Plasma brain-derived neurotrophic factor in bipolar and unipolar depression

BDNF nelle depressioni bipolare ed unipolare

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Summary

Objective

There is increasing evidence that Brain-Derived Neurotrophic Factor may be involved in the pathophysiology of depression and the actions of antidepressants. At the same time, the differential diagnosis between unipolar and bipolar depression is often a challenge with important treatment implications. The aim of the present study was to analyze the relationship between Brain-Derived Neurotrophic Factor levels and clinical variables in subjects with unipolar versus bipolar depression.

Method

Thirty-three outpatients (17 with unipolar and 16 with bipolar depression) and 15 healthy controls were consecutively enrolled at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies of the University of Pisa. Brain-Derived Neurotrophic Factor concentrations were measured with an enzyme-linked immunosorbent assay method. Severity of depression was assessed by means of the 21-item Hamilton Rating Scale for Depression and the Clinical Global Impressions – Severity of Illness scale. Fifteen healthy subjects, with no history of past or current chronic physical or mental disorders and not taking regular medications, were recruited as the control group.

Results

Compared to healthy controls, plasma Brain-Derived Neurotrophic Factor concentrations were significantly reduced in patients with unipolar or bipolar depression, with no significant difference between the two groups. Statistical analyses showed significant intergroup differences in the age of onset, presence of psychotic symptoms and cognitive disturbances (Table I). Significant and negative correlations were found in the total sample between Brain-Derived Neurotrophic Factor levels and the Hamilton Rating Scale for Depression total scores ($r = -0.511$, $p = 0.002$), the retardation factor scores ($r = -0.416$, $p = 0.016$) and Clinical Global Impressions "severity of illness" scores ($r = -0.385$, $p = 0.027$). When the same analyses were repeated in each group separately, these findings were confirmed only in patients with bipolar depression (Figs. 1, 2).

Conclusion

Our results show that lower Brain-Derived Neurotrophic Factor levels may be related to both severity of depression and retardation symptoms in bipolar depression. Further studies need to ascertain whether and how the Brain-Derived Neurotrophic Factor levels may be associated with any psychopathological dimensions of the depressive state and be used as a biological marker to differentiate bipolar from unipolar depression.

Key words

Brain-Derived Neurotrophic Factor • Plasma • Unipolar depression • Bipolar depression

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Introduction

Several findings suggest an important role of Brain-Derived Neurotrophic Factor (BDNF) in the pathophysiology of mood disorders [1-4]. Specifically, decreased serum and plasma BDNF levels have been reported in major depressive disorder (MDD) patients than in normal control subjects [5-9]. The relationship between serum BDNF levels and the severity of illness may suggest a role of BDNF as a biomarker of affective episodes [3].

The use of medication in studies of serum BDNF levels in bipolar disorder (BD) has been always considered a potential bias [10], since strong and consistent evidence suggests that antidepressant treatment normalize serum BDNF levels [5 7]. Only a recent study reported for the first time decreased BDNF levels in euthymic patients with unipolar and bipolar (type I and II) depression, regardless of the medication status [11]. Moreover, lower serum BDNF levels is confirmed both in medicated and drug-free bipolar patients which strengthens the notion that BDNF levels may be considered a biomarker of mood episodes in BD independently from drug treatment [10]. However, the potential utility of BDNF levels as a biomarker for illness and antidepressant efficacy remains still unclear.

BDNF changes in depression have been related to clinical characteristics, such as severity of illness [12] or presence of psychotic symptoms [13]. A recent study showed that, in depressed patients, low BDNF levels are related to duration and severity of depression, as well as to core symptoms, such as retardation, dissociative symptoms and sleep disturbances [14].

To our knowledge, although it has been hypothesized that BDNF levels may be an adjunctive tool to discriminate bipolar from unipolar depression [15], no study explored the relationship between BDNF levels and clinical variables in subjects with unipolar versus bipolar depression.

