Journal of Psychiatric Research 50 (2014) 36–41

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Oxidative stress in early stage Bipolar Disorder and the association with response to lithium

Rafael T. de Sousa [a], Carlos A. Zarate Jr. [b], Marcus V. Zanetti [a,c], Alana C. Costa [a], Leda L. Talib [a], Wagner F. Gattaz [a,c], Rodrigo Machado-Vieira [a,b,c,*]

[a] Laboratory of Neuroscience, LIM-27, Institute and Department of Psychiatry, University of Sao Paulo, Brazil
[b] Experimental Therapeutics and Pathophysiology Branch (ETPB), National Institute of Mental Health, NIH, Bethesda, MD, USA
[c] Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of Sao Paulo, Brazil

ARTICLE INFO

Article history:
Received 4 September 2013
Received in revised form
8 November 2013
Accepted 26 November 2013

Keywords:
Oxidative stress
Lithium
Bipolar Disorder
Depression
Neuroprotection

ABSTRACT

Background: Several studies have described increased oxidative stress (OxS) parameters and imbalance of antioxidant enzymes in Bipolar Disorder (BD) but few is know about the impact of treatment at these targets. However, no study has evaluated OxS parameters in unmedicated early stage BD and their association with lithium treatment in bipolar depression.

Methods: Patients with BD I or II ($n = 29$) in a depressive episode were treated for 6 weeks with lithium. Plasma samples were collected at baseline and endpoint, and were also compared to age-matched controls ($n = 28$). The thiobarbituric acid reactive substances (TBARS), and the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities were measured.

Results: Subjects with BD depression at baseline presented a significant increase in CAT ($p = 0.005$) and GPx ($p < 0.001$) levels, with lower SOD/CAT ratio ($p = 0.001$) and no changes on SOD or TBARS compared to healthy controls. Regarding therapeutics, lithium only induced a decrease in TBARS ($p = 0.023$) and SOD ($p = 0.029$) levels, especially in BDII. Finally, TBARS levels were significantly lower at endpoint in lithium responders compared to non-responders ($p = 0.018$) with no difference in any biomarker regarding remission.

Conclusion: The present findings suggest a reactive increase in antioxidant enzymes levels during depressive episodes in early stage BD with minimal prior treatment. Also, decreased lipid peroxidation (TBARS) levels were observed, associated with lithium's clinical efficacy. Overall, these results reinforce the role for altered oxidative stress in the pathophysiology of BD and the presence of antioxidant effects of lithium in the prevention of illness progression and clinical efficacy.

Published by Elsevier Ltd.

1. Introduction

It has been proposed a progressive course of Bipolar Disorder (BD) associated with longer illness duration, cognitive decline, decreased functioning and impaired cellular resilience leading to deleterious consequences on signal transduction and synaptic plasticity (Machado-Vieira et al., 2013). Thus, intervention in the early stage of BD may be a valuable tool to improve the course of the illness and provide a better prognosis (Berk et al., 2013). Increased Oxidative Stress (OxS) generates deleterious consequences on signal transduction, synaptic plasticity, and cellular resilience, especially by inducing lipid peroxidation in membranes, proteins and DNA (Grintzalis et al., 2013; Mahadik et al., 2001; Soeiro-de-Souza et al., 2013). DNA damage, which can be induced by oxidative stress, has been found to be associated with the severity of depressive symptoms in BD (Andreazza et al., 2007b).

Thiobarbituric acid reactive substances (TBARS) levels are a direct index of cell lipid peroxidation whereas antioxidant system involves coordinated effects of antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Reddy et al., 1991).

Imbalance in antioxidant enzymes has been reported in several studies of BD and is consistently associated with increased OxS

* Corresponding author. Institute and Department of Psychiatry, School of Medicine, Rua Ovidio Pires de Campos, 785, CEP 01060-970 Sao Paulo, SP, Brazil.
E-mail addresses: machadovieirar@gmail.com, machadovieirar@mail.nih.gov (R. Machado-Vieira).

0022-3956/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jpsychires.2013.11.011

(Andreazza et al., 2008). Only one study evaluated OxS parameters in BD patients with short duration of illness and found increased activity of antioxidant system in mania (Machado-Vieira et al., 2007). No study, however, has evaluated OxS in recent-onset BD patients in unmedicated depressive episodes.

Also, consistent evidences support the role of a subtle mitochondrial compromise in BD (Clay et al., 2011; Manji et al., 2012). Initially, magnetic resonance spectroscopy studies showed increased lactate levels in BD, suggesting a metabolic shift (reviewed in Stork and Renshaw, 2005). Post-mortem studies using brains of BD patients have shown decreased expression of mitochondrial electron transport chain genes (Konradi et al., 2004; Sun et al., 2006). Mitochondrial dysfunction increases production of reactive oxygen species, leading to enhanced OxS. OxS parameters have been found to be increased in BD post-mortem brains (Andreazza et al., 2010) and also in the peripheral blood of subjects with BD (Andreazza et al., 2008). Only one study evaluated subjects with BD during a depressive episode in a smaller sample, and found a slight increase in CAT levels compared to controls (Andreazza et al., 2007a).

