



Peripheral insulin-like growth factor 1 in bipolar disorder



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ABSTRACT

Bipolar disorder is a recurrent and highly incapacitating illness, related to inflammation and changes in the insulin-like growth factor 1 (IGF-1). The objective of this study was to evaluate serum levels of IGF-1 in bipolar disorder patients and its relation to inflammation.

We included 31 patients with bipolar disorder and 33 healthy controls. Serum concentrations of IGF-1, growth hormone (GH), insulin and tumor necrosis factor α (TNF- α) were analyzed.

The serum levels of IGF-1 seem to be increased in bipolar disorder patients (248.84 ± 104.91 ng/mL) compared to controls (169.18 ± 74.16 ng/mL). Comparing reference values of IGF serum concentrations between groups, we found that 32% of patients had increased IGF-1 serum concentrations while only 3% of subjects are above normal range. We did not find statistically significant differences between groups in the concentration of insulin, GH, and TNF- α .

This study suggests an association between IGF-1 in the pathophysiology of bipolar disorder. It is possible that this peripheral increase is related to a central nervous system increased resistance to IGF-1, thus reducing its neuroprotective action.

1. Introduction

Bipolar disorder is a chronic, highly disabling disease, associated with a high morbidity and suicide rates (Yatham et al., 2013). Although its pathophysiology is not well understood, there is evidence that the disease is associated with imbalance of the immune and endocrine systems (Valverde et al., 2005). Since systemic toxicity and dysfunction has been repeatedly demonstrated in bipolar disorder (Kapczinski et al., 2010; Magalhães et al., 2011), there is interest in identifying molecules that are links between the central nervous system (CNS) and the periphery. As such, these targets could explain the association between illness severity, staging and the presence of medical illness (Gama et al., 2013; Grande et al., 2012; Kapczinski et al., 2014; Stertz et al., 2013).

Insulin-like growth factor-1 (IGF-1) is a 70 amino acid peptide with structural homology to insulin with which it shares the receptor (Lee

et al., 2003). Although this neurotrophin is preferably produced in the liver and pancreas, it also exists in other organs. This peptide is present in the developing brain, but its neurotrophic function is more relevant in the adult brain (Bondy and Lee, 1993). IGF-1 crosses the blood-brain barrier and has been shown to promote neurogenesis and synaptogenesis in response to neuronal damage (Aleman and Torres-Alemán, 2009; Niblock et al., 2000). It is mainly present in brain areas with a high neuron density, such as the cerebellum, olfactory bulb, hypothalamus, hippocampus and cortex (Russo et al., 2005).

IGF-1 is one possible mediator involved in the maintenance of cognitive function in bipolar disorder. Its deficiency seems to be related to cognitive changes as well as the decrease in the size of the hippocampus (Al-Delaimy et al., 2009; Fernandez and Torres-Alemán, 2012). Additionally, increased serum IGF-1 appears to be associated with improved long-term memory and working memory in children with GH deficiency (Arwert et al., 2005; Nyberg and Hallberg,

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2013). However, resistance to IGF-1 appears to be involved in neurodegenerative processes, in particular a reduction in binding to the IGF-1 receptor has been described in patients with neurodegenerative diseases with metabolic syndrome (Gatenby and Kearney, 2010; Spielman et al., 2014; Talbot et al., 2012) (O'Connor et al., 2008). Another study showed that, apart from low levels of insulin, was observed a decreased insulin and IGF-1 receptors in the CNS patients with Alzheimer's disease (Moloney et al., 2010).

The increase of inflammatory cytokines has been observed in people with bipolar disorder, especially during the late stages of the disease (Kauer-Sant'Anna et al., 2009). The increase in the cytokine TNF- α appears to be associated with IGF-1 resistance in neuronal culture (Venters et al., 1999) and with reduced neuroprotective effect of IGF-1 in CNS (Trejo et al., 2004). Therefore, a better understanding of the relationship between the immune and the endocrine systems in bipolar disorder is critical as well as would help to design new therapeutic strategies to regulate both systems and, therefore, improve outcome.

The aim of this study was to evaluate serum levels of IGF-1 in patients with bipolar disorder compared with control subjects and its relationship to inflammation.

2. Methods

2.1. Subjects

Thirty-one consecutive patients were recruited from the outpatient bipolar disorders program at the Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Patients met bipolar disorder criteria according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). Thirty-three healthy controls were recruited from blood bank of the same hospital. They had no history of psychiatric illnesses or neurological disorders, assessed by the non-patient version of the Structured Clinical Interview for DSM-V (SCID). Medical history of each patient was available in electronic record of the hospital and was carefully analyzed. Additionally, patients and healthy controls were asked about their general medical history and current medication as follow: a) Do you have been diagnosed a specific healthy problem? B) Are you receiving any medicine at the moment?

