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Peripheral blood nerve growth factor levels in major psychiatric disorders

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ABSTRACT

Nerve growth factor (NGF) plays crucial roles in promoting neural growth and survival, and mediating synaptic and morphological plasticity. Several studies investigated the correlation between peripheral NGF levels and major psychiatric disorders, including schizophrenia (SCZ), major depressive disorder (MDD) and bipolar disorder (BPD); however, the findings were inconsistent. This meta-analysis sought to investigate blood NGF levels in patients with psychiatric disorders compared with healthy subjects and examined potential effects of blood fraction, medication and disease status. A total of 21 eligible studies, encompassing 1342 patients suffering from psychiatric disorders and 1225 healthy subjects, were enrolled in the present meta-analysis. No obvious publication bias was observed either for SCZ, MDD or BPD by the Begg's test ($P > 0.05$). Random-effects meta-analysis showed that SCZ ($Z = 2.14$, $P = 0.033$, SMD $= -1.08$, 95% CI $= -2.07$ to -0.09) and MDD ($Z = 2.57$, $P = 0.010$, SMD $= -0.61$, 95% CI $= -1.08$ to -0.14) patients had significantly reduced NGF levels, compared with healthy controls. Notably, this decrease was enhanced in un-medicated patients of SCZ ($P = 0.004$) and medicated or chronic patients of MDD ($P < 0.001$). No significant difference of NGF levels was observed between BPD patients and controls ($P > 0.05$). These results supported an association between the reduction of NGF levels and psychiatric disorders. It remains unclear whether the change of NGF levels is a prerequisite for its function in psychiatric disorders development or merely an epiphenomenon unrelated to the pathophysiologic mechanisms.

1. Introduction

Schizophrenia (SCZ), major depressive disorder (MDD) and bipolar disorder (BPD) are three major kinds of neuropsychiatric disorders and are recognized as the leading causes of mortality (Ghaemi, 2006). The prevalence is estimated to be approximately 1% for SCZ and more than 3% for MDD and BPD (Craddock et al., 2005; Kessler et al., 2003). Although pharmacological treatments have been available for SCZ, MDD and BPD for a long time, their efficacy is poor for a substantial portion of patients (Lieberman et al., 2005). Stasis of novel drug development for psychiatric disorders is potentially due to limited knowledge of their pathophysiology.

Although the etiology of psychiatric disorders remains largely unknown, impairment of neuroplasticity has been hypothesized to be implicated in the pathophysiology of SCZ (Balu and Coyle, 2011) and affective disorders (Carlson et al., 2006), and numerous functional proteins contribute to maintaining the plasticity of neurons, among which are the neurotrophins family members, including nerve growth factor (NGF), brain derived neurotrophic factor

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(BDNF), Neurotrophin-3 (NT-3), and so on (Shaltiel et al., 2007).

NGF is mainly produced in the central nervous system, including hippocampus, cortex and hypothalamus, and plays crucial roles in promoting neural growth and survival, and in mediating synaptic and morphological plasticity (Jardi et al., 2014). Recent studies have demonstrated that NGF has been also found in peripheral blood outside the central nervous system, either from release of central source across the blood-brain barrier, or from direct secretion of immune system cells (Bonini et al., 2003). Mounting preclinical and clinical evidence has connecting the peripheral NGF levels to disease activity and progress in psychiatric disorders (Inal-Emiroglu et al., 2015b; Martinez-Cengotitabengoa et al., 2016; Wiener et al., 2015). Furthermore, NGF levels are dramatically influenced by psychiatric medications, such as antipsychotics and mood stabilizers (Ajami et al., 2014; Bilgen et al., 2014).

For SCZ, several investigations revealed decreased serum or plasma NGF levels in patients compared with healthy subjects (Kale et al., 2009; Parikh et al., 2003; Zakharyan et al., 2014), while other case-control or prospective studies reported completely contrary results (Ajami et al., 2014; Martinez-Cengotitabengoa et al., 2016). Moreover, peripheral blood NGF levels remain significantly unchanged between SCZ patients and controls cohorts with several small sample sizes (Jockers-Scherubl et al., 2003, 2006). The same situation can be found for MDD (de Azevedo Cardoso et al., 2014; Kheirouri et al., 2016; Liu et al., 2014b; Wiener et al., 2015) and BPD (Barbosa et al., 2011; Inal-Emiroglu et al., 2015b; Kim et al., 2013) studies, and whether peripheral NGF levels are decreased, increased or unchanged remains difficult to be determined. These inconsistent results might be due to limited sample sizes, likely lacking statistical power, and heterogeneous patient populations, *i.e.*, ethnicity and more importantly disease status. Meta-analysis is a widely accepted technique to reconcile discrepancies among studies. Except for producing solid conclusions by combining data from independent studies together, meta-analysis serve as a powerful method to dissect potential source of heterogeneity (Egger et al., 1998).

