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Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes

Angelo B.M. Cunha [a], Benicio N. Frey [b,c], Ana C. Andreazza [b,c], Júlia D. Goi [a], Adriane R. Rosa [c], Carlos A. Gonçalves [b], Aida Santin [c], Flavio Kapczinski [c,*]

[a] *Department of Neuropsychiatry, Centro de Ciências da Saúde, Universidade Federal de Santa Maria, Faixa de Camobi Km 9, 97105 900 Santa Maria, RS, Brazil*
[b] *Department of Biochemistry, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2600/Anexo, 90035 003 Porto Alegre, RS, Brazil*
[c] *Bipolar Disorders Program, Centro de Pesquisas, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, 90035 003 Porto Alegre, RS, Brazil*

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Abstract

Genetic and pharmacological studies have suggested that brain-derived neurotrophic factor (BDNF) may be associated with the pathophysiology of bipolar disorder (BD). The present study investigated serum BDNF levels in manic, depressed, euthymic BD patients and in matched healthy controls, using an enzyme-linked immunosorbent assay (sandwich-ELISA). Serum BDNF levels were decreased in manic ($p = 0.019$) and depressed ($p = 0.027$) BD patients, as compared with euthymic patients and controls. Serum BDNF levels were negatively correlated with the severity of manic ($r = -0.37$, $p = 0.005$) and depressive ($r = -0.30$, $p = 0.033$) symptoms. These findings further support the hypothesis that the BDNF signaling system may play a role in the pathophysiology of BD.

Keywords: Bipolar disorder; Brain-derived neurotrophic factor; Depression; Mania; Mood stabilizers; Pathophysiology

Bipolar disorder (BD) is a prevalent, highly disabling illness, characterized by the presence of manic and depressive symptoms [1]. Although genetic and familial studies strongly suggest that a neurobiological basis may underlie the pathophysiology of BD [13], its exact etiology is poorly understood. Gene studies have consistently demonstrated that genetic heritability increases the predisposition to BD [3]. In addition, several family based association studies have reported that polymorphisms in the brain-derived neurotrophic factor (BDNF) gene may be involved in the pathophysiology of BD [7,14,17,23]. In particular, one single nucleotide polymorphism, caused by the substitution of valine to methionine at codon 66 (val66met), has been associated with poorer neuropsychologial performance [20] and better response to lithium prophylaxis [21]. Pharmacological studies have demonstrated that the mood stabilizers lithium and valproate modulate intracellular signaling pathways associated with neuronal plasticity and survival [2]. Further, it has been demonstrated that chronic administration of lithium and valproate increased BDNF expression in rat brain [6] and that the induction of the BDNF/TrkB pathway underlies some neuroprotective effects of lithium [9]. Previous studies have reported that serum BDNF is reduced in major depression (unipolar) disorder [10,22] and in drug-naïve and lithium-treated manic BD patients [16]. The present study aims to investigate serum BDNF levels in BD patients during mania, depression and euthymia, as compared to healthy controls.

The present study was approved by the local ethics committee (Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil) and all subjects provided written informed consent before entering in the study. Thirty-two euthymic, 21 depressed, and 32 manic patients were recruited from the Bipolar Disorders Program—Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, and the Inpatient Psychiatric Unit—Hospital Universitário de Santa Maria, Santa Maria, Brazil. Diagnoses were carried out using the Structured Clinical Interview for DSM-IV-Axis I (SCID-I) [5]. In this study, only BD type-I patients were

* Corresponding author. Tel.: +55 513 2227309; fax: +55 512 1018846.
E-mail address: kapcz@terra.com.br (F. Kapczinski).

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Table 1
Characteristics of bipolar disorder patients and healthy controls

