressed patients in included studies moderate the pooled ES. In addition, we did subgroup analysis based on the psychiatric diagnosis, mood status (depressed or remitted state), old-aged depression or not, and sample sources (plasma or serum).

Publication bias was assessed by plotting the ES against the precision (inverse of standard error) for each study (funnel plot), then the symmetry of the dots in the funnel plot was visually examined. We also used Egger's regression analysis to statistically test for significance of any possible publication bias (Egger et al., 1997).

Statistics in meta-analyses were performed by applying Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA). Two-sided p values <0.05 were considered statistically significant. We reported the methods and the results of meta-analyses by following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting checklist (Stroup et al., 2000).

3. Results

The search in PubMed resulted in 57 results for initial consideration in the meta-analysis. By examining their titles and abstracts, 31 articles were excluded because they were review articles ($n = 10$), non-human studies ($n = 19$), comments on other studies ($n = 1$), or case report ($n = 1$). Next we examined the text of remaining 26 articles by inclusion criteria, 6 of them were excluded because they did not include patients with depressive disorder (Barbosa et al., 2011; Blasko et al., 2006; Dmitrzak-Weglarz et al., 2013; Fontenelle et al., 2012; Kotyuk et al., 2013a; Ricci et al., 2010), one article was excluded because they measured brain GDNF level (Michel et al., 2008), 3 articles without control subjects (Rybakowski et al., 2013; Sun et al., 2013; Wang et al., 2014), 2 articles of genetic association but not GDNF protein level (Kotyuk et al., 2013b; Ma et al., 2013), and one article examining GDNF mRNA but not protein level (Otsuki et al., 2008) were excluded. Finally, 12 articles (de Azevedo Cardoso et al., 2014; Diniz et al., 2012; Heberlein et al., 2010; Marksteiner et al., 2011; Pallavi et al., 2013; Rosa et al., 2006; Takebayashi et al., 2006; Tseng et al., 2013; Wang et al., 2011; Zhang et al., 2014, 2010, 2008) were included into the current meta-analysis, and the selection process was shown in Fig. 1. The characteristics of included articles were described in Table 1. The patient subjects of study by Tseng et al. (2013) included two independent subgroups, depressed and remitted patients, so this article was regarded as two studies.