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State-dependent increase in the levels of neurotrophin-3 and neurotrophin-4/5 in patients with bipolar disorder: A meta-analysis

Ping-Tao Tseng [a], Yen-Wen Chen [b], Kun-Yu Tu [a], Hung-Yu Wang [a], Weilun Chung [a], Ching-Kuan Wu [a], Shih-Pin Hsu [b], Hung-Chang Kuo [b], Pao-Yen Lin [c, d, *]

[a] Department of Psychiatry, Tsyr-Huey Mental Hospital, Kaohsiung, Jen-Ai's Home, Taiwan
[b] Department of Neurology, E-Da Hospital, Kaohsiung, Taiwan
[c] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[d] Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

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ABSTRACT

Bipolar disorder (BD) is one of the most serious psychiatric disorders in the world, but its pathophysiology is still unclear. Regulation of neurotrophic factors have been thought to play a role in this process. There have been inconsistent findings regarding the differences in blood neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) between patients with BD and healthy controls (HCs). The aim of the current meta-analysis is to examine the changes in the levels of NT-3 and NT-4/5 in BD patients at different affective states. Eight articles (including 465 BD patients and 353 HCs) were included in the analysis, and their results were pooled by using a random effects model. We found the levels of both NT-3 ($p = 0.0046$) and NT-4/5 ($p = 0.0003$) were significantly increased in BD patients, compared to HCs. Through subgroup analysis, this increase persisted only in patients in depressed state ($p = 0.0038$ for NT-3 and $p = 0.0001$ for NT-4/5), but not in manic or euthymic state. In addition, we found the differences in NT-3 and NT-4/5 were significantly associated with the duration of illness, but not by the mean age or female proportion. Our results suggest a state-dependent increase in NT-3 and NT-4/5 levels in patients with BD. Further studies are needed to examine dynamic changes of these neurotrophins in BD patients along the disease course.

1. Introduction

Bipolar disorder (BD) is one of the common psychiatric diseases and can lead to serious consequences, including higher risk of medical comorbidities (Zhang et al., 2013), substance abuse (Evans et al., 2004), suicide (Takebayashi et al., 2010), and heavy economic burden (He et al., 2014). Although the etiology of BD is not well understood (Muneer, 2016), altered activity of neurotrophins (NTs) have been believed to play a role in the pathophysiology of BD (Pfaffenseller et al., 2013). The NT family, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5), have been shown to play various roles in the development of nervous system (Liu et al., 2014). Most previous studies have focused on BDNF when examining NTs in patients with BD (Wang et al., 2014). A prior meta-analytic study has shown that blood BDNF level was reduced in manic or depressed state of BD, but not in euthymic state (Lin, 2009).

Compared to BDNF, NT-3 was less studied in psychiatric research. NT-3 is expressed in the hippocampus, which is the key structure of emotion modulation and memory formation (Shimazu et al., 2006). It can stimulate and control neurogenesis through the activation of tyrosine kinase NT receptor C (trkC) (Pae et al., 2008), which facilitates synaptic plasticity and increases the number of synaptic sites in the hippocampus (Je et al., 2006). In addition, NT-3 plays an important role in the survival of specific neurons in the brain, such as noradrenergic neurons (Arenas and Persson, 1994)

List of abbreviation: BD, bipolar disorder; NT, neurotrophin; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; NT-3, neurotrophin-3; NT-4/5, neurotrophin-4/5; trkB, tyrosine kinase NT receptor B; trkC, tyrosine kinase NT receptor C; ES, effect size; SD, standard deviation; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; BMI, body mass index; HC, healthy control; CI, confidence interval.

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

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and the progenitor cells in the hippocampus (Shimazu et al., 2006). NT-3 has been demonstrated to be associated with the regulation of serotonin and noradrenaline, to be involved in the treatment effect of mood stabilizers (Pae et al., 2008), and to interact with and compensate for the alteration of other neurotrophic factors in neuropsychiatric illnesses, including BDNF (Agerman and Ernfors, 2003; Schutte et al., 2000).

NT-4/5, as a member of the neurotrophin family, has some properties which differ from those of NT-3. NT-3 mainly acts on trkC, while NT-4/5 acts mainly on trkB and p75NTR, which can influence neurite outgrowth (Runge et al., 2012) or induce cell apoptosis and modify the selectivity and affinity of binding of specific NT (Dawbarn and Allen, 2003), respectively. In some aspects, NT-4/5 acts in a manner similar to BDNF, but has a more potent effect than BDNF, such as having a better protective effect on striatal dopaminergic neurons, which are believed to be one of the key neurons in the pathophysiology of BD (Sauer et al., 1995).

In the past decade, a few studies have examined alteration of NT-3 and/or NT-4/5 in patients with BD, but had discrepant results. Some studies have found that peripheral NT-3 and/or NT-4/5 levels are significantly higher in patients with BD than in HCs (Fernandes et al., 2010; Kapczinski et al., 2011; Loch et al., 2015; Walz et al., 2007, 2009). Another report has demonstrated an opposite result (Otsuki et al., 2008), and some studies have revealed no difference (Aydemir et al., 2014; Barbosa et al., 2014; Munkholm et al., 2014). The inconsistency might be due to differences in study design, precise psychiatric diagnoses, mood states of BD, age of the subjects, gender distribution, usage of different psychotropic agents, severity of disease, or different sample sources (plasma or serum).

