Psychiatry Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Psychiatry Research

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

# Serum brain-derived neurotrophic factor levels in subjects with major depressive disorder with previous suicide attempt: A population-based study

Fernanda Pedrotti Moreira[a,e], Cristiane Jackson Borges[a,e], Carolina David Wiener[a,b,e], Paula Moraes da Silva[a,e], Luis Valmor Portela[c,e], Diogo R. Lara[d,e], Ricardo Azevedo da Silva[a,e], Luciano Dias de Mattos Souza[a,e], Karen Jansen[a,e], Jean Pierre Oses[a,e,f,*]

[a] Translational Science on Brain Disorders, Clinical Neuroscience Laboratory, Department of Health and Behavior, Catholic University of Pelotas, RS, Brazil
[b] Postgraduate Program in Epidemiology, Federal University of Pelotas, RS, Brazil
[c] Neurotrauma Laboratory, Department of Biochemistry, Institute of Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
[d] Neurochemistry and Psychopharmacology Laboratory, Cellular and Molecular Biology Department, Faculty of Bioscience, Pontifical Catholic University of Rio Grande do Sul (PUC-RS), Porto Alegre, Brazil
[e] Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil
[f] Technology Application in Neurosciences, Department of Electronic Engineering and Computer, Catholic University of Pelotas, Brazil

ARTICLE INFO

*Keywords:*
BDNF
Suicide attempt
Depression
Biomarker

ABSTRACT

Major depressive disorders (MDD) and suicide are significant public health concerns. Recent studies have been demonstrated that alterations in Brain Derived Neurotrophic Factor (BDNF) can be associated with this psychiatric disorders, MDD and suicide. Thus, the aim of this study was to evaluate differences in serum levels in individuals with MDD and with or without suicide attempt (SA), from a population-based sample. This was a paired cross-sectional study nested in a population-based study. The psychopathology screen was performed with the Mini-International Neuropsychiatric Interview (MINI). The total population of the sample consisted of 147 subjects distributed in three groups: 49 healthy controls, 49 subjects with MDD and 49 subjects with MDD and SA (MDD + SA). The BDNF serum levels were significantly reduced in subjects with MDD and MDD + SA compared to the healthy controls. However, there were no significant differences between the MDD and MDD + SA groups with respect to BDNF serum levels. These results suggest that SA did not interfere in the serum levels of BDNF, indicating that this neurotrophin may be related to the diagnosis of MDD and not to suicide attempt.

## 1. Introduction

Suicide is a complex phenomenon and a significant public health concern. It is among the three leading causes of death among those aged between 15 and 45 years (WHO, 2014). Suicide attempt (SA) is defined as a non-fatal auto aggression act of wide variety and may result in sequel of varying magnitudes, and is an important risk factor for future completed suicide (Bertolote et al., 2005). Prevalence rates of life-long suicide attempts range from 0.4% to 4.2%. It is estimated that for each suicide case there are at least ten sufficiently severe attempts to require medical attention and that suicidal behaviors are up to 40 times more frequent than completed suicides (Mello-Santos et al., 2005), considering that for each documented attempt there are four others that were not recorded (WHO, 2014). Population level estimates suggest that 80–90% of attempted and completed suicides occur in the context of a mental illness (Conwell et al., 1996; Eisen et al., 2016).

Among psychiatric disorders, individuals with major depressive disorder (MDD) have a high rate of morbidity and mortality, with a suicide risk (SR) rate equivalent to 15% (Mann, 2002). Although the etiology of suicide and MDD is certainly complex, some risk factors are thought to contribute to the risk of suicidal behavior, including biological, psychological, social, and environmental factors. Many theories have been proposed to explain the biological substrates of suicide behavior (Chen and Lu, 2006; Eisen et al., 2016). One of the main biomarkers proposed in association studies with suicide attempted and suicide is a neurotrophin named brain-derived neurotrophic factor (Eisen et al., 2015; Grah et al., 2014). BDNF is found in the brain and throughout the body in the bloodstream (Dwivedi, 2012). It is crucial a few neural processes, such as neurogenesis, neuroplasticity, and neurotransmission (Dwivedi, 2012; Huang and Lee, 2006). Thus, changes in BDNF levels may play a role in the pathogenesis of suicidal behavior. Studies have shown that changes in brain structure and function, such

