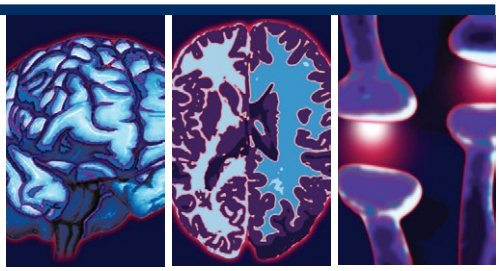

Associations between Serum Brain-Derived Neurotrophic Factors and Bipolar Disorder

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Abstract

Background:

Brain-derived neurotrophic factor (BDNF) is known related to the psychopathology of bipolar disorder. However, the results of the relationship between BDNF levels and bipolar disorder were inconsistent. In this study, we aimed to investigate the relationship between BDNF levels, the different phases and clinical phenotypes of bipolar disorder.

Methods: Over a 4-year period, bipolar patients in different disease phases, including mania phase, depressive phase and remission, were recruited. All participants had peripheral blood drawn to analyze the serum BDNF levels. We also investigated the relationships between serum BDNF levels, violence, suicidal behavior and Young Mania Rating Scale score (YMRS) before and after 4-week treatment.

Results: A total of 102 participants in different disease phases, including acute mania (n=44), acute depressive episode (n=20) and remission (n=38) of bipolar disorder were invited for this study. The serum BDNF levels of patients with acute mania or depressive phases were significantly lower than bipolar patients in remission phases using ANCOVAs with age and sex adjustment (mania: p=0.013, depression: p=0.003, respectively). Bipolar mania patients with violence had lower BDNF levels than those without violence (p=0.025). Among 42 followed-up patients, increased BDNF level from baseline was noted after one-month treatment, but there is not statistically significant by means of paired t test (mania: p=0.845 and depression: p=0.931, respectively).

Conclusions: Our study found that lower serum BDNF levels are strongly associated with the depressive and manic phase of bipolar disorder than remission phase. In addition, bipolar mania patients with violence had lower BDNF levels than those without violence. In the future, it needs a large sample to prove these results.

Keywords:

Bipolar disorder, Depression, Mania, BDNF, Suicide, Violence

Introduction

Bipolar disorder is a highly prevalent, disabling mental illness worldwide, and is often accompanied by high mortality rates, comorbidity and economic burdens [1,2]. Some evidence has suggested that the pathogenesis of bipolar disorder is neuro-developmental impairments [3] and an impairment of neuroplasticity with neuroprogressive changes was observed during the course of bipolar disorder [4].

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Brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the central nervous system (CNS), plays an important role in neurogenesis, neuronal survival, and synaptic plasticity [5,6]. BDNF levels measures in blood could reflect illness activity in the brain due to a positive correlation of BDNF levels between blood and cortex in mice, rats and pigs [7]. In addition, the tropomyosin receptor kinase (TrkB), a receptor of BDNF on cell membrane, is involved in bipolar disorder [8,9]. Several studies have adopted the BDNF as a molecular candidate for developing bipolar disorder [6,10]. Recent studies had demonstrated that BDNF levels are lower in patients during active phases than BDNF levels in healthy controls [10-14]. Changes in serum BDNF levels in different phases and in following pharmacological interventions for acute affective phase in patients with bipolar disorders were addressed in several studies, but the results are still inconclusive [8,13,15-17]. The serum BDNF protein level is reported to be a useful adjunctive tool for accurately diagnosing depressive bipolar disorder [18] and a marker for treatment response in bipolar disorder [11,14,19].

Bipolar disorder confers the higher risk of suicide and violence among major psychiatric disorders [20,21]. The reduction of BDNF level is associated with suicidal behavior in major depression [22]. These results supported that BDNF played a pivotal role in the pathophysiology of suicidal behavior. In particular, most of the violence in bipolar disorder occurs during the manic phase [21] and there is no studies focusing on the relationship beween BDNF levels and violence.

Taken together, in this study, we aimed to investigate the serum BDNF levels of patients with bipolar disorder in (1) different affective phases and (2) various clinical phenotypes including violence, suicide, family tendency, and (3) following 4-week treatment.

Methods

■ Participants

Over a 4-year period (August 2007 to September 2008, November 2012 to December 2013, December 2014 to November 2016), participants diagnosed with bipolar disorder were recruited at Chang Gung Memorial Hospital in Kaohsiung, Taiwan. All research projects were approved by the Institutional Review Board of Chang Gung Memorial Hospital. Written informed consent was obtained from each participant after the explanation of the procedures and the objectives of the study. Some data of serum BDNF levels in patients with bipolar disorder and healthy controls had been published [9,12].

