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Evidence for protective effect of lipoic acid and desvenlafaxine on oxidative stress in a model depression in mice

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ABSTRACT

Oxidative stress is implicated in the neurobiology of depression. Here we investigated oxidative alterations in brain areas of animals submitted to the model of depression induced by corticosterone (CORT) and the effects of the antioxidant compound alpha-lipoic acid (ALA) alone or associated with the antidepressant desvenlafaxine (DVS) in these alterations. Female mice received vehicle or CORT (20 mg/kg) during 14 days. From the 15th to 21st days different animals received further administrations of: vehicle, DVS (10 or 20 mg/kg), ALA (100 or 200 mg/kg), or the combinations of DVS10 + ALA100, DVS20 + ALA100, DVS10 + ALA200, or DVS20 + ALA200. Twenty-four hours after the last drug administration prefrontal cortex (PFC), hippocampus (HC) and striatum (ST) were dissected for the determination of the activity of superoxide dismutase (SOD), reduced glutathione (GSH) and lipid peroxidation (LP) levels. CORT significantly increased SOD activity in the PFC and HC, decreased GSH levels in the HC and increased LP in all brain areas studied when compared to saline-treated animals. Decrements of SOD activity were observed in all groups and brain areas studied when compared to controls and CORT. The hippocampal decrease in GSH was reversed by ALA100, DVS10 + ALA100, DVS20 + ALA100 and DVS20 + ALA200. The same DVS + ALA combination groups presented increased levels of GSH in the PFC and ST. The greater GSH levels were observed in the PFC, HC and ST of DVS20 + ALA200 mice. LP was reversed in the groups ALA200 (PFC), DVS10 + ALA100, DVS20 + ALA100 (PFC, HC and ST), and DVS20 + ALA200 (PFC, HC). Our findings contribute to the previous preclinical evidences implicating ALA as a promising agent for augmentation therapy in depression.

1. Introduction

Major depressive disorder (MDD) is a serious and recurrent disorder manifested with symptoms at the psychological, behavioral and physiological levels. Depression affects 17–20% of the population worldwide and may result in premature death, major social and economic consequences (Jain, 2009; Rohde et al., 2009). Depressed mood, diminished interest/pleasure and fatigue or loss of energy are among the core symptoms of MDD (Fried and Nesse, 2015).

Oxidative stress has been implicated in the pathogenesis of major psychiatric disorders, such as bipolar disorder and MDD (Ng et al., 2008). Indeed, these disorders are related to immune and mitochondrial dysregulations what, in turn, leads to the production of free radicals and oxidative imbalance (Bakunina et al., Epub ahead of print).

Oxidative stress results from increased production of reactive oxygen species (ROS), decreased antioxidant defenses or failure to repair oxidative damage. Reactive oxygen species are free radicals or reactive anions/molecules containing oxygen atoms such as hydroxyl radical, superoxide, hydrogen peroxide, and peroxynitrite. The ROS can cause cell damage by enzyme inactivation, lipid peroxidation and DNA modification (Fridovich, 1986; Halliwell, 1999). Usually ROS are metabolized into less toxic molecules by the action of antioxidant enzymes, namely, superoxide dismutase (SOD), catalase (CAT) or glutathione (GSH) peroxidase (Winterbourn, 1993). Superoxide dismutase, which catalyzes the conversion of superoxide radicals to hydrogen peroxide (H_2O_2), is one of the most important antioxidant enzymes and interacts with other neuroprotective substances (Gsell et al., 1995).

Abbreviations: ALA, alpha-lipoic acid; CAT, catalase; CORT, corticosterone; DVS, desvenlafaxine; GSH, reduced glutathione; HC, hippocampus; LP, lipid peroxidation; MDA, malondialdehyde; MDD, major depressive disorder; PMD, psychotic major depression; PFC, prefrontal cortex; ROS, reactive oxygen species; SNRI, serotonin and noradrenaline reuptake inhibitor; SOD, superoxide dismutase; SSRI, selective serotonin reuptake inhibitors; ST, striatum.

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Clinical (Ng et al., 2008) and preclinical (Mello et al., 2013) studies have reported a number of oxidative disturbances in depression, including elevated lipid peroxidation levels, decreasing activity of GSH, CAT, and SOD (Bilici et al., 2001) and consequently may contribute to the dysfunction of serotonergic and noradrenergic systems (Takuma et al., 2004).

There are various antioxidant mechanisms in the brain that neutralize the harmful effects produced by ROS. Specifically in MDD the loss of efficiency of antioxidant mechanisms associated to a low total antioxidant capacity could be indicative of oxidative stress or increased susceptibility to oxidative damage (Young, 2001).

Antidepressants are among the therapeutic agents most commonly prescribed for the treatment of MDD. Desvenlafaxine succinate (DVS), an active metabolite of venlafaxine is a dual serotonin and noradrenaline reuptake inhibitor (SNRI) that has shown superior clinical efficacy over other SNRI (Kornstein et al., 2014; Lourenco and Kennedy, 2009).

Despite sustained clinical and preclinical research efforts, the neurobiology of MDD is not completely understood. Based on the involvement of oxidative stress in the neurobiology of MDD, preclinical studies have suggested that antioxidants may have antidepressant properties (Eren et al., 2007; Zafir and Banu, 2009) or can be used as augmentation strategies (Silva et al., 2013). In this sense, it appears reasonable to propose that clinical trials are conducted with antioxidant drugs, such as alpha-lipoic acid (ALA) for the treatment of MDD.