* Correspondence to: Translational Science on Brain Disorders, Clinical Neuroscience Laboratory. Department of Health and Behavior, Catholic University of Pelotas, Rua Gonçalves Chaves, 373 - Sala 418C, Pelotas, RS CEP: 96015-560, Brasil.
*E-mail address:* jean.pierre.oses@gmail.com (J.P. Oses).

http://dx.doi.org/10.1016/j.psychres.2017.09.033
Received 21 March 2017; Received in revised form 30 August 2017; Accepted 11 September 2017

as reductions in neuronal cell numbers, density and size, as well as decreased cortical thickness and changes in synaptic circuits, may be associated with depression, stress, and suicidal behavior (Garcia, 2002; Wagner et al., 2012). Thus, the pathogenesis of suicidal behavior may be linked to altered neuronal plasticity, which impairs the brain's ability to respond adequately to environmental stimuli. (Fossati et al., 2004; Garcia, 2002).

Recent studies have postulated that neuronal levels of neurotrophic factors have been associated with MDD and suicidal behavior (Bersani et al., 2000; Castren and Kojima, 2017). Both MDD and suicidal behavior involve altered neural plasticity in its pathogenesis, resulting in an abnormal central nervous system (CNS) response to stressors and environmental outcomes (Eisen et al., 2016). The neurotrophic factors have a wide range of roles in development and function of the nervous system. They activate the neuroendocrine cells and the neuronal responses, regulate the growth and proliferation of glial cells, modulate the activity of endogenous opioid peptides, activate the HPA axis, exerting effects on corticotrophin releasing hormone-producing neurons, and act on the endothelial cells of the cerebral vasculature or on the glial cells in the circumventricular organs (Sher, 2011a). In addition, the neurotrophic factors can also affect the metabolism of the noradrenergic, serotonergic and dopaminergic systems (Paska et al., 2013).

Some studies that investigated changes of BDNF in individuals with MDD and suicide found reduced levels of this protein, when compared to controls (Castren and Kojima, 2017; Grah et al., 2014; Kim et al., 2007). A recent study has evaluated the changes in NGF serum, another neurotrophic factor, in individuals with MDD and with or without risk of suicide and found reduced serum levels of NGF in individuals with MDD, when compared to controls. However, the same authors did not find significant differences in NGF levels between the MDD and MDD with suicide risk groups (Wiener et al., 2015). Our hypothesis is that BDNF is altered in individuals with MDD + SA. In this context, a search for neurochemical markers for suicide becomes important. The use of biological markers for suicide may be a relevant tool to assist in the diagnosis of this disorder. The aim of this study was to evaluate differences in serum levels of BDNF in individuals with MDD and with or without suicide attempt, from a population-based sample.

## 2. Methods

### 2.1. Subjects

This was a paired cross-sectional study nested in a population-based study of individuals between the ages of 18 and 35 years. The original sample consisted of 1380 participants living in the city of Pelotas, (Brazil). The study was held from June 2011 to October 2012. Those who accepted the invitation to participate in the study answered a questionnaire to provide demographic data and information about psychoactive substance use (tobacco, cocaine and marijuana use) through a self-administered questionnaire. To evaluate alcohol use disorder, the participants answered the CAGE questionnaire (Buchsbaum et al., 1991). Socio -economic evaluation was carried out using the IEN criteria (National Economic Index—Índice Econômico Nacional), which is based on the accumulation of material assets and on the schooling of the head of the household (Barros and Victora, 2005). This study was approved by the Research Ethics Committee of the institution (2010/15).

For the propose of this present study, clinical diagnosis of current major depressive disorder (MDD) and suicide attempt (SA) was measured by the Mini International Neuropsychiatric Interview (M.I.N.I) (Amorim et al., 1998), structured clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.