	Control group	Bipolar patients			*p*-value
		Euthymic	Manic	Depressed	
Gender (female)	65.6%	62.5%	43.8%	71.4%	0.162*
Mean age (S.D.), years	40.69 (12.12)	40.28 (11.99)	40.13 (12.6)	40.71 (9.25)	0.997**
Mean years of schooling (S.D.)	8.69 (3.64)	9.94 (4.80)	7.69 (3.65)	7.53 (4.77)	0.117**
Mean number of medications (S.D.)	–	2.41 (0.95)	3.41 (1.39)	2.86 (1.23)	0.016**
Mean age of first mood episode (S.D.)	–	23.13 (11.38)	27.19 (10.87)	21.24 (13.89)	0.320**
Mean years of illness (S.D.)	–	17.34 (11.88)	12.78 (9.62)	19.50 (14.17)	0.209**
Mean HDRS score (S.D.)	–	4.28 (4.16)	5.16 (3.39)	22.81 (4.36)	0.001**
Mean YMRS score (S.D.)	–	3.16 (5.44)	34.47 (7.06)	5.10 (3.19)	0.001**
Presence of psychotic symptoms	–	12.5%	68.8%	28.6%	0.001*
Mean serum BDNF (S.D.) pg/μL Protein	0.20 (0.07)	0.19 (0.08)	0.14 (0.04)	0.15 (0.13)	0.019[a] 0.027[b]

HDRS, hamilton depression rating scale; YMRS, young mania rating scale; BDNF, brain-derived neurotrophic factor.
* Chi-square test.
** One-way ANOVA test.
[a] Manic vs. euthymic/control.
[b] Depressed vs. euthymic/control.

enrolled. Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) [25] and the Hamilton Depression Rating Scale (HDRS) [8], respectively. Patients were considered euthymic if they scored <7 on both YMRS and HDRS scales. Manic and depressed patients fulfilled criteria for current manic or depressive episode, respectively, according to SCID-I. The control group consisted of 32 healthy volunteers matched by age, gender and education, who manifested interest in participating in the study. Psychiatric assessment was carried out using SCID-I, non-patient version. Control subjects were non-smokers, were not on medication, and had no history of major psychiatric disorders, dementia, mental retardation, cancer or tumor in their first-degree relatives.

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at 3000 × *g* for 5 min, and serum was kept frozen at −80 °C until assayed. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluents and standard curve ranged from 7.8 to 500 pg of BNDF. Plates were then washed four times with wash buffer, added monoclonal anti-BNDF rabbit antibody (diluted 1:1000 with sample diluents), and incubated for 3 h at room temperature. After washing, a second incubation with anti-rabbit antibody peroxidase conjugated (diluted 1:1000) for 1 h at room temperature was carried out. After addition of streptavidin-enzyme, substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin as a standard.

The outcome measures of the four groups were compared using the one-way ANOVA test for heterogeneity. The individual differences were assessed using a Tukey test if the ANOVA was significant. Pearson's correlation coefficient was performed to examine the relationship between YMRS and HDRS with serum BDNF levels. *p*-values <.05 were considered significant.

The characteristics of BD patients and controls are summarized in Tables 1 and 2. BD patients and controls did not differ in terms of gender, age or years of schooling. BD patients were similar in age of first mood episode and length of illness. As expected, manic patients had significantly higher rates of manic symptoms than depressed and euthymic patients ($p = 0.001$) and depressed patients had significantly higher rates of depressive symptoms than manic and euthymic patients ($p = 0.001$). In addition, manic patients had significantly more psychotic symptoms (presence of delusions or hallucinations) than depressed or euthymic BD subjects ($p = 0.001$). Serum BDNF levels were lower in BD patients during both manic ($p = 0.019$) and depressive ($p = 0.027$) episodes, as compared with euthymic patients and healthy controls (Fig. 1, Table 1). This finding suggests that the effects of pharmacological treatment on BDNF levels may be associated with mood stabilization. In addition, serum BDNF levels were negatively correlated with YMRS ($r = -0.37$, $CI_{95\%}$

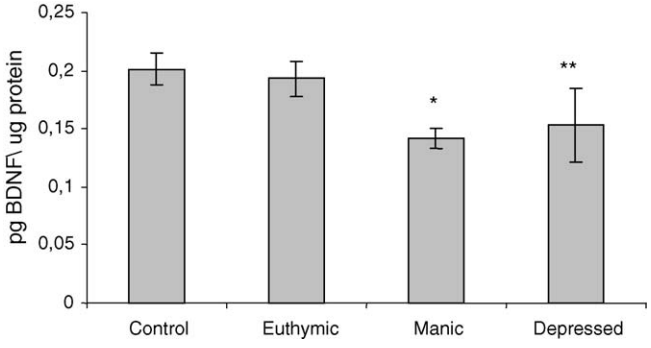

Fig. 1. Serum BDNF levels in BD patients and healthy controls. Legend: one-way ANOVA; Tukey posttest; $p = 0.019$; $p = 0.027$.