The diagnosis of bipolar disorder in participants was made by the psychiatrist (Dr. Huang) according to the Structured Clinical Interview for DSM-IV Axis I Disorders [23]. Subjects with acute mania state (Young Mania Rating Scale score, YMRS>26) were invited to participate [24]. In addition, the severity of depressive symptoms was assessed using the 17-item Hamilton Rating Scale for Depression [25]. Participants with remission state of bipolar disorder were defined as individuals who received medication for a period of at least 6 months at the out-patient department and scored <7 on YMRS with no core item of the YMRS [26]. We only assessed whether patients with bipolar disorder had shown any physical violence to others without using the modified overt aggression scale or had suicide attempts prior to our study one year ago. Family tendency was defined as >1 first-degree relatives of patients having a history of bipolar disorder. All patients received blood pressure, routine blood tests, chest X-ray, and electrocardiogram to exclude the subjects with systemic diseases and infectious diseases.

Among the followed-up patients, we investigated the association between body mass indices (BMI), age, sex, suicidal attempt, violence, family history and serum BDNF levels before and after a 4-week treatment. Mood stabilizer consisting of either valproate (600~1500mg/d), or lithium (900~1200 mg/d) were administered during the hospitalization. Some patients' treatment regimens also include other psychotropic drugs, including risperidone (1~4mg/d), olanzapine (5-15mg/d), lorazepam (1~3mg/d), or hypnotic (zolpidem 10~20mg/day).

■ Laboratory analysis

Venous blood samples (5ml) were drawn for serum BDNF levels measured by an ELISA Kit (BDNF Emax Immunoassay System, Promega Co). Absorbencies (at 450 nm) were detected by using a microtiter plate reader. The intra-assay and inter-assay variations in BDNF levels were both less than 10%.

Statistical Analysis

All results are presented as means ± standard deviation (SD). The participants were sorted

into different diagnostic categories according to disease statuses (i.e., patients with acute mania, acute depressive episode and remission of bipolar disorder) or clinical phenotypes (i.e., those who had and those who did not have a suicide behavior, violence, family tendency). Data analysis was performed by using an analysis of covariance (ANCOVA) with age and sex adjustment for group mean differences in different groups. BDNF levels of the patient with different state were compared using an ANCOVA with age and gender adjustments for group mean differences in different groups. Within the patient group, the relationships of BDNF levels, age, sex, BMI, violence, suicide behavior and family tendency were evaluated by means of Pearson's correlation test. Pretreatment and post-treatment serum BDNF levels of the followed-up patients were evaluated using the paired t test. All statistical data analyses were performed using SPSS, version 12. For each test, a p value less than 0.05 was used to indicate statistical significance.

Results

■ Demographic Data

Over a 4-year period, a total of 102 participants including acute mania (n=44), acute depressive episode (n=20) and remission (n=38) of bipolar disorder were recruited for this study. **Table 1** exhibits the demographic data, and serum BDNF levels at baseline in all participants. Patients with remission bipolar disorder were significantly older than depressed patients (40.6 ± 11.1 years vs 34.1 ± 11.8 years; *P*=.048). Comparison with the remission subgroup, there was significant difference in BMI between the mania or depressive subgroups and remission subgroup **(Table 1)**.

■ BDNF Levels in acute phase (mania and depressive) and remission phase

The ANCOVA with age and sex adjustment showed that bipolar mania patients *(F=6.933, P =0.010)* and bipolar depression (*F=9.447, P=0.003*)) had significantly lower BDNF levels than patients with remission of bipolar disorder. However, there is no significant difference between acute bipolar mania and bipolar depression patients. (*F=1.383, P=0.244*).

■ BDNF levels in bipolar patients with different clinical phenotypes

Using ANCOVAs with age and gender adjustments, we found that patients who had a violence behavior had lower serum BDNF protein levels than those who did not (*F=5.402, P=0.025*). However, no significant difference was elicited between serum BDNF levels in patient with suicide and without suicide *(F=1.406, P=0.243)* **(Table 2)**.

