Serum Brain-Derived Neurotrophic Factor in Euthymic Bipolar Patients on Prophylactic Lithium Therapy

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Key Words

Bipolar disorder · Lithium · Brain-derived neurotrophic factor

Abstract

Aim: The aim of the study was to evaluate serum brain-derived neurotrophic factor (BDNF) levels in a group of euthymic bipolar patients on long-term prophylactic lithium treatment and to delineate putative relationships between lithium efficacy and BDNF concentrations. **Methods:** 141 euthymic bipolar patients (51 male, 90 female) on long-term lithium treatment were studied. Three categories of prophylactic lithium response were delineated: excellent lithium responders (ER; 30 patients), partial lithium responders (PR; 61 patients) and lithium nonresponders (NR; 50 patients). The control group consisted of 75 age- and gender-matched healthy subjects. **Results:** The lithium-treated patients as a whole group had lower BDNF levels compared to the healthy controls. However, after breaking down the patients into ER, PR and NR, it appeared that only NR had significantly lower BDNF levels compared with the healthy control subjects. No association between the age of the patients, duration of bipolar illness, and serum lithium and BDNF levels was found. **Conclusion:** The results point to a relationship between lithium prophylactic efficacy and plasma BDNF levels in euthy-

mic bipolar patients where lithium NR had reduced BDNF levels. These findings suggest that serum BDNF is associated with lithium efficacy in bipolar disorder.

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Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth factor family, which is involved in neuronal survival, differentiation, synaptogenesis and maintenance [1]. BDNF has been proposed as a candidate molecule in the pathophysiology of affective disorders [2–4].

Furthermore, an association between cognitive performance and BDNF gene, specific for bipolar illness, has been observed [5]. BDNF is present in the central nervous system and in peripheral blood, where it is stored in platelets and released in the plasma via activation of the clotting process [6]. Serum BDNF levels have been reported to significantly decrease in patients with major depressive disorder during acute episode [7–10] and to return to normal during remission [11]. The results of studies on peripheral BDNF levels in bipolar disorder (BD) are presented in table 1.

Table 1. Studies on serum BDNF in BD

Author	Studied group	Serum BDNF levels	Clinical correlates
Cunha et al. [12]	32 manic, 21 depressed, 32 euthymic BD-I patients and matched healthy controls	BDNF levels decreased in manic and depressed BD patients compared with euthymic patients and controls; no decrease in BDNF in euthymic patients	BDNF levels negatively correlated with severity of manic and depressive symptoms
Machado-Vieira et al. [13]	30 manic patients, 30 matched healthy controls	Mean BDNF levels significantly decreased in drug-free/naive patients compared to healthy controls	Severity of mania negatively correlated with plasma BDNF levels
Kauer-Sant'Anna et al. [14]	163 consecutive BD outpatients	Bipolar patients with a history of TE – increased prevalence of alcohol and anxiety comorbidity, and lower levels of serum BDNF ($p < 0.01$) compared to those without a history of TE	–
Gama et al. [15]	60 patients with schizophrenia, 30 euthymic BD patients, 26 healthy controls	BDNF levels significantly higher in SZ patients ($p < 0.001$) when compared to either controls or euthymic BD patients	–
Monteleone et al. [16]	24 euthymic UD, 17 euthymic BD-I, 11 euthymic BD-II and 11 depressed UD patients, 22 drug-free healthy controls (15 patients drug treated, remaining ones drug free for at least 4 weeks)	Compared to healthy controls, serum BDNF concentrations were significantly reduced in all patient groups with no significant difference among them; decreased serum BDNF levels in euthymic patients with UD, BD-I and BD-II	Drug treatments and comorbid psychiatric disorders had no effect on lowered circulating BDNF levels in affective patients
de Oliveira et al. [17]	22 manic and depressed drug-free, 22 medicated BD-I patients, 22 matched controls	BDNF levels in drug-free and medicated BD patients decreased when compared to controls; BDNF levels did not differ between medicated and drug-free BD patients	Results suggest that correlation of lower serum BDNF with BD mood episodes is maintained even in medicated patients
Fernandes et al. [18]	10 depressed MDD, 40 depressed BD-I patients, 30 healthy controls	BDNF levels in depressed BD patients lower compared to MDD patients and controls	Serum BDNF levels as an adjunct tool to discriminate bipolar from unipolar depression
Tramontina et al. [19]	10 BD patients with acute mania prospectively examined at inpatient unit admission and discharge	BDNF levels decreased in BD patients during mania compared to controls; this difference was no longer significant after treatment; sharp increase in BDNF levels after treatment of acute mania	BDNF serum levels may be associated with treatment response in acute mania
Kauer-Sant'Anna et al. [20]	60 patients with BD-I, 60 matched healthy controls	BDNF decreased only in patients in late stage of BD; BDNF levels significantly lower in later stage than early stage of BD	BDNF levels negatively correlated with length of illness