In the present study, we conducted a meta-analysis of the association between peripheral blood NGF levels and psychiatric disorders. This study aimed to assess: 1) if peripheral NGF levels were changed (increased or decreased) or unchanged in patients of psychiatric disorders; 2) multiple possible factors influencing effect size of differences between patients and controls through subgroup analysis.

2. Materials and methods

The present meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement (Moher et al., 2009). A protocol for this meta-analysis was designed for data collection and extraction, as well as statistical procedures. The study was approved by the ethics committee of Southwest Jiaotong University.

2.1. Search strategy and eligible study inclusion criteria

Meta-analyses were performed in accordance with the methods described previously (Rao et al., 2016a, 2016b). Two investigators (S-QR and YY) independently searched any eligible studies from PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com/), and PsycINFO (http://www.apa.org/pubs/databases/psycinfo/) with the following searching items: "(nerve growth factor or NGF) and (SCZ or schizoaffective or depression or bipolar or mood disorder or affective disorder)". Studies which were published in English language before 1st of May 2016 were considered. Hand search of reference lists of retrieved articles were performed to identify other eligible studies.

Eligible studies included in our meta-analysis must meet the following criteria: (1) studies reporting NGF levels in peripheral serum or plasma; (2) cross-sectional or longitudinal studies comparing NGF levels in healthy control subjects and patients of mental disorders, or follow-up studies investigating NGF levels in mental disorder patients before and after pharmacological intervention; (3) disease status in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD-10) diagnostic criteria; (4) peer-reviewed articles regardless of publication status, i.e. posters, conference abstracts, etc. Exclusion criteria were as follows: (1) duplicate publications; (2) studies reporting NGF levels in cultured blood cells (in vitro); (3) data unavailable. When samples from two or more studies overlapped, only the study involving the largest sample size was retained.

2.2. Data extraction

The following data were extracted from individual studies, including author and publication year, sample size, diagnostic criteria, age and gender distribution, age of symptom onset, symptom scaling, medication use, mean NGF concentrations, standard deviation (S.D.), measurement method, blood fraction. Two independent researchers (S-QR and YY) performed data extraction. If data was unavailable from original manuscripts, the authors were contacted. Disagreement with data was settled by discussion among all researchers. Where data was presented in subgroups, data for the overall group was combined according to the method described in the Cochrane Handbook for Systematic Reviews of Interventions.

2.3. Statistical analysis

We applied the Stata12.0 statistical software package (http://www.stata.com/) to conduct publication bias analysis and meta-analyses (Rao et al., 2016b). The difference of NGF levels between patients of mental disorders and controls (effect size, ES) were described as standardized mean difference (SMD) based on Hedges' adjusted g, which was generated by sample size, mean and S.D. (where mean and S.D. were unavailable, the *P*-value was used). Pooled ES was calculated using the random-effect model when between-study heterogeneity was present, or the fixed-effect model otherwise. Cochran's χ^2-based Q-statistic was performed to assess the heterogeneity between studies, which was considered significant at $P < 0.05$. The impact of heterogeneity on meta-analysis estimates was quantified with the I^2 statistic that takes values between 0 and 100%, with 0–25% representing no heterogeneity, 25–50% moderate heterogeneity, 50–75% large heterogeneity and 75–100% extreme heterogeneity (Lau et al., 1997). Degree of potential publication bias was checked using the Begg's test.

All statistics were two-sided and $P < 0.05$ was considered statistically significant, if indicated otherwise, while $P < 0.10$ represented a trend.

3. Results

3.1. Eligible studies

The electronic database search generated 3708 potentially relevant studies from PubMed, Embase and PsycINFO database. After removing obviously irrelevant titles and abstracts, 59 articles related to the present subject were screened for full-text. Among them, 28 studies were excluded due to various reasons that were specified in Fig. 1, i.e. patients not suffering from major psychiatric