BRIEF REPORT

Increased oxidative stress as a mechanism for decreased BDNF levels in acute manic episodes

Aumento do estresse oxidativo como um mecanismo para a diminuição dos níveis de BDNF em episódios maníacos agudos

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Abstract

Objective and Method: *There is a growing amount of data indicating that alterations in brain-derived neurotrophic factor and increased oxidative stress may play a role in the pathophysiology of bipolar disorder. In light of recent evidence demonstrating that brain-derived neurotrophic factor levels are decreased in situations of increased oxidative stress, we have examined the correlation between serum thiobarbituric acid reactive substances, a measure of lipid peroxidation, and serum brain-derived neurotrophic factor levels in bipolar disorder patients during acute mania and in healthy controls.* ***Results:*** *Serum thiobarbituric acid reactive substances and brain-derived neurotrophic factor levels were negatively correlated in bipolar disorder patients (r = -0.56; p = 0.001), whereas no significant correlation was observed in the control group..* ***Conclusion*****:** *These results suggest that alterations in oxidative status may be mechanistically associated with abnormal low levels of brain-derived neurotrophic factor observed in individuals with bipolar disorder.*

Descriptors: *Bipolar disorder; Brain-derived neurotrophic factor; Mania Depression; Oxidative stress; Thiobarbituric acid reactive substances*

Resumo

Objetivo e Método: *Existem crescentes evidências indicando que alterações no fator neurotrófico derivado do cérebro e aumento do estresse oxidativo podem estar envolvidos na fisiopatologia do transtorno bipolar. Considerando os achados recentes de que os níveis de fator neurotrófico derivado do cérebro estão diminuídos em situações de aumento de estresse oxidativo, nós testamos a correlação entre os níveis séricos de substâncias reativas do ácido tiobarbitúrico, um índice de peroxidação lipídica, e os níveis séricos de fator neurotrófico derivado do cérebro em pacientes portadores de transtorno bipolar durante mania aguda e em controles saudáveis.* ***Resultados*****:** *Os níveis séricos de substâncias reativas do ácido tiobarbitúrico e fator neurotrófico derivado do cérebro apresentaram uma correlação negativa em pacientes bipolares (r = -0,56; p = 0,001), enquanto não houve correlação significativa no grupo controle.* ***Conclusão:*** *Estes resultados sugerem que alterações de estresse oxidativo podem ser mecanisticamente associadas com níveis reduzidos de BDNF observados em indivíduos com transtorno bipolar.*

Descritores: *Transtorno bipolar; Fator neurotrófico derivado do cérebro; Mania depressão; Estresse oxidativo; Substâncias reativas com ácido tiobarbitúrico*

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Introduction

Bipolar disorder (BD) is a prevalent condition in adults determining a significant impairment in quality of life.[1] There is an emerging body of evidence suggesting that brain-derived neurotrophic factor (BDNF) may play a role in the pathophysiology of BD. We recently showed that serum levels of BDNF are decreased during both manic and depressive mood episodes, being normalized in euthymia.[2] These changes in BDNF levels were negatively correlated with the severity of manic and depressive symptoms. Moreover, first-line mood stabilizers, such as lithium and valproate, are known to increase BDNF levels.[3] Despite the reported association of lower levels of serum BDNF with BD morbidity and its reversal by effective treatment, the underlying neurobiological mechanisms of BDNF decrease in acute mood episodes are unknown.

Interestingly, there is evidence showing that oxidative stress may be increased in conditions where BDNF is described to be decreased in BD. For instance, there is evidence of increased oxidative stress, particularly during mood episodes.[4] Moreover, preclinical studies have shown that lithium and valproate exert antioxidant effects *in vitro* and *in vivo.*[5,6] Under situations where oxidative damage reduces cAMP response element binding (CREB) expression, and CREB as well as p-CREB content, oxidative stress is associated with a decrement in BDNF expression and content.[7] To the best of our knowledge, the correlation between oxidative stress and BDNF levels has not been investigated in a clinical sample. In the present study, we have reanalyzed our data on BDNF and oxidative stress[2,4] and investigated the correlation between serum thiobarbituric acid reactive substances (TBARS – a measure of lipid peroxidation) and serum BDNF levels in BD patients during acute mania and in healthy controls. We hypothesized that there would be a negative correlation between serum TBARS and BDNF levels in manic BD patients, but not in healthy controls.