■ BDNF Levels Before and After the 4-week Treatment

Of 102 bipolar disorder patients, only 42 patients (23 patients with bipolar mania, 19 patients with bipolar depression) remained in the study after a period of 4-week treatment and completed the assessments of YMRS. Using the paired t test, the serum BDNF levels of the 23 mania patients and 19 depressive patients appeared to increase

Table 1: Serum BDNF levels and demographic data of all participants.

Diagnostic groups	Age (years)	Sex♠	BMI (kg/m²)	Serum BDNF levels (ng/ml)
STABLE *(n=38)*	40.6 ± 11.1	0.6 ± 0.5	26.8 ± 4.9	7.7 ± 0.6
MANIA *(n=44)*	38.4 ± 11.3	0.4 ± 0.5	24.3 ± 5.4	5.5 ± 0.5
P value	0.390	0.281	0.035*	0.010*
STABLE *(n=38)*	40.6 ± 11.1	0.6 ± 0.5	26.8 ± 4.9	7.7 ± 0.6
DEPRESSION *(n=20)*	34.1 ± 11.8	0.4 ± 0.5	22.9 ± 3.5	4.3 ± 0.9
P value	0.043*	0.277	0.002*	0.003*
MANIA *(n=44)*	38.4 ± 11.3	0.4 ± 0.5	24.3 ± 5.4	5.5 ± 0.5
DEPRESSION *(n=20)*	34.1 ± 11.8	0.4 ± 0.5	22.9 ± 3.5	4.3 ± 0.9
P value	0.162	0.815	0.271	0.244

♠ Female=0. Male=1
BMI=body mass index. BDNF=brain-derived neurotrophic factor.
*P<0.05

from the baseline, but did not reach statistical significance (*t=-0.198, p=0.845 (mania), t=-0.087, p=0.931* (depression), respectivity) (Table 3).

Discussion

The principal findings in this study, which focused on patients with bipolar disorder, are as follows: (1) there were decreased serum BDNF levels in patients with acute mania and depressive episodes of bipolar disorder, (2) BDNF levels were significantly lower in acute mania episodes of bipolar patients with violence (3) there was no alteration in serum BDNF levels after 4-week treatment.

■ BDNF Levels in acute phase (mania and depressive) and remission phase

Our data showed that the serum BDNF levels were significantly decreased in bipolar patients in a manic phase and depressive phase compared with BDNF levels in patients with bipolar disorder in remission phases. This finding corresponds with the result of some previous reports [11,14,17,27], but not all [13,28]. However, serum BDNF levels did not differ significantly between bipolar patients in a manic phase and a depressive phase, which is compatible with previous reports [13,28], and incompatible with the previous report [17]. Many studies have suggested BDNF levels are significantly reduced

Table 2: Serum BDNF levels and demographic data of 44 patients with acute manic episodes with clinical phenotypes.

Items	Age (years)	Sex♠	BMI (kg/m²)	Serum BDNF levels (ng/ml)
Suicide or not				
Suicide *(n=5)*	34.8 ± 14.8	0.60 ± 0.55	21.0 ± 2.1	3.6 ± 3.8
Non-suicide *(n=39)*	38.9 ± 10.9	0.41 ± 0.50	24.8 ± 5.5	5.8 ± 4.0
P value	0.453	0.432	0.141	0.243
Violence or not				
Violence *(n=9)*	43.6 ± 9.5	0.56 ± 0.53	23.2 ± 2.5	2.8 ± 2.6
Non-violence *(n=35)*	37.1 ± 11.4	0.40 ± 0.50	24.6 ± 5.9	6.3 ± 4.0
P value	0.126	0.413	0.273	0.025*
Family tendency				
Family history *(n=10)*	32.9 ± 12.4	0.30 ± 0.48	21.8 ± 5.7	6.5 ± 4.5
No family history *(n=34)*	40.0 ± 10.6	0.47 ± 0.51	25.1 ± 5.1	5.3 ± 3.9
P value	0.078	0.347	0.084	0.485

BMI=body mass index. BDNF=brain-derived neurotrophic factor.
♠ Female=0. Male=1
* P<0.05

Table 3: Demographic, clinical characteristics and BDNF levels of the 42 followed-up patients.