MDD = Major depressive disorder; TE = traumatic events; SZ = schizophrenia; UD = unipolar depression.

In most studies performed on bipolar patients, serum BDNF levels have been significantly reduced both during depressive and manic episodes, and negatively correlated with the severity of such an acute episode. Moreover, the BDNF levels have exhibited a tendency toward returning

to normal after successful pharmacological treatment and have remained normal during euthymia [12, 13, 16, 19, 21].

Preclinical studies suggest that the expression of BDNF might be a downstream target of antidepressant

treatments and mood stabilizers such as lithium and valproate. BDNF exerts antidepressant activity in animal models of depression [22, 23]. Antidepressants and chronic electroconvulsive treatments increase the expression of BDNF and its receptor in rat brain [24, 25]. Several studies have also demonstrated that lithium may increase the BDNF content in rat hippocampus and frontal cortex [26–29], which suggests that the regulation of neurotrophic factors might be associated with pharmacological effects of lithium [30].

Plasma BDNF levels in depressed patients significantly increase after antidepressant treatment; however, in some studies, such an increase has been observed only in groups of responders to treatment, while the change in nonresponders was not significant [9, 31–34]. That may suggest that antidepressant response may be associated with the increase in BDNF levels. Similarly, a decrease in plasma BDNF protein has been found in BD patients during acute (manic and depressive) episodes but not in euthymia [12], suggesting that the regulation of BDNF might be implicated in mood stabilization. Molecular genetic studies performed in Poznan have revealed that the effect of lithium prophylaxis is associated with the polymorphisms of the BDNF gene [35, 36].

A possible relationship between lithium prophylactic response and serum BDNF levels has not been investigated so far. The aim of this study was to assess whether there existed a relationship between the prophylactic efficacy of lithium and serum BDNF concentration.

Methods

Subjects

A total of 141 patients (51 male, 90 female), aged 30–77 years (mean $\pm$ SD: 53.7 $\pm$ 12.7 years) with bipolar affective disorders attending the Outpatient Lithium Clinic at the Department of Psychiatry of the Poznan University of Medical Sciences were studied. A consensus diagnosis by 2 psychiatrists was made for each patient, according to DSM-IV criteria (Structured Clinical Interview for DSM-IV Axis I Disorders) [37]. The patients had been treated with lithium carbonate for at least 5 years (5–27 years; mean: 15.7 years). The patients had been attending the same outpatient clinic for the entire period of lithium administration. The serum concentration of lithium had been maintained in the range between 0.5 and 0.8 mmol/l. The course of illness was assessed retrospectively, based on the analysis of medical outpatient charts, inpatient records and semi-structured interviews, as described previously [35]. On the day of study, all patients were euthymic, defined on the 17-item Hamilton Depression Rating Scale [38] as a score of 7 or less, and on the Young Mania Rating Scale [39] as a score of 7 or less.

The efficacy of lithium treatment was assessed according to the following criteria: excellent lithium responders (ER) had no affective episodes on lithium; partial lithium responders (PR) showed a 50% reduction in the episode index (number of episodes per year compared to pre-lithium period), and lithium nonresponders (NR) showed a <50% reduction, no change or worsening on the episode index. To all ER, lithium had been given as a monotherapy. Among the remaining patients, 20 had been concomitantly receiving carbamazepine (PR: 6; NR: 14), 9 valproates (PR: 4; NR: 5), 15 antidepressant drugs (PR: 7; NR: 8) and 14 neuroleptic drugs (PR: 4; NR: 10) for a period of several years. None of the patients was treated with electroconvulsive therapy. There were no pregnancies in patients studied during lithium treatment, either.