All participants signed the informed consent for the study, which was approved by the local ethics committee. This study is also in accordance with Declaration of Helsinki (2013).

The exclusion criteria for all participants were: a history of autoimmune diseases, chronic infection/inflammatory disorders, or any severe systemic disease, and use of immunosuppressive therapy. All participants provided written informed consent, and the local ethics committee approved the study.

2.2. Assessments

Sociodemographic, clinical, and pharmacologic data were collected using a structured interview and examining the patients' clinical records. Experienced rater assessed depressive and manic symptoms, respectively, administered the Hamilton Depression Rating Scale (HAMD) and the Young Mania Rating Scale (YMRS). Clinical Global Improvement (CGI) was administered to evaluate the course of the illness (Guy, 1976) and the Functioning Assessment Short Test (FAST) was used to assess functional impairment (Cacilhas et al., 2009).

2.3. Blood sample

Ten milliliters of blood were withdrawn from each subject by venipuncture respecting the same schedule collection (always in early morning after a fasting period). The blood samples collected in tubes without anticoagulant were immediately processed and serum was stored at -80°C for later analysis.

Serum levels of insulin were measured by chemiluminescence

technique using ADVIA CENTAUR XP equipment. GH and IGF-1 were analyzed by the SIEMENS® and IMMULITE 2000®. Samples were measured in replicates according manufacturer's instructions for each biochemical assay.

The serum concentration of TNF-alpha was determined by flow cytometry using the BD™ Cytometric Bead Array (CBA) Flex Set Enhanced Sensitivity to TNF-alpha Interleukin (BD Biosciences, San Diego, CA). The technique and data analysis were performed according to the manufacturer's recommendations. The data acquisition was carried out on the FACS Calibur flow cytometer (BD Biosciences, San Diego, CA) and the results were analyzed using the BD CBA Analysis Software FCAP Array™ software (BD Biosciences, San Diego, CA).

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows. Comparisons of demographic variables (age and gender) between BD patients and controls were made using independent *t*-tests. Independent Mann-Whitney for continuous variables (IGF-1, TNF- α , GH, insulin). Correlations between IGF-1 levels and CGI, HAMD, YMRS and FAST were performed using Spearman's correlation.

3. Results

The average age of patients and controls were 41.74 ± 11.76 and 41.00 ± 11.94 ($t=0.063$, $df=62$, $p=0.803$), respectively. The sample comprised mainly females in both groups (80.60% in patients and 81.80% in control groups, $\chi^2=0.014$, $df=2$, $p=1.000$). No differences between groups were found concerning age and sex. Other characteristics of the sample are listed in Table 1.

The patient group had significantly higher levels of IGF-1 (248.84 ± 104.91 ng/mL) compared to controls (169.18 ± 74.16 ng/mL, Mann-Whitney *U* test=3.487, $p=0.001$) (Fig. 1). IGF-1 concentration has reference values, which are dependent on the age. Taking into account these values, 32% of bipolar patients had increased IGF-1 serum concentrations, while only 3% of control subjects are above normal range. Correlations between serum levels of IGF-1 and HAMD ($\rho=-0.041$ and $p=0.841$), YMRS ($\rho=-0.275$ and $p=0.165$), CGI ($\rho=-0.047$ and $p=0.815$) and FAST ($\rho=-0.214$ and $p=0.284$) were not statistically significant. Levels of insulin, GH and TNF- α are shown in Table 2. No differences between groups were observed in these parameters.

Table 1
Sample characteristics.

	Patients (n=31) (mean SD)	Controls (n=33) (mean SD)	<i>t</i> / χ^2	<i>p</i>
Age	41.74 ± 11.76	41.00 ± 11.94	0.063	0.803
Females	25 (80.60%)	27 (81.80%)	0.014	1.000
Bipolar Disorder				
Type I	24 (77.4)	–		
Type II	6 (22.6%)	–		
HAMD	7.93 ± 5.67	–		
YMRS	0.81 ± 3.28	–		
CGI	2.37 ± 1.30	–		
CGI-Depression	2.15 ± 1.26	–		
CGI-Mania	1.07 ± 0.39	–		
FAST	27.54 ± 13.92	–		
Mood stabilizer	26 (40.6)	–		
Antipsychotic	14 (21.9)	–		
Antidepressant	22 (34.4)	–		

HAMD - Hamilton Depression Rating Scale. YMRS - Young Mania Rating Scale. CGI - Global Assessment of Functioning. FAST - Functioning Assessment Short Test.

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