Those who were able to understand or answer the questions were also excluded from the study. Moreover, following items were used as exclusion criteria in control group: presence of anxiety/psychotic disorder; and use of any psychoactive substance (alcohol abuse, tobacco, cocaine and marijuana use) or psychopharmacological drugs. From this, we recruited all people with MDD and SA (MDD + SA). Additionally, two groups were matched by sex and age: healthy control group (people without a history of mental disorders) and active control group (MDD) that included people with current MDD but with no past history of SA. Thus, the total population of the sample consisted of 147 subjects distributed in three groups: 49 healthy controls, 49 subjects with MDD and 49 subjects with MDD and SA (MDD + SA).

### 2.2. Blood sample collection and BDNF assessment

For the biochemical analyses, 10 mL of blood were drawn from each subject by venipuncture into an anticoagulant-free vacuum tube. All venous blood samples were taken after the interview (between 8 a.m. and 11 a.m.). The blood was immediately centrifuged at 4000 × *g* for 10 min, and serum was kept frozen at − 80 °C until analysis. Serum BDNF levels were measured with a sandwich-ELISA using an available immunoassay kit according to the manufacturer's instructions (DuoSet ELISA Development, R & D Systems, Inc., Minneapolis, MN, USA). Serum BNGF levels were expressed in pg/mL.

### 2.3. Statistical analysis

Statistical analyses were performed using the Graph Pad Prism 6.0 (GraphPad Software Inc., San Diego, USA) and IBM SPSS Statistic 21.0 (IBM Corporation, New York, USA) software for Windows. Sociodemographic characteristics are shown by the absolute and relative frequencies or by mean ± standard deviation. To verify the association between groups, the chi-square test and analysis of variance (ANOVA) were used. The serum levels of BNGF had non-Gaussian distributions and were logarithmically transformed before the adjusted analysis. Thus, the comparison between serum BDNF levels and the three diagnosis groups were performed by Kruskal-Wallis test followed by Dunn - Bonferroni *post hoc*. The serum BDNF levels were presented as median and interquartile range. To control for possible confounding variables, the Linear regression was used in multivariable analysis the variables that presented associations with $p \leq 0.20$ in the raw analysis. Results with $p \leq 0.05$ were considered statistically significant.

## 3. Results

The total sample consisted of 147 subjects: 49 with MDD, 49 with MDD + SA and 49 healthy controls. Each group was composed of 41 (33.3%) women and 8 (33.3%) men, with a mean age of 27.59 ± 5.14 years. Homogeneous samples showed no significant differences with regards to gender ($p = 1.00$), ethnicity ($p = 0.382$) and age ($p = 0.949$). For socioeconomic index ($p \leq 0.001$), years of education ($p = 0.001$), tobacco use ($p \leq 0.001$) alcohol abuse ($p = 0.015$), and current psychiatric medication use ($p \leq 0.001$) we found statistical differences among groups. Serum BDNF levels were significantly reduced in the MDD (8.09 (5.73 – 10.98) ng/mL) and MDD + SA (8.72 (6.42 – 11.47) ng/mL) groups, when compared to healthy controls (26.95 (24.57 – 31.42) ng/mL; $p \leq 0.001$) (Table 1).

Table 2 shows that adjusted analysis for demographic variables (Brazilian Economic index and years of education) and lifestyle habits (abuse/dependence alcohol, abuse/dependence on tobacco and current psychiatric medication use). And, after controlling for confounders, serum BDNF levels were significantly reduced in the MDD and MDD + SA when compared to controls.

Fig. 1 shows serum levels of BDNF for MDD, MDD + SA and healthy control groups. The Dunn-Bonferroni *post-hoc* test for multiple comparison revealed a significant difference between MDD and healthy controls ($p \leq 0.001$), as well as MDD + SA and healthy controls ($p \leq 0.001$). However, no statistically significant difference was found between individuals with MDD as compared to MDD + SA regarding the