Seventy-five healthy controls were matched by age and gender. The control subjects had no history of major psychiatric disorders, dementia, mental retardation and severe/unstable somatic diseases.

The study was approved by the ethics committee at the Poznan University of Medical Sciences. All subjects gave their written consent after the nature of the procedures had been fully explained to them.

BDNF Assessment

First, 10 ml of blood was drawn from each subject by venipuncture into a free-anticoagulant vacuum tube for biochemical analyses. BDNF serum levels were measured using a commercial kit of sandwich ELISA according to the manufacturer's instruction (Quantikine; R&D Systems Inc., Minneapolis, Minn., USA). All the assays of BDNF levels were performed blind to the subjects' clinical response to lithium and to their status (ER, PR and NR).

Statistical Analyses

All statistical analyses were carried out by Statistica version 8.0 for Windows. As most of the variables investigated were not normally distributed, nonparametric tests were employed. Inter-group differences were assessed by the Mann-Whitney test (2-group comparisons) and Kruskal-Wallis ANOVA (comparisons among more than 2 groups). All results were expressed as means and SD.

Results

In our group, 30 patients (21.3%) were classified as ER, 61 patients (43.3%) as PR and 50 patients (35.4%) as NR to lithium treatment. The clinical characteristics of the group of patients are presented in table 2.

The age at the onset of illness, duration of treatment with lithium as well as the number of affective episodes before lithium treatment did not differ between these 3 subgroups of patients. ER did not have any affective episodes on lithium, and the number of affective episodes during lithium treatment was greater in NR compared to PR. NR had a lower lithium dose compared to the re-

Table 2. Clinical characteristics of lithium-treated bipolar patients and controls

	Patients (n = 141)	ER (n = 30)	PR (n = 61)	NR (n = 50)	Controls (n = 75)
M:F ratio, n	51:90	11:19	18:43	22:28	23:52
Age, years	53.7 ± 12.7	58.1 ± 13.3	53.5 ± 12.0	51.3 ± 12.7	55.7 ± 11.7
Duration of illness, years	24.4 ± 10.8	24.9 ± 12.6	22.9 ± 10.2	25.7 ± 10.0	–
Duration of lithium treatment, years	15.7 ± 8.9	14.8 ± 8.7	16.7 ± 8.6	15.2 ± 9.6	–
Number of episodes before lithium	7.1 ± 5.2	7.5 ± 4.2	7.6 ± 6.7	6.3 ± 3.4	–
Number of episodes on lithium	5.2 ± 6.1	0.0 ± 0.0	4.6 ± 3.3	10.4 ± 7.2 ^{1, 2}	–
Lithium carbonate dose, mg/day	1,035.4 ± 227.6	1,042.9 ± 249.5	1,057.1 ± 212.3	992.3 ± 239.7 ^{1, 2}	–
Serum lithium level, mmol/l	0.67 ± 0.06	0.65 ± 0.05	0.67 ± 0.07	0.68 ± 0.07	–

Values denote means ± SD. ¹ p < 0.01, difference between ER and NR. ² p < 0.01, difference between PR and NR (Mann-Whitney test).

Table 3. Serum BDNF levels in lithium-treated bipolar patients and controls

	Patients (n = 141)	Controls (n = 75)	ER (n = 30)	PR (n = 61)	NR (n = 50)
Serum BDNF level, ng/ml	24.2 ± 17.0 ¹	27.4 ± 10.4	26.7 ± 16.8	26.5 ± 17.9	21.9 ± 15.5 ²

Values denote means ± SD. ¹ p = 0.051, difference between lithium-treated patients and healthy controls; ² p = 0.025, difference between NR and healthy controls.

