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Increased neurotrophin-3 in drug-free subjects with bipolar disorder during manic and depressive episodes

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ABSTRACT

Bipolar disorder (BD) has been increasingly associated with abnormalities in neuroplasticity. Previous studies demonstrated that neurotrophin-3 (NT-3) plays a role in the pathophysiology of mood disorders. The influence of medication in these studies has been considered a limitation. Thus, studies with drug-free vs. medicated patients are necessary to evaluate the role of medication in serum NT-3 levels. About 10 manic and 10 depressive drug-free, and 10 manic and 10 depressive medicated patients with BD type I were matched with 20 controls for sex and age. Patients were assessed using SCID-I, YMRS and HDRS. Serum NT-3 levels in drug-free and medicated patients is increased when compared with controls (2.51 ± 0.59, 2.56 ± 0.44 and 1.97 ± 0.33, respectively, $p < 0.001$ for drug-free/medicated vs. control). Serum NT-3 levels do not differ between medicated and drug-free patients. When analyzing patients according to mood states, serum NT-3 levels are increased in both manic and depressive episodes, as compared with controls (2.47 ± 0.43, 2.60 ± 0.59 and 1.97 ± 0.33, respectively, $p < 0.001$ for manic/depressive patients vs. controls). There is no difference in serum BDNF between manic and depressive patients. Results suggest that increased serum NT-3 levels in BD are likely to be associated with the pathophysiology of manic and depressive symptoms.

1. Introduction

Bipolar disorder (BD) is a highly disabling illness, characterized by the presence of manic and depressive symptoms (Yatham et al., 2009). Although a growing body of evidence strongly suggests that a neurobiological basis may underlie the pathophysiology of BD, its etiology is poorly understood. In recent years, many psychiatric disorders, particularly mood disorders such as BD, have been recognized as conditions that affect neurotrophins (Cunha et al., 2006; Gama et al., 2007; Walz et al., 2007; Kapczinski et al., 2008a,b; de Oliveira et al., 2009; Fernandes et al., 2009a; Kapczinski et al., 2009a,b). An emerging body of evidence links the expression of these neurotrophic factors to mood disorders. Brain-derived neurotrophic factor (BDNF) is so far the best studied member of this family, being put forward as a predictor of response to treatment (Kapczinski et al., 2008a; Fernandes et al., 2009b; Kapczinski et al., 2009a; Tramontina et al., 2009) and as a possible biomarker of diagnosis to discriminate unipolar from bipolar depression (Fernandes et al., 2009a). Neurotrophin-3 (NT-3), an important member of the neurotrophin family, couples to the same signal transduction pathways as BDNF through their respective receptors. Decreased expression of these factors could lead to alterations in the structure and function of subpopulations of hippocampal neurons (Duman and Monteggia, 2006). In addition, it has been reported that NT-3 modulates basal synaptic transmission and long-term potentiation in rat hippocampus (Kato et al., 2003).

There is a paucity of studies about NT-3 in peripheral serum. To our knowledge, there is only one report of serum NT-3 levels in BD, which shows that NT-3 is increased during both manic and depressive episodes, but not in euthymia (Walz et al., 2007).

A question that frequently emerges in studies about serum neurotrophins in BD is the influence of medication use. This is considered to be an important limitation in most of the studies concerning neurotrophins. Little is known about whether the use

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of medication in these studies alters their final results. Recently, we have shown that serum BDNF levels are similar in BD regarding subjects on and off medication (de Oliveira et al., 2009). As aforementioned, serum NT-3 data are scarce in the BD field; whether the use of mood stabilizers and antipsychotics plays or not a role in serum NT-3 levels in mood states of BD remains unclear. Therefore, there is a need for studies that compare serum NT-3 in patients on and off medication.

The aim of this report is to investigate whether drug-free patients have differential levels of circulating serum NT-3 levels, when compared to medicated patients with BD. For this purpose, we evaluated serum NT-3 concentrations in medicated and drug-free BD type I during manic and depressive episodes.

2. Methods and materials

2.1. Subjects and measurement

Manic and depressive drug-free and medicated patients with BD type I were recruited from the Bipolar Disorders Program and Psychiatry Inpatient Unit – Hospital de Clinicas de Porto Alegre and Pronto Atendimento da Vila Cruzeiro do Sul, Porto Alegre, Brazil, between 2006 and 2008. To be included in this study, patients had to present with a manic or depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) and Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID-I) criteria. The diagnosis of manic and depressive episodes was established according to SCID-I (APA, 2000). The severity of manic and depressive episodes was evaluated using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), respectively.