In view of the paucity of information on this topic, the aim of the present study was to investigate BDNF plasma levels in unipolar vs. bipolar depressed patients, and to explore the possible relationships between this biological parameter and the clinical features of the illness.

Methods

Subjects

Thirty-three outpatients (21 women and 12 men, age between 22 and 65 years, mean ± SD: 46.4 ± 14.3), suffering from a current major depressive episode, were consecutively enrolled in the study at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies of the University of Pisa. Patients met Diagnostic and Statistical Manual for Mental Disorders [16] criteria for unipolar (n = 17) and bipolar type I (n = 16) depressed patients. The diagnosis was made by senior psychiatrists and confirmed by means of the Mini International Neuropsychiatric Interview (MINI) [17]. Exclusion criteria were the following: 1) presence of organic brain disorder, 2) substance abuse, 3) pregnancy, 4) any severe or chronic physical illness. Patients were either medication-naïve (n = 6), drug-free at least for 2 weeks (n = 9) or medicated (n = 18) with different combinations of drugs. No woman took contraceptive drugs, 7 women were in menopause. All fertile women were tested in the mid-follicular phase.

Affective symptomatology was measured by means of the 21-item Hamilton Rating Scale for Depression ($HRSD_{21}$) [18] and the Clinical Global Impressions – Severity of Illness scale (CGI-S) [19]. Major depressive Episode was defined by a $HRSD_{21}$ total score of 24 or higher and a CGI score of 4 or higher, as assessed by experienced research clinicians.

Fifteen healthy subjects (3 men and 12 women, mean age ± SD: 36.9 ± 9.2 years), with no history of past or current chronic physical or mental disorders and not taking regular medications, were recruited as the control group.

Before entering the study, patients gave written, informed consent. The study was approved by the Ethics Committee of the University of Pisa in accordance with the declaration of Helsinki (1996) and with the guidelines of Good Clinical Practice (1995).

Brain-Derived Neurotrophic Factor Assay

Ten ml of venous blood were drawn in the morning, between 8:00 and 9:00 a.m., following overnight fasting, into EDTA-coated tubes that were kept on ice, centrifuged at 2000xg for 10 minutes at 4°C and refrigerated at -20°C. To measure the amount of total BDNF, acidification and subsequent neutralization of the samples followed before proceeding with the enzyme-linked immunosorbent assay (ELISA) protocol, according to the manufacturer's instruction (Promega, Wallisellen, Switzerland). Ninety-six-well plates were coated with anti-BDNF monoclonal antibody and incubated at 4°C for 18 hours. The plates were incubated in

a blocking buffer for 1 hour at room temperature, then samples were added. The samples and BDNF standards were maintained at room temperature and shook for 2 hours, then washed with the appropriate buffer. The plates were then incubated with anti-human BDNF polyclonal antibody at room temperature for 2 hours, washed and incubated with anti-IgG antibody conjugated to horseradish peroxidase for 1 hour at room temperature. The plates were incubated in peroxidase substrate and tetramethylbenzidine solution to produce a colour reaction. The reaction was stopped with 1 M HCl. The absorbance at 450 nm was measured with a microplate reader (Model 550, Bio Rad Laboratories) to determine BDNF values that are expressed as pg/ml.

Statistical analyses

Since BDNF levels and HRSD scores were not normally distributed, non-parametric tests were used. To compare these variables between two independent samples, the Mann-Whitney test was used. To compare continuous and categorical variables, Student's T-test and the Chi-square or Fischer's test were used, respectively. To analyse the relationship between variables, Spearman's correlation was conducted. A p value of $< .05$ was set as threshold for statistical significance. All analyses were carried out using the SPSS version 14.0, by means of personal computer programmes.

Results

Demographic characteristics, clinical features and plasma BDNF levels are shown in Table I. No significant difference in gender distribution was detected among the groups. Compared to healthy control subjects, plasma BDNF concentrations were significantly reduced in both unipolar and bipolar depressed patients with no significant difference among them. Statistical analyses showed significant intergroup differences in the age of onset, presence of psychotic symptoms and cognitive disturbances (Table I).

