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Research paper

Brain antioxidant effect of mirtazapine and reversal of sedation by its combination with alpha-lipoic acid in a model of depression induced by corticosterone

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ABSTRACT

Background: Depression is accompanied by activated neuro-oxidative and neuro-nitrosative pathways, while targeting these pathways has clinical efficacy in depression. This study aimed to investigate the effects of mirtazapine (MIRT) alone and combined with alpha-lipoic acid (ALA) against corticosterone (CORT) induced behavioral and oxidative alterations.

Methods: Male mice received vehicle or CORT 20 mg/kg during 14 days. From the 15th to 21st days they were divided in groups administered: vehicle, MIRT 3 mg/kg or the combinations MIRT + ALA100 or MIRT + ALA200. On the 21st day of treatment, the animals were subjected to behavioral tests. Twenty-four hours after the last drug administration hippocampus (HC) and striatum (ST) were dissected for the determination reduced glutathione (GSH), lipid peroxidation (LP) and nitrite levels.

Results: CORT induced anxiety- and depressive-like behaviors as observed by increased immobility time in the tail suspension test and decreased sucrose consumption. MIRT or MIRT + ALA are effective in reversing anxiety- and depressive-like behaviors induced by CORT. CORT and MIRT alone prolonged sleeping time and this effect was reversed by MIRT + ALA. CORT significantly increased LP, which was reversed by MIRT or MIRT + ALA. Nitrite levels were increased in CORT-treated animals and reversed by MIRT + ALA200 (HC), MIRT or MIRT + ALA (ST).

Limitation: A relative small sample size and lack of a washout period between drug administration and behavioral testing.

Conclusions: MIRT or MIRT + ALA reverse CORT-induced anxiety- and depressive-like behaviors probably via their central antioxidant effects. Augmentation of MIRT with ALA may reverse sedation, an important side effect of MIRT. Randomized controlled studies are needed to examine the clinical efficacy of this combination in human depression.

1. Introduction

Depression is a disabling mental disorder, with high incidence and chronic course characterized by depressed mood (APA, 2014; Kessler et al., 2003). This disorder is a multifactorial condition due to genetic, biochemical, psychological, social and family influences being, for this reason, studied under different approaches (APA, 2014; Who, 2001).

There is now evidence that depression is characterized by activated neuro-oxidative and neuro-nitrosative pathways, which may drive neuroprogressive processes, namely neurotoxicity and excitotoxicity,

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and neuronal degenerative processes, including changes in neuroplasticity, neurogenesis and apotopsis (Liu et al., 2015; Maes, 2011, 2008; Moylan et al., 2014). Preclinical and clinical studies have reported the involvement of oxidative imbalance in the neurobiology of depression (Ng et al., 2008; O'Donnell et al., 2014; Silva et al., 2016). The main oxidative biomarkers observed in depression are increased lipid peroxidation, increased nitric oxide production, generation of autoimmune responses directed to oxidatively modified epitopes, and lowered levels of key antioxidants, including reduced glutathione (GSH), vitamin E and C, coenzyme Q10 and zinc (Dhir and Kulkarni, 2007; Eren et al., 2007; Ergün et al., 2006; Fujisaki et al., 2003; Lima et al., 2016; Mello et al., 2013; Silva et al., 2016; Wang et al., 2008). A meta-analysis further underscores that depression is accompanied by increased oxidative biomarkers and lowered levels of antioxidants (Liu et al., 2015).

Depression is a stress-related neuropsychiatric disorder (Raison and Miller, 2003). Furthermore, acute and subchronic exposure to stress stimulates hypothalamic–pituitary–adrenal (HPA)-axis activity, which is in part related to attenuation of glucocorticoid negative feedback mechanisms (Mizoguchi et al., 2003; Tafet and Nemeroff, 2015). Moreover, chronic stress activates oxidative pathways thereby increasing lipid peroxidation and the catabolism of monoamines, while reducing antioxidant enzyme activities (Moylan et al., 2014).

Based on HPA-axis hyperactivity following stress and depression, a preclinical model of depressive-like alterations was developed, whereby depressive behaviors were induced by repeated administration of corticosterone (CORT) (Zhao et al., 2008a). The rodents submitted to this depression model show increases in immobility time in the forced swimming test, a gold standard test for the screening of antidepressant drugs (Iijima et al., 2010), suggesting that repeated administration of glucocorticoids may mimic the symptoms of depression (Johnson et al., 2006; Silva et al., 2013; Sousa et al., 2015). Chronic treatment of rodents with CORT induces multiple anxiety- and depressive-like changes in behavior, neurochemistry and brain morphology similar to those observed in treatment resistant depression (TRD) (Murray et al., 2008) suggesting that this model may be used as a TRD model (Ago et al., 2013).