Twenty drug-free patients (10 manic and 10 depressed) were included in this study. This group did not receive any psychotropic medication for at least two weeks (five weeks if fluoxetine or *depot* medication was used) before blood sampling. The 20 medicated patients (10 manic and 10 depressed) and 20 controls were matched for age and gender to drug-free bipolar subjects. Controls were recruited from the Hospital de Clinicas de Porto Alegre catchment area. This group was screened with the non-patient version of the SCID to exclude current psychiatric morbidity. Those that had first-degree relatives with BD, schizophrenia or other psychiatric disorders were excluded. Controls were not on medication. All participants gave a written informed consent before entering the study, which was approved by the local ethics committee.

2.2. Biochemical measurement

Five milliliters of blood were withdrawn from each subject at afternoon by venipuncture into a free-anticoagulant vacuum tube. Blood was immediately centrifuged at 4000*g* for 10 min, and serum was kept frozen at −80 °C until assayed. Serum NT-3 levels were assessed with an ELISA-sandwich from a commercial kit which was handled according to the manufacturer's instructions (Chemicon, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 12 h with the samples diluted 1:3 in sample diluent and the standard curve ranged from 7.8 to 500 pg of NT-3. Then,

Table 1
Characteristics of drug-free and medicated bipolar patients and controls.

Characteristics	Group*			*p* value
	Drug-free patients	Drug-treated patients	Controls	
Male sex – no. (%)[a]				
All patients	5/20 (25.0)	5/20 (25.0)	5/20 (25.0)	1.000
Manic patients	4/10 (40.0)	4/10 (40.0)	5/20 (25.0)	1.000
Depressive patients	1/10 (10.0)	1/10 (10.0)	5/20 (25.0)	1.000
Age – years[b]				
All patients	38.85 ± 12.36 (20)	39.11 ± 7.46 (20)	39.43 ± 10.27 (20)	0.955
Manic patients	44.00 ± 12.08 (10)	44.67 ± 9.63 (10)	39.43 ± 10.27 (20)	0.920
Depressive patients	32.83 ± 10.53 (10)	36.33 ± 7.81 (10)	39.43 ± 10.27 (20)	0.528
Length of illness – years[c]				
All patients	14.06 ± 8.81 (20)	13.87 ± 9.26 (20)	–	0.860
Manic patients	16.00 ± 8.19 (10)	11.75 ± 9.18 (10)	–	0.290
Depressive patients	12.12 ± 9.52 (10)	16.00 ± 8.37 (10)	–	0.330
Presence of psychosis				
All patients	15/20 (75.0)	12/20 (60.0)	–	0.370
Manic patients	9/10 (90.0)	8/10 (80.0)	–	0.490
Depressive patients	5/10 (50.0)	3/10 (30.0)	–	0.870
YMRS score[c,d]				
Manic patients	31.26 ± 10.67 (10)	28.00 ± 16.37 (10)	–	0.607
Depressive patients	4.00 ± 3.32 (10)	2.83 ± 2.77 (10)	–	0.511
HDRS score[c,d]				
Manic patients	6.43 ± 8.22 (10)	10.33 ± 13.79 (10)	–	0.580
Depressive patients	23.86 ± 8.61 (10)	23.00 ± 7.01 (10)	–	0.849
NT-3 in pg/mg protein[b,e]				
All patients	2.51 ± 0.59 (20)	2.56 ± 0.44 (20)	1.97 ± 0.33 (20)	0.001
Manic patients	2.38 ± 0.38 (10)	2.57 ± 0.48 (10)	1.97 ± 0.33 (20)	0.003
Depressive patients	2.63 ± 0.73 (10)	2.56 ± 0.44 (10)	1.97 ± 0.33 (20)	0.002

Abbreviations: YMRS (Young Mania Rating Scale); HDRS (Hamilton Depression Rating Scale); and NT-3 (neurotrophin-3).
* Columns show mean ± standard deviation (SD) for all categories except male sex and presence of psychosis. The number of participants in each group is shown in parenthesis.
[a] Chi-square test.
[b] One-way ANOVA test with Tukey *post-test*.
[c] Unpaired *t* test.
[d] YMRS and HDRS in drug-free patients = drug-treated groups for manic and depressive patients.
[e] NT-3 in controls < drug-free/drug-treated groups for all patients, and for manic and depressive patients separately.