Evidence suggests that the presence of OxS might be associated with the consistently found hyperactivation of the glutamatergic and dopaminergic systems in BD (Berk et al., 2011). Glutamatergic hyperactivity leads to increased calcium influx (Plein and Berk, 2001) which increases OxS (Shao et al., 2005). On the other hand, enhanced OxS has been suggested to increase glutamate (Lovell et al., 2000; Volterra et al., 1994). The excessive dopamine production increases OxS due to the production of reactive oxygen species in dopamine metabolism (Miyazaki and Asanuma, 2008). Moreover, the opposite mechanism also happens when OxS induces dopamine uptake, thus increasing dopamine activity (Kim and Andreazza, 2012) in a vicious cycle.

Other systems associated with BD are γ-Aminobutyric acid (Brambilla et al., 2003) and serotonergic systems (Fountoulakis et al., 2012), which are found to show decreased activity. Similar to other systems, OxS is associated with decreased γ-Aminobutyric acid release (Palmeira et al., 1993). Increased metabolism of serotonin, which decreases serotonergic function, is found to be associated with increased oxidative stress (Bianchi et al., 2005; Nocito et al., 2007). Consistent with these findings, evidences suggest that treatment with antidepressants can decrease OxS (Bilici et al., 2001).

Lithium is recommended as a first-line treatment for bipolar depression (Haeberle et al., 2012; Yatham et al., 2013) and it has shown several neuroprotective and neurotrophic actions (Machado-Vieira et al., 2009). Lithium has been shown to increase brain-derived neurotrophic factor (BDNF) (de Sousa et al., 2011), regulate intracellular Ca^{+2} (Wasserman et al., 2004), activate CREB (Ozaki and Chuang, 1997), increase Akt (Yazlovitskaya et al., 2006), and inhibit apoptotic caspase-3 (Ghribi et al., 2002). Similarly, lithium has been shown to protect against glutamatergic excitotoxicity (Nonaka et al., 1998). This agent has shown to decrease OxS in preclinical models (Schäfer et al., 2004), in bipolar mania (Machado-Vieira et al., 2007) and healthy volunteers (Khairova et al., 2012). Nonetheless, the effects of lithium on OxS parameters specifically in bipolar depression have never been studied.

The present study evaluated OxS parameters (TBARS, SOD, CAT and GPx) in unmedicated bipolar depression versus controls as well as the potential antioxidant effects of lithium in a therapeutically relevant paradigm. Our hypothesis was that subjects in a bipolar depression episode would present increased OxS (TBARS) and imbalance of antioxidant enzymes during depressive episodes and that lithium would lower OxS levels and enhance antioxidant enzymes levels.

2. Methods

2.1. Subjects

Subjects were evaluated between August 2010 and June 2012 at the Institute of Psychiatry, University of Sao Paulo, Brazil. Twenty-nine patients, 21 (72.4%) women, with 28.4 (±5.5) years of age and diagnosis of BD I (38%) or BD II (62%) in a depressive episode were included, as diagnosed by the Structured Clinical Interview for Axis I DSM-IV-TR Disorders (SCID) (First et al., 1995). Patients who had a score ≥18 on the 21-item Hamilton Depression Scale (HAM-D) (HAMILTON, 1960) were eligible for the study. Also, 26 (89.6%) patients were drug-free for at least 6 weeks prior to their enrollment and 21 (72.4%) subjects were treatment-naïve at baseline. Exclusion criteria included presence of chronic medical illness, comorbid substance abuse or dependence in the past year, rapid cycling in the past 12 months, previous head trauma, current major axis I psychiatric disorder, subjects submitted to electroconvulsive therapy and current significant abnormal laboratory tests.

The comparison group was constituted by 28 age-matched healthy controls (within 3 years of difference of BD patients); these 16 men (57.1%) and 12 women (42.8%) (age = 28.0 ± 7.2) were recruited through advertisement in the local community. Controls were excluded if they had lifetime history of any mental disorder (by SCID), including substance abuse or dependence, or if they had any disease with central nervous system involvement or any first-degree relative with a mental disorder. This study was approved by the local institutional review board, and all participants provided written informed consent before study entry.

2.2. Study design

Patients had blood samples collected at baseline and at endpoint (week 6), while healthy controls had only one-point sample collection. At baseline, patients were started on open-label lithium carbonate at 450 mg/day, with flexible doses increase according to clinical improvement, controlling plasma lithium levels to ensure compliance and avoid toxicity (<1.2 mEq/L).

Most patients were on lithium monotherapy, although hypnotic (benzodiazepine or zolpidem) use as needed was allowed and 4 patients were also in use of antipsychotics or mood stabilizer. Psychometric assessments were made at baseline and on week 1, week 2, week 4, and week 6 (endpoint). Assessment of symptoms was performed with the HAM-D, Young Mania Rating Scale (YMRS) (Young et al., 1978), and Clinical Global Impression. Clinical response was defined as a decrease of 50% or more in the HAM-D at endpoint and remission as HAM-D < 8 and YMRS < 8 at endpoint.

2.3. Assays

Blood samples were collected from 8:00 to 10:00 AM using vacutainer tubes. All subjects were in 8-h fasting. Samples were centrifuged at 20 °C and 1620 × *g* for 15 min. Plasma was obtained, frozen, and stored at −80 °C. Given the complexity of the study, not all the patients and controls had samples available to be included in all analyses. All samples were assessed in duplicate. TBARS levels (malondialdehyde − thiobarbituric acid adduct) and SOD, CAT, and GPx activities were determined using spectrophotometry according to commercially available kits from Cayman Chemical Company®. Since SOD and CAT act sequentially, the results are also expressed as SOD/CAT ratio. CAT and GPx levels are presented as nM/min/mL, SOD as U/mL and TBARS as nM/mL.