Table 4. Correlations of serum BDNF levels with clinical factors

	Lithium group (n = 141)	ER (n = 30)	PR (n = 61)	NR (n = 50)
Age	–0.07 (0.39)	0.01 (0.98)	–0.17 (0.19)	–0.05 (0.71)
Duration of illness	–0.18 (0.09)	–0.15 (0.46)	–0.25 (0.15)	–0.16 (0.40)
Duration of lithium treatment	–0.16 (0.14)	–0.09 (0.65)	–0.18 (0.31)	–0.17 (0.37)
Number of episodes before lithium	–0.05 (0.61)	–0.30 (0.14)	0.12 (0.50)	–0.09 (0.64)
Number of episodes on lithium	–0.05 (0.63)		–0.06 (0.71)	0.17 (0.36)
Serum lithium level	0.04 (0.80)	–0.09 (0.75)	–0.23 (0.34)	0.46 (0.10)

Values denote Spearman's ρ with p in parentheses.

maintaining lithium groups; however, the plasma lithium level was similar in all lithium groups.

A comparison of the BDNF levels in the patients with various responses to lithium treatment with the controls is presented in table 3.

The lithium-treated patients as a whole group had lower BDNF levels compared to the healthy controls (p = 0.051; Mann-Whitney test). However, after breaking down the patients into ER, PR and NR, it appeared that

only NR had significantly lower BDNF levels compared with healthy control subjects (p = 0.025; Mann-Whitney test). The serum BDNF levels of ER and PR were similar to those of the healthy controls.

The correlation of serum BDNF levels with clinical factors is presented in table 4. No associations of BDNF levels with the age of the patients, duration of bipolar illness and clinical course before and during lithium treatment, or with lithium level were found.

In the group of NR, no relationships between serum lithium level, the use of additional medications and serum carbamazepine or valproic acid levels were found.

Discussion

The main finding of our study is to have demonstrated that in euthymic bipolar patients who did not benefit from lithium prophylactic treatment, serum BDNF levels were significantly lower than in healthy controls. On the other hand, in ER and PR, the levels were comparable to those of healthy subjects.

The results obtained may correspond to other pharmacological studies showing the relationship between BDNF level and the therapeutic response to drugs used in mood disorders. In major depressive disorder, normalization of BDNF levels has been associated with clinical response to antidepressant treatment [9, 32–34]. In BD, it may also be inferred that, while BD patients in remission have a serum level of BDNF similar to that of healthy controls, and the BDNF levels of patients during mania or depression are reduced, a normalization of BDNF levels might be connected with clinical response to pharmacological treatment [12, 40].

On the other hand, the finding of this study may also correspond to the results of our previous studies measuring the association between lithium response and cognitive and neuropsychological function in euthymic patients on lithium. The study by Rybakowski et al. [5] shows that, compared with healthy controls, cognitive functions as measured by the Wisconsin Card Sorting Test are preserved in ER and PR, but significantly impaired in NR. Similarly, in the study by Suwalska et al. [41], a sustained attention deficit measured during eu-

thymia was significantly smaller in ER than in PR and NR.

These findings suggest that serum BDNF is associated with lithium efficacy in BD, but the causation has not been fully elucidated. BDNF could be involved in the mechanism of lithium mood-normalizing action, or the response to lithium may lead to changes in BDNF levels.

We did not find associations between BDNF levels and patients' age, duration of illness, number of episodes before and during lithium treatment, and serum lithium level. This finding is in accordance with the study by Monteleone et al. [16], in which no significant correlations have been found between serum BDNF levels and age of controls and patients, age at the onset of illness, duration of illness and number of depressive episodes either in the entire patient sample or in each diagnostic group. We did not confirm the results of the study by Kauer-Sant'Anna et al. [20], in which BDNF levels were negatively correlated with length of illness.

A limitation of our study could be the lack of assessment of serum BDNF levels in bipolar patients before commencement of lithium treatment. On the other hand, the length of lithium treatment allowed to precisely assess the quality of the lithium prophylactic effect in all patients. Our findings showing decreased serum BDNF levels in BD patients who are unresponsive to prophylactic lithium may support the hypothesis of a role of BDNF in the therapeutic action of lithium in BD.

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