Significant differences were detected between unipolar and bipolar depressed patients in the

TABLE I.
Demographic, clinical and biological characteristics of the study sample. *Caratteristiche demografiche, cliniche e biologiche del campione in studio.*

	Unipolar depressed patients (n = 17)	Bipolar depressed patients (n = 16)	Healthy subjects (n = 15)	p
Age (mean ± SD), years	46.06 ± 10.78	46.75 ± 17.67	46.9 ± 9.2	N.S.
Gender, female	13 (76.5%)	8 (50%)	12 (80%)	N.S.
Age at onset (mean ± SD), years	36.94 ± 12.26	25.81 ± 12.83	N/A	0.016
Psychotic symptoms	1 (5.9%)	10 (62.5%)	N/A	0.001
Lifetime comorbid psychiatric disorders	9 (52.9%)	11 (68.8%)	N/A	N.S.
HRSD21 (mean ± SD)	23.00 ± 5.66	27.81 ± 5.27	N/A	0.010
CGI (mean ± SD)	4.29 ± 0.59	5.44 ± 0.63	N/A	0.000
HRSD factor score (mean ± SD) – Anxiety/somatization – Weight – Cognitive disturbances – Diurnal variation – Retardation – Sleep disturbance	 1.29 ± 0.18 0.71 ± 0.77 0.62 ± 0.51 0.79 ± 0.66 1.47 ± 0.68 0.86 ± 0.44	 1.35 ± 0.41 0.31 ± 0.70 1.19 ± 0.38 0.47 ± 0.56 2.45 ± 0.42 0.60 ± 0.41	N/A	 N.S. N.S. 0.002 N.S. 0.000 N.S.
BDNF plasma levels (mean ± SD, pg/ml)	3024.49 ± 1790.23	2119.02 ± 1339.85	5400 ± 2.3	< .01 (UD *vs*. CS) < .001 (BD *vs*. CS)

HRSD: Hamilton Rating Scale for Depression; BDNF: Brain-Derived Neurotrophic Factor.

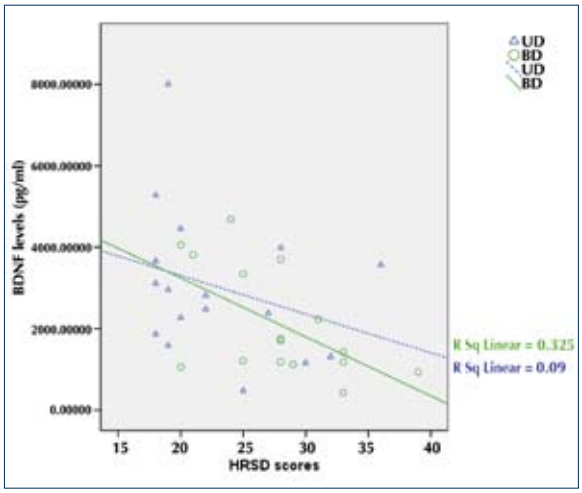

FIGURE 1.
Relationship between plasma BDNF levels and total HRSD scores in patients with unipolar and bipolar depression. *Associazione tra i livelli plasmatici di BDNF ed i punteggi totali all'HRSD nei pazienti con depressione uni- e bipolare.*