Alpha-lipoic acid (ALA) is an antioxidant naturally synthesized in human body. The structural formula of this molecule presents two thiol groups that can be oxidized or reduced. Both the oxidized (ALA) and the reduced (dihydrolipoic acid) forms act as antioxidants (Ferreira et al., 2009). Dihydrolipoic acid is able to regenerate other antioxidants of low molecular weight, such as GSH, coenzyme Q10, and vitamins A and C (Bilska et al., 2007). It is also attributed to this substance an anti-inflammatory activity, and, therefore, the effect of short- and long-term reduction in oxidative processes related to neurodegenerative diseases.

A number of animal models have been developed to study depressive symptomatology and neurobiology (Sterner and Kalynchuk, 2010). In rodents, accumulated evidence has indicated that repeated exogenous administration of corticosterone (CORT) produces reliable behavioral and neurobiological alterations that could be related to human MDD (Zhao et al., 2008). The recent evidences that this model is related to psychotic major depression (PMD) reinforce its importance (Iijima et al., 2010). This evidence came from meta-analysis showing that PMD patients present higher levels of cortisol hypersecretion when compared to nonpsychotic patients (Nelson and Davis, 1997). Thus, CORT-induced depression model in rodents is a valid tool for evaluating the efficacy of potential antidepressants, explore the mechanism of action of antidepressants and also improve our knowledge about the neurobiology of MDD (Iijima et al., 2010; Zhao et al., 2008). Notwithstanding the importance of CORT-induced model of depression, the involvement of brain pro-oxidant alterations in this model was not yet evaluated.

Based on our recent preclinical findings that DVS or ALA alone or in combination reversed the behavioral alterations induced by CORT model of depression (Silva et al., 2013), in the present study we hypothesized that pro-oxidant alterations in brain areas related to depression neurobiology [e.g. prefrontal cortex (PFC), hippocampus (HC), and striatum (ST)] would underlie the depressive-like alterations induced by CORT and that the antidepressant mechanism of ALA and DVS relies partially on their antioxidant properties.

2. Material and methods

2.1. Animals

Female Swiss mice (25–30 g) were obtained from the Animal House of the Federal University of Ceara, Brazil. The use of female animals was based on the higher incidence of depression in women (Kessler, 2003). For this reason we successfully adapted the CORT-induced model of depression from male (Zhao et al., 2008) to female mice (Silva et al., 2013). The animals were kept in a room with a controlled temperature of 23 ± 1 °C, under a standard light–dark cycle with ad libitum access to food and water, except during the experiments. Food was removed 4 h prior to the oral gavage procedure and returned 20 min after. Ten animals per group were used, and all the experiments were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH, 1996). All efforts were made to minimize the suffering of the animals and to reduce the number of animals used in the experiments. The study was approved by the Animal Ethics Committee of the Faculty of Medicine of the Federal University of Ceara, under protocol number 114/11.

2.2. Drugs

Corticosterone (CORT, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in a saline solution containing 0.1% dimethyl sulfoxide and 0.3% Tween-80. Corticosterone 20 mg/kg was administered as a single daily subcutaneous injection, from 09:00 to 11:30 a.m. for twenty-one consecutive days. The dosage and route of administration for CORT was selected based previous studies (Silva et al., 2013; Zhao et al., 2008). Alpha-lipoic acid (ALA, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in distilled water and 0.2% carboxymethyl cellulose and orally administered (p.o.) for 7 consecutive days at doses of 100 or 200 mg/kg. Desvenlafaxine succinate monohydrate (DVS, Pristiq®, Wyeth Lab) was dissolved in distilled water and administered orally (p.o.) for 7 consecutive days at the doses of 10 or 20 mg/kg. DVS was administered alone or 1 h before the administration of ALA. The dosages for DVS were calculated from human doses using a body surface area (BSA) normalization method (Reagan-Shaw et al., 2008).

2.3. Treatment

The animals were randomly divided into one of the following five experimental groups (n = 6–10 animals/group).

Control group: mice received a daily injection of saline solution containing 0.1% dimethyl sulfoxide and 0.3% Tween-80 by route subcutanea (s.c) or cellulose by oral gavage (p.o), without previous experimental manipulation, for 21 days consecutive. Once the animals in this group showed no statistical differences these data were pooled and the two groups were together considered control animals.
Treated groups with drugs alone: mice received DVS (10 or 20 mg/kg, p.o.) or ALA (100 or 200 mg/kg, p.o.) for 7 days.
CORT-induced depression model: mice in this group received daily subcutaneous injections of CORT (20 mg/kg, s.c.) once a day, between 09:00 and 11:30 a.m., for 21 days (Zhao et al., 2008).
Treated groups with two associated drugs: in these groups the mice received a repeated injection of CORT (20 mg/kg, s.c.) for 14 days. From 15th the mice received CORT + DVS (10 or 20 mg/kg) or CORT + ALA (100 or 200 mg/kg).
Treated groups with three associated drugs: after 14 days of treatment with CORT (20 mg/kg, s.c.), mice received CORT + DVS (10 or 20 mg/kg, p.o.) and after an interval of 1 h received ALA (100 or 200 mg/kg, p.o.). The time interval between the administration of DVS and ALA was set at 1 h because a previous study showed that the maximum mean plasma concentration of DVS in mice occurred 1 h after oral administration of the drug (DeMaio et al., 2011).

Twenty-four hours after the last drug administration, the animals were decapitated and the brain areas prefrontal cortex (PFC), hippocampus (HC) and striatum (ST) dissected for the measurement of oxidative stress. The cerebral structures were homogenized in ten volumes (1:10 w/v) of 20 mM sodium phosphate buffer, pH 7.4, containing