Mirtazapine (MIRT) is an atypical antidepressant with noradrenergic and serotonergic effects, being one of the few antidepressants that do not have major effects on the reuptake of monoamines (Thase et al., 2010). This drug was developed in 1996 and its relevance reside on the manifestation of fewer side effects when compared to tricyclic antidepressant drugs and a faster onset of action (Peña et al., 2005). Despite this, sedation and weight gain are important side effects that limits MIRT use (Thase et al., 2010).

Nevertheless, antidepressant therapies present major limitations, most importantly the late onset of action and limited clinical efficacy (Rush, 2007). Recent reviews showed that augmentation of antidepressant treatments with different antioxidant compounds may increase the efficacy of antidepressants (Maes et al., 2012). In this regard, our research group have studied the antidepressant effects of alpha-lipoic acid (ALA), an endogenous natural antioxidant (Silva et al., 2016, 2014, 2013; Sousa et al., 2015). Our previous results showed that ALA alone and combined with desvenlafaxine presented antidepressant-like effects in CORT-induced model of depression (Silva et al., 2016, 2013).

Thus, in the present study we hypothesized, based on the promising results obtained in previous preclinical study evaluating ALA antidepressant-like effects (Silva et al., 2016, 2014, 2013; Sousa et al., 2015), that the combination of ALA with MIRT would potentiate the antidepressant effects of MIRT and/or improve CORT-induced oxidative alterations in the brain. We also aimed at addressing one important limitation related to MIRT use, i.e. sedation in these animals.

2. Material and methods

2.1. Animals

Male *Swiss* mice (25–30 g) were obtained from the Animal House of the Federal University of Ceará, Brazil (Total 295 animals). 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. All 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 experiments. The project was approved by the Animal Ethics Committee of the Faculty of Medicine of the Federal University of Ceará, under protocol no. 02/2014.

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; Sousa et al., 2015; Zhao et al., 2009). Alpha-lipoic acid (ALA, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in an aqueous solution of 0.2% carboxymethy cellulose and administered by gavage for 7 consecutive days at doses of 100 or 200 mg/kg according to previous studies (Silva et al., 2013). Mirtazapine (MIRT, Remeron, Schering-Plough®) was dissolved in distilled water and administered by gavage for 7 consecutive days at the dose of 3 mg/kg according to a previous study (Engel et al., 2013). In the sleeping time test, a sub-hypnotic dose of sodium pentobarbital (35 mg/kg) diluted in distilled water was intraperitoneally (i.p.) administered 30 min before the test. All solutions were administered in a volume of 0.1 mL/10 g of body weight.

2.3. Experimental design

The animals were randomly divided into eight experimental groups as shown in Fig. 1. In the present study, different animals were used for biochemical tests assay and for behavioral determinations.

i) Control group: mice received daily injections of saline solution containing 0.1% dimethylsulfoxide and 0.3% Tween-80 (s.c.) for 21 consecutive days;
ii) CORT-induced model of depression: 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 21days (Silva et al., 2016, 2013; Sousa et al., 2015; Zhao et al., 2008a, 2008b).
iii) Groups treated with MIRT alone: mice received daily injections of saline solution containing 0.1% dimethylsulfoxide and 0.3% Tween-80 (s.c.) for 14 consecutive days. From 15th to 21st days of administration, the animals received MIRT (3 mg/kg, p.o.).
iv) Groups treated with MIRT and ALA associated (MIRT + ALA): mice received daily injections of saline solution containing 0.1% dimethylsulfoxide and 0.3% Tween-80 (s.c.) for 14 consecutive days. From 15th to 21st days of administration, the animals received MIRT (3 mg/kg, p.o.) and one hour after ALA (100 or 200 mg/kg, p.o.).
v) CORT-induced depression model treated with MIRT alone (CORT + MIRT): mice received repeated injections of CORT during 14 days to induce depressive-like behavior. From the 15th to 21st days of administration, the animals received CORT and MIRT (3 mg/kg).
vi) CORT-induced depression model treated with the combination of MIRT + ALA (CORT + MIRT + ALA): From the 15th to 21st days of