Method

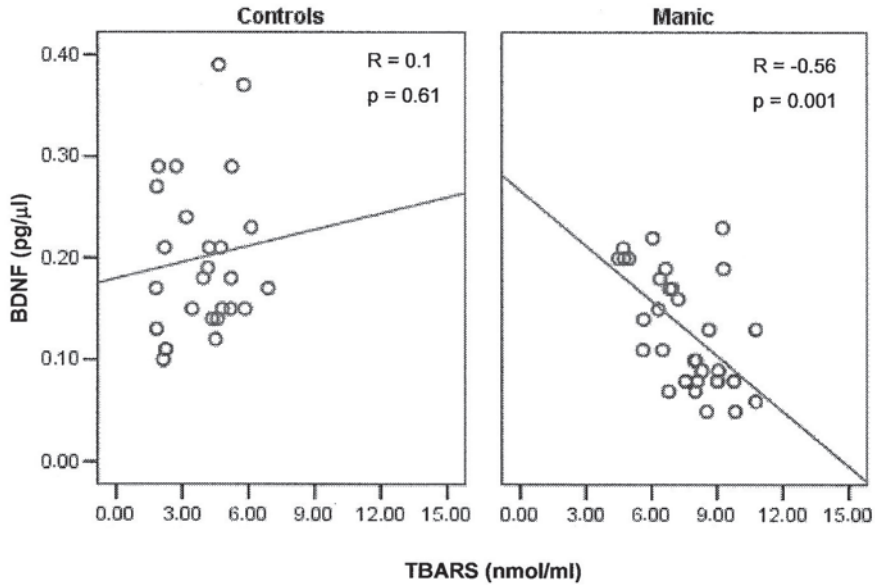
Detailed demographic and clinical information about the subjects have been described elsewhere.[2,4] We reanalyzed our data on serum BDNF and TBARS levels using Pearson correlation coefficient, given that BDNF and TBARS values were normally distributed. In brief, 32 manic BD patients were recruited from the Inpatient Psychiatric Unit of the University Hospital (Santa Maria, Brazil). This work was approved by the local ethics committee and all of the subjects provided written informed consent. Patients were interviewed using the Structured Clinical Interview for DSM-IV-Axis I. Thirty-two healthy controls were matched for age, gender and education. Control subjects were not on medication and had no history of major psychiatric disorders, dementia, mental retardation, and no such disorders were present in their first-degree relatives. Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube for biochemical analyses. Serum BDNF levels were measured using a commercial kit of sandwich-ELISA according to the manufacturer's instruction (Chemicon, USA). The standard curve demonstrated a direct relationship between optical density and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin as standard. TBARS were measured using the method described by Wills.[4] All assays were performed blind to the subject's status.

Results

In BD patients, there was a significant negative correlation between serum TBARS and BDNF levels ($r = -0.56$; $p = 0.001$; Figure 1). No significant correlation between serum TBARS and BDNF levels was observed in the control group ($r = 0.1$; $p = 0.61$).

Discussion

These results suggest that increased oxidative stress is associated with lower BDNF levels, although a causal relationship cannot be inferred. Several mechanisms by which oxidative stress could decrease BDNF have been suggested, including decreased CREB, increased NF-kB DNA-binding activity[8,9] or energy depletion.[7] Notably, decreased CREB levels and increased NF-kB gene expression have been found in postmortem brains of BD subjects[10,11] and an energy crisis due to mitochondrial dysfunction has been implicated in the pathophysiology of BD.[12] It should also be mentioned that alterations in the redox status can trigger



TBARS = thiobarbituric acid reactive substances; BDNF = brain-derived neurotrophic factor

Figure 1 - Correlation between serum TBARS and BDNF levels in manic patients and healthy controls

endoplasmic reticulum stress, which in turn suppresses activity-dependent BDNF expression.[13]

The present data raise the intriguing possibility that the decrease in BDNF levels in acute affective episodes could be mechanistically related to increased oxidative stress. Correcting the oxidative imbalance in BD may offer a new means of controlling the detrimental effects of mood episodes on cognition and bodily systems, and if it also prevented the associated decrements in BDNF would provide more direct evidence for the hypothesized causal relationship between increased oxidative stress and lower levels of BDNF. As we have previously mentioned,[2,4] medication status may have influenced the present results. Antidepressants are known to increase serum BDNF in humans[14] and data from animal models demonstrate that mood stabilizers can increase cerebral BDNF[15] and regulate cerebral TBARS levels in rodents *in vivo.*[6] A preliminary case-report suggested that treatment with lithium and antipsychotics may normalize serum TBARS levels in humans,[16] but studies with larger samples are clearly warranted to better determine this issue.

In conclusion, we found that serum TBARS was negatively correlated with serum BDNF levels in manic BD patients, but not in healthy volunteers. These findings suggest that increased oxidative stress may be associated with lower BDNF levels under pathological conditions such as acute mania.

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Note: HCPA = Hospital de Clínicas de Porto Alegre; UFSM = Universidade Federal de Santa Maria; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; NASARD = National Alliance for Research on Schizophrenia and Depression; SMRI = Stanley Medical Research Institute; FIPE = Fundo de Incentivo à Pesquisa e Ensino.
For more information, see Instructions for authors.

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