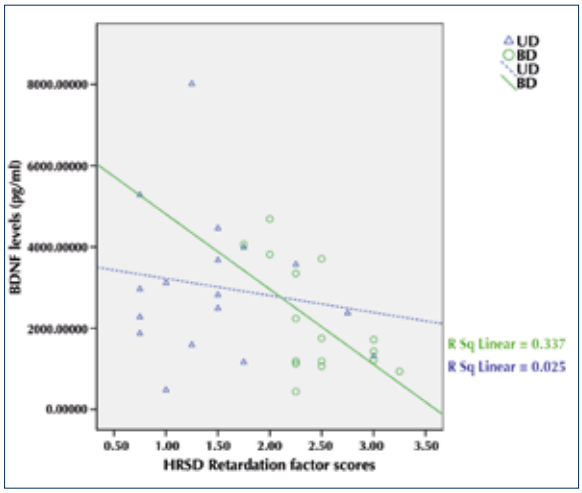

FIGURE 2.
Relationship between plasma BDNF levels and the HRSD Retardation factor scores in patients with unipolar and bipolar depression. *Associazione tra i livelli plasmatici di BDNF ed il punteggio al fattore "Rallentamento" dell'HRSD nei pazienti con depressione uni- e bipolare.*

HRSD total score, which was 23.00 ± 5.66 and 27.81 ± 5.27, (mean ± SD; p = 0.001) and CGI "severity of illness" item score, which was 4.29 ± 0.59 and 5.44 ± 0.63 (mean ± SD; p = 0.001) in the unipolar and bipolar patients, respectively. Of the 18 medicated patients, 16 (88.9%) were bipolar, 2 (11.1%) unipolar. BDNF levels did not significantly differ between medicated and drug-free patients (p = 0.065).

Significant and negative correlations were found in the total sample between BDNF levels (mean ± SD, pg/ml) and the HRSD total scores (r = -0.511, p = 0.002), the retardation factor scores (r = -0.416, p = 0.016) and CGI "severity of illness" item scores (r = -0.385, p = 0.027). When the same analyses were repeated in each group separately, the previous findings were confirmed only in the bipolar depressed patients (Figs. 1, 2).

Discussion

This study explored the relationship between plasma BDNF levels and clinical features in patients with unipolar and bipolar depression. We showed a significant negative correlation between BDNF levels and total HRSD scores and CGI "severity of illness" scores, in the whole sample and only in the bipolar group. Moreover, even the HRSD retardation factor scores was negatively correlated with BDNF levels in the total sample and in the bipolar group. BDNF levels in bipolar patients were decreased, but not significantly, when compared to unipolar patients, despite drug treatment status. The significant difference in severity of illness between the two groups might partially explain this result, confirming the hypothesis that BDNF levels normalisation was related to the clinical improvement, rather than drug treatment itself. These findings are in agreement with Monteleone et al. [11], who reported no significant difference in serum BDNF levels between drug-free and drug-treated unipolar and bipolar patients. Another study strengthens the notion that BDNF serum levels may be considered a biomarker of mood episodes in bipolar disorder, regardless medication status, showing lower concentrations even in medicated bipolar patients [10]. Several authors [20-22] provided preliminary evidence in bipolar patients that the key factor for restoring BDNF serum levels may not be the medication itself, but rather clinical improvement.

Even the HRSD retardation factor scores was correlated negatively with BDNF levels in the total sample and in the group of bipolar patients. This finding is consistent with the notion that psychomotor retardation is one of the core symptoms of bipolar depression, where it occurs more frequent-

ly respect to unipolar depression [23-25]. As previously reported, psychomotor retardation has been linked generally to the severity of the illness [24] or to melancholia [26]. An HPA axis dysfunction in some phenotypes of depressed patients, particularly the melancholic ones [27 28], may cause decreased BDNF expression and impaired hippocampal neurogenesis which has been linked to the development of depression [29-31].

This study suffers several limitations. The most important was that sample size was small; furthermore, there was an unbalanced gender distribution in the unipolar group favouring women. Another problem was related to the higher severity of depression, as measured by the CGI and HRSD total scores, in bipolar, when compared to unipolar patients. The significantly different severity of illness between the two groups might partially explain the fact that a significant correlation between BDNF levels and clinical features was found only in bipolar patients.

In conclusion, our results show that lower BDNF levels may be related to both severity of depression and retardation symptoms in bipolar depression. Further studies need to ascertain whether and how BDNF levels may be used as a biological marker to differentiate bipolar from unipolar depression.

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