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Cognitive psychotherapy treatment decreases peripheral oxidative stress parameters associated with major depression disorder

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ABSTRACT

Introduction: Studies have already pointed out the contribution of oxidative stress in the pathophysiology of major depressive disorder (MDD). The aim of the present study was to investigate the oxidative-antioxidative systems in MDD and in response to cognitive psychotherapies. Oxidative stress were analyzed in 49 MDD patients at baseline, post-treatment, and follow-up; and 49 control subjects without history of psychiatric disorders.
Results: MDD subjects presented an increase in oxidative damage related to control subjects for thiobarbituric acid reactive species (TBARS), nitric oxide, and a decrease in total thiol content. Cognitive psychotherapies were able to counteract peripheral oxidative stress in MDD patients, reducing TBARS levels ($p < 0.001$) in the follow-up, nitric oxide ($p < 0.001$) in the post-treatment and follow-up, and increasing the total thiol content ($p < 0.01$) in the post-treatment and follow-up.
Conclusion: Oxidative stress was associated with MDD and the regulation of these parameters might represent an important mechanism associated with the clinical improvement of cognitive psychotherapy.

1. Introduction

Major depressive disorder (MDD) is a common, recurrent and incapacitating psychiatric illness associated with significant morbidity and mortality (Nemeroff, 2007). The exact neurochemical mechanisms underlying the pathophysiology of MDD are not completely understood. However, some peripheral changes in inflammatory and oxidative-related pathways are frequently observed in depressive phenomenology. The relevance of inflammation in this disorder has been proposed by several studies linking peripherally derived immune cells and inflammatory molecules with a variety of neurochemical, neuroendrocrine and behavioral alterations observed in depressive patients and in pre-clinical models (Leonard, 2013). In this way, it is well accepted that inflammatory processes can frequently result in increased reactive oxygen and nitrogen species production (RO&NS) and oxidative stress both in the periphery and in the central nervous system (Leonard & Maes, 2012; Leonard, 2013).

Oxidative stress is characterized by an imbalance between the production of RO&NS and the antioxidant capacity of the organism. Changes in oxidative stress parameters contribute to the development of neurodegenerative disorders by targeting different substrates in the cells, causing protein, DNA and RNA oxidation, or lipid peroxidation (Popa-Wagner, Mitran, Sivanesan, Chang, & Buga, 2013; Siwek et al., 2013). Importantly, the brain is particularly susceptible to oxidative damage since it metabolizes 20% of total body oxygen and has a limited amount of antioxidant capacity (Gutteridge & Halliwell, 2010).

The association between several parameters of oxidative stress, impairment in the antioxidant defenses and MDD was evidenced in several clinical and pre-clinical studies (Bilici, Efe, Köroğlu & Uydu, 2001; Khanzode, Dakhale, Khanzode, Saoji, & Palasodkar, 2003; Ozcan, Gulec, Ozerol, Polat, & Akyol, 2004). The

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measurement of serum lipid peroxidation is one of the most extensively evaluated indices in patients with psychiatric disorders (Galecki, Szemraj, Bieńkiewicz, Florkowski & Galecka, 2009). Moreover, elevated activity of the antioxidant enzyme superoxide dismutase (SOD) was previously associated with MDD, bipolar disorder and schizophrenia (Herken, Uz, Ozyurt, & Akyol, 2001; Kuloglu et al., 2002; Savas et al., 2006). In addition, even produced in excess, nitric oxide (NO) can originate reactive nitrogen species (RNS) and becomes harmful to the cell, and both NO and RNS play a role in the pathogenesis and development of MDD (Maes, Galecki, Chang, & Berk, 2011).

In this respect, the long-term treatment with antidepressant drugs has been demonstrated to restore the antioxidant enzyme activities as well as the oxidative damage and inflammatory profile in MDD patients (Bilici et al., 2001; Galecki et al., 2009; Herken et al., 2007; Hernandez et al., 2013). However, available pharmacotherapy for depression is often associated with several undesirable effects, and its effectiveness achieves only a certain portion of the population (Berton & Nestler, 2006; Wong & Licinio, 2001). In this context, brief psychotherapies, especially cognitive psychotherapies, are effective alternative methods to treat individuals experiencing mild to moderate depression (Beck, Rush & Emery, 1997; Bockting et al., 2011; Hollon et al., 1992; Lopes, Gonçalves, Fassnacht et al., 2014; Mondin et al., 2014; Stice et al., 2010; Strunk & DeRubeis, 2001). Cognitive Behavioural Psychotherapy (CBP) aims to help patients to identify and change negative, self-destructive thought patterns, it also aims a self-reflexive condition where patients can manipulate their beliefs overcoming suffering state and promoting long lasting changes (Anthes, 2014; de Souza & Cândido, 2010). On the other hand, Cognitive Narrative Psychotherapy (CNP) aims to help individuals to narrate their own life history in a richer and more rewarding manner (Angus & McLeod, 2004; Gonçalves & Machado, 1999). Both types of psychotherapy have been shown to be effective in the remission of depressive symptoms (Gazal et al., 2013; Lopes et al., 2015; Lopes, Gonçalves, Fassnacht et al., 2014; Lopes, Gonçalves, Machado et al., 2014; Mondin et al., 2014; Stice et al., 2010; Strunk & DeRubeis, 2001).