Items	Age	Baseline BMI (kg/m²)	BDNF protein (ng/mL) at baseline	BDNF protein (ng/mL) at endpoint	Pair t value	P value	YMRS	YMRS
Mania group								
Total (n=23)	39.5 ± 12.2	22.6 ± 3.2	4.3 ± 4.2	4.6 ± 6.7	-0.198	0.845	36.7 ± 7.6	8.0 ± 12.9
M (n=13)	42.4 ± 11.4	22.6 ± 2.9	4.9 ± 4.4	4.7 ± 7.8	0.078	0.939	37.1 ± 6.7	6.5 ± 9.8
F (n=10)	35.7 ± 12.7	22.6 ± 3.8	3.5 ± 4.0	4.5 ± 5.3	-0.959	0.363	36.1 ± 8.9	10.1 ± 16.5
							17-item HDRS at baseline	**17-item HDRS at endpoint**
Depression group								
Total (n=19)	34.8 ± 11.6	22.9 ± 3.6	4.4 ± 4.7	4.5 ± 4.1	-0.087	0.931	44.0 ± 7.0	6.3 ± 9.5
M (n=7)	42.9 ± 9.5	23.1 ± 4.7	4.8 ± 4.4	4.7 ± 4.0	0.069	0.947	47.9.6 ± 7.9	10.6 ± 14.8
F (n=12)	30.2 ± 10.2	22.7 ± 2.9	4.2 ± 5.0	4.4 ± 4.3	-0.120	0.906	41.8 ± 5.7	3.8 ± 3.0

BMI, body mass index; BDNF, brain-derived neurotrophic factor; YMRS, Young Mania Rating Scale; 17-item HDRS, 17-item Hamilton Depression Rating Scale.

during manic or depressive episode compared to healthy controls [13,14,27]. In addition, Piccinni, *et al.* found that the plasma BDNF levels were significantly decreased in the course of mixed episodes of bipolar disorder [29]. On the other hand, BDNF levels increased after treatments leading to clinical recovery of acute mania or depression [14,30,31]. The result of our study revealed the BDNF alteration as a potential marker in disease progression and treatment effectiveness. Although the above results need replication in independent studies with larger samples, we supposed that BDNF plays a key role in eliciting the dynamic neurobiological and clinical alterations observed in different phases.

■ BDNF Levels Before and after the 4-week Treatment

Our results revealed that the serum BDNF protein levels increased after a 4-week treatment, but this did not reach the statistical significance. This finding was compatible with previous report [9,31], but not with the results of other studies [32,33]. Whether the BDNF levels alter significantly after treatment or stay unchanged has been a matter of much debate, with discordant data [11,13,14,34]. The reasons for these conflicting findings include mood stabilizer or antipsychotics metabolic polymorphisms and other confounding factors, including differences in patient characteristics (such as duration of mood stabilizer or antipsychotics intake, different clinical profiles, and sample size) and the tested materials (serum *vs* plasma). The real impact of various mood stabilizer or antipsychotics on BDNF levels still needs further investigation.

■ BDNF levels in bipolar patients with different clinical phenotypes

Another important finding in this study is that serum BDNF levels in bipolar mania patients who had violence behaviors were lower than those in bipolar mania patients who did not have violence behavior. There is no data discussing about the association between violence in bipolar mania patients and BDNF levels. One possible interpretation for the low BDNF levels in violent patients is that impaired serotonin function would induce down regulation of BDNF expressions. The mechanism of BDNF modulate violence behavior may be considered via serotonin system. The importance of the 5-HT system in aggression is established [35] and may be found a negative relationship between cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT catabolism, and aggression in patients with personality disorders in the human studies [36]. Serotonin and BDNF have been linked to regulate neurogenesis, synaptic plasticity, and neuronal survival, and these two signals coregulate one another [37]. The relationship between BDNF and violence in bipolar disorder needed to be studied for demonstrating the ability of the BDNF to modulate aggressive behavior.

Limitation

First, the small sample size may have weakened the power of the statistical analyses. Second, prescription of mood-stabilizer and antipsychotics made the interpretation difficult. However, the same medications were maintained for at least four weeks before blood collection. Third, ELISA kit utilized in this study is unfortunately not able to discriminate between isoforms of BDNF (pro-BDNF and mature BDNF).

The fourth limitation was that BDNF levels were assessed in serum, thus representing an indirect measurement of brain BDNF levels.

Conclusion

Our study revealed that lower serum BDNF levels are associated with the depressive and manic phase of bipolar disorder than remission phase. There was no significant alteration in serum BDNF levels after medical treatment. In addition, bipolar mania patients with violence had lower BDNF levels than those without violence. In the future, studies with larger sample sizes are needed to investigate the relationships between BDNF levels and bipolar disorder.

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Statement of Interest

None

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