The aims of the current meta-analysis are (1) to compare the differences in peripheral NT-3 and NT-4/5 between patients with BD and HCs and (2) to examine the potential variables that influence the difference.

2. Methods

2.1. Literature search and inclusion process

We set the target as those observational studies or related trials related to the NT levels in patients with BD. Literature search was performed by three of the authors (Tseng PT, Tu KY, and Wang HY) through the PubMed and Scopus databases for all articles available by February 21st, 2016. They used the keywords for the search: "(neurotrophin-3 OR neurotrophin-4/5) AND (bipolar disorder OR depress OR mania OR euthymia)". There was no special limitation in language. These authors screened the titles and abstracts of all the search results to rule out review articles, non-human studies, and case reports. When there was an inconsistency among authors, agreement was reached through consensus. Reference lists from identified papers and relevant review articles were also carefully examined for studies not indexed in the above electronic databases. Next, the full texts of selected search results after screening were scrutinized by applying the following inclusion criteria: (1) studies including patients with BD and healthy controls (HCs), and (2) studies investigating NT-3 or NT-4/5 protein levels in peripheral blood. The process of literature search and inclusion is depicted in Fig. 1. Here, the HC was defined as those subjects without major psychiatric illness. In addition, review articles or case reports were excluded at this stage. We excluded the literature published in languages other than English. In addition, we excluded studies which did not provide enough information about the NT comparison between BD patients and HCs.

There was no need for ethical approval for this study because we did not use detailed personal data of any patient.

2.2. Meta-analytic methods

The primary outcome compared blood NT3 and NT-4/5 levels between BD patients and HCs. For each identified study, the effect sizes (ESs), which expressed the differences in NT-3 and NT-4/5 levels between BD patients and HCs, were set as the standardized mean difference, using Hedges' adjusted *g*. Values of ESs greater than 0 indicated the peripheral NT levels were higher in BD patients than in HCs. If available, we chose the means and standard deviations (SDs) of the NT levels in each study, or we tried to derive the ESs from other statistical parameters, such as the *t* value, *p* value, and the sample sizes. If the detailed data could not be derived from the literature, we attempted to contact the authors. All the effect sizes of individual studies were synthesized using the random effects model in the current meta-analysis. In addition, we evaluated the heterogeneity among studies in our meta-analysis using Q statistics and their related p-value and I^2 statistic, which is the percentage of the variability in the estimate of effects that is due to heterogeneity rather than random error. A larger value of I^2 statistic value indicates higher heterogeneity. In order to evaluate possible association, we used meta-regression to examine the possible sources of heterogeneity. We investigated publication bias using funnel plots and Egger's regression analysis (Egger et al., 1997). Furthermore, in order to evaluate possible confounding factors, we performed meta-regression of the possible confounding clinical variables, such as mean age, gender (female proportion), body mass index (BMI), duration of illness, disease severity (using Hamilton Depression Rating Scale (HAM-D) or Young Mania Rating Scale (YMRS)), and age of onset.

We conducted all meta-analytic procedures by using the Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA). Two-tailed p values < 0.05 were considered statistically significant. We reported the methods and the results of meta-analyses by following Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline (Suppl. Table 1) (Stroup et al., 2000).

3. Results

3.1. Studies included in the current meta-analysis

Seventy-six articles were initially found through database and manual searches (see Fig. 1). After excluding review articles (n = 24) and non-human studies (n = 35), a total of 17 articles were selected for detailed eligibility screening based on inclusion criteria. Nine of the 17 articles were excluded because they did not provide NT-3 or NT-4/5 blood protein levels in BD patients and HCs (Anisman and Hayley, 2012; Fakhri et al., 2014; Gronli et al., 2009; Otsuki et al., 2008; Rybakowski et al., 2013; Sibille et al., 2004; Stevens et al., 2012; Turner et al., 2012; Yafai et al., 2013). Finally, 8 articles (including 465 BD patients and 353 HC) were included into our meta-analysis (Aydemir et al., 2014; Barbosa et al., 2014; Fernandes et al., 2010; Kapczinski et al., 2011; Loch et al., 2015; Munkholm et al., 2014; Walz et al., 2007, 2009). Six of the articles presented data for BD patients with different mood status and provided additional information for analysis (Barbosa et al., 2014; Fernandes et al., 2010; Kapczinski et al., 2011; Munkholm et al., 2014; Walz et al., 2007, 2009). The characteristics of included articles were summarized in Table 1.

3.2. Meta-analysis of NT-3 levels between BD patients and HC

First, we compared the blood NT-3 levels between BD patients (n = 260) and HC (n = 273), extracted from 6 studies (Barbosa et al., 2014; Fernandes et al., 2010; Kapczinski et al., 2011; Loch et al.,