Although, the effectiveness of brief psychotherapy has been consistently demonstrated in the literature, the biological mechanisms associated with the clinical improvement are poorly explored. Studies showed that cognitive behavioral psychotherapy is able to improve the inflammatory profile in MDD patients by reducing the activation of intracellular pathways involved in the production and secretion of inflammatory cytokines, such as the Toll-like Receptor-4 (TLR-4) and Nuclear Factor Kappa-Beta (NF-κβ) mRNA (Kéri, Sazbó & Kelemen, 2014), as well as high sensitive C-reactive protein, Interleukin-18 (IL-18) and oxidized low-density lipoprotein levels in hemodialysis patients with sleep disturbance (Chen et al., 2011). Furthermore, a recent work from our group also showed that symptoms remission promoted by cognitive behavior psychotherapy, are accompanied by lower peripheral levels of Interleukin-6 (IL-6) in depressed women (Gazal et al., 2013). Thereby, the present study aims to firstly verify the association of peripheral oxidative stress with MDD, and then evaluate if these parameters are modulated by cognitive psychotherapies.

2. Methods

2.1. Study design and participants

This study included 49 patients with MDD and 49 control subjects without history of psychiatric disorders, paired by age and gender. Individuals making use of tobacco were excluded. The diagnosis was conducted by trained senior psychology students using the structured diagnostic interview—MINI International Neuropsychiatric Interview according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria. MDD diagnosis was confirmed by the Structured Clinical Interview for DSM (SCID) (Del-Bem et al., 2001; Sheehan et al., 1998).

2.1.1. MDD sample selection

MDD group consisted of 49 individuals experiencing mild to moderate depression selected from a randomized clinical trial performed in young adults aged 18–29, to assess the effectiveness of cognitive psychotherapy models in remission of depressive symptoms (Mondin et al., 2014). To better correlate the effects of cognitive psychotherapies in peripheral oxidative parameters, we have selected from the original study only patients who did not refuse to complete the follow-up (Fig. 1). Evaluations were conducted at baseline, post-treatment and six-month follow-up. Important to note that during the follow-up none of the patients evaluated were making use of psychiatric medication including antidepressants, benzodiazepines or mood stabilizers.

Patients were enrolled from June 2010 to June 2012. Post-intervention assessments were conducted from August 2010 to August 2012 and six-month later patients were assessed again to evaluate depressive symptoms and symptoms remission, as well as oxidative stress parameters. All ethical procedures established by the National Health Council, resolution number 196, October of 1996 were followed. The project was approved by the ethical committee of the Catholic University of Pelotas, southern Brazil, under protocol number 2009/24 and all participants signed the informed consent. Detailed information on study design was described in a previous study published by Mondin et al. (2014).

2.1.2. Controls sample selection

The control group consisted of 49 individuals enrolled from a population-based study of people aged 18–35, recently carried out in the city of Pelotas (Brazil) (Monfrim et al., 2014). The control subjects, without history of mood or anxiety disorder, were randomly selected and paired by age and gender with the MDD individuals. Sample selection was performed from June 2011 to October 2012. The study was approved by the ethical committee of the Catholic University of Pelotas, Brazil (protocol number 2010/15) and all participants signed the informed consent.

2.2. Interventions

Senior psychology students conducted the interventions after specific training with experienced professionals on two models of psychotherapy. A pilot study was conducted with older patients in order to ensure appropriate model implementation. The participants who met the eligibility criteria were randomized using the sealed envelope method, where subjects randomly choose a sealed envelope which contains one of the two models of intervention: Cognitive Behavioral Psychotherapy (CBP) or Cognitive Narrative Psychotherapy (CNP).

Both intervention models consisted in seven weekly structured sessions. All sessions were individual and 1 h long. Treatment protocols were created based on manuals developed for both models. The manual for CBP is grounded on Beck et al. (1997) theory and the manual of CNP was structured based on the proposal of Gonçalves & Machado (1999).

Depressive symptoms were assessed with the Hamilton Rating Scale for Depression (HAMD) (Williams, 1988), which was also used in order to measure symptoms severity before and after cognitive psychotherapies and in the six-month follow-up. This instrument has 17 items classified quantitatively according to the intensity of the symptoms. The total score is the sum of all items and the scores can range from 0 to 54. Scores between 0 and 6 indicate absence