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Riparin II ameliorates corticosterone-induced depressive-like behavior in mice: Role of antioxidant and neurotrophic mechanisms

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ABSTRACT

Riparin II (RIP II) is an alkamide isolated from *Aniba riparia* that has presented antidepressant and anxiolytic effects in acute stress behavioral models. This study aimed to investigate the activity of RIP II in a corticosterone-induced depression mice model. Corticosterone (20 mg/kg, s.c.) was administered once a day for 21 days. RIP II (50 mg/kg, p.o.) or fluvoxamine (FLU, 50 mg/kg, standard antidepressant, p.o.) was administered after corticosterone (CORT) injection, for the last 7 days of CORT treatment. Mice were exposed to the following behavioral tests: forced swimming, tail suspension, open field, sucrose preference, elevated plus maze and ymaze. After behavioral evaluation, brain areas (prefrontal cortex, hippocampus and striatum) were dissected for neurochemical evaluation: oxidative stress parameters (MDA, nitrite and GSH) and BDNF dosage. Repeated CORT administration caused depressive-like behavior in mice as indicated by increased despair effects in forced swimming and tail suspension tests and anhedonia in sucrose preference test. In addition, CORT decreased BDNF levels in the mice hippocampus and induced oxidative load in the brain with significative increase in pro-oxidant markers (lipid peroxidation and nitrite levels) and a decline in anti-oxidant defense system (reduced glutathione levels), indicating a direct effect of stress hormones in the induction of the brain oxidative stress. On the other hand, RIP II treatment reversed CORT-induced depressive-like behavior. Furthermore, this treatment reversed the impairment in BDNF levels and oxidative brain insults caused by CORT. This may demonstrate the mechanisms involved in antidepressant-like effect of RIP II. These findings further support that RIP II may be implicated as pharmacological intervention targeting depression associated with HPA-axis dysregulation.

1. Introduction

Depression is a common and recurrent disorder and the leading cause of disability in the world (O'Leary et al., 2015). It is estimated that there are about 350 million people affected worldwide. Depression should be differentiated from normal emotional responses to the challenges of everyday life, since in more severe cases it can lead to serious problems, such as suicide. According to the World Health Organization, more than 800,000 people die each year from suicide, and this is the second leading cause of death in 15–29-year-olds (WHO, 2017).

The main symptoms of depression are fatigue, depressed mood, loss of pleasure, social isolation and loss of energy. However, it is known that many other symptoms are found together in depressive patients, such as anxiety, sleep disorders and cognitive deficits (Fried and Nesse, 2015; American Psychiatric Association, 2017).

It is believed that the etiology of depression is a result of abnormalities in genetic and environmental factors (Krishnan and Nestler, 2008). Stress has been described as the main environmental factor in the predisposition of individuals to depression (Keller et al., 2007; Andrews et al., 2011; Willner et al., 2013). It was observed a hypothalamic-pituitary-adrenal axis hyperactivity due to high levels of cortisol, as well as the impairment of the negative feedback regulatory

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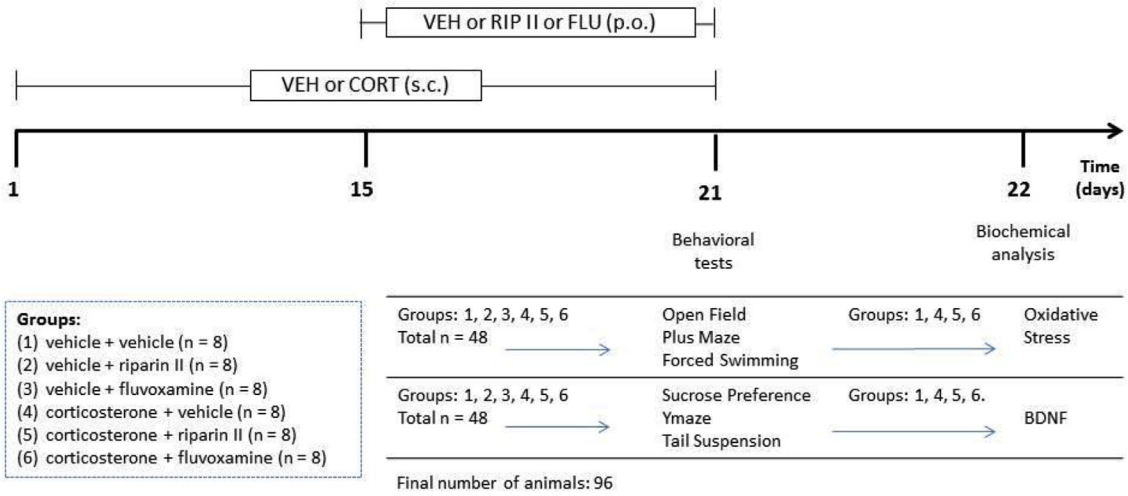

Fig. 1. Schematic overview of experimental design.

mechanism (McEwen, 2007; Aguilera, 2011; Zunszain et al., 2011).

It is known that depression occurs about two to three times more often in female subjects. In addition, this is also considered a risk factor for treatment-resistant depression (Kornstein and Schneider, 2001; Kessler, 2003; Ferrari et al., 2013). The mechanism involved remains unclear, but one of the major hypotheses is that females are more sensitive in the hypothalamic-pituitary-adrenal axis (HPA) related hormones than males (Young and Korszun, 2010; DeSantis et al., 2011). Some researchers have shown the association between low level of estrogen and higher risk of major depression disorders (Young et al., 2000; Maartens et al., 2002; Payne, 2003), and that estrogen treatment can manage hormonal-related depression in females (Soares, 2014, 2017). In animals, was observed that lacking of estrogen increases immobility time and decreases swimming in forced swimming test (Imwalle et al., 2005; Xu et al., 2017).

Corticosterone, the rodent stress hormone equivalent to cortisol in humans, is also elevated in stress conditions. Therefore, the model of chronic exposure to corticosterone has been described as effective in precipitating features similar to depression in animals. These features can be observed in behavioral and neurochemical tests, so this model is a useful tool in the study of depression, including the treatment-resistant depression (Zhao et al., 2008; Silva et al., 2013; Vasconcelos et al., 2015).

It is known that most patients treated with conventional antidepressants do not respond adequately to treatment. In this context, natural products constitute a great source for the development of new drugs since compounds devised by nature are often far superior in terms of diversity, specificity, binding efficiency and propensity to interact with biological targets (Carlson, 2010). In recent studies in our group, riparin II (RIP II), an alkamide isolated from *Aniba riparia*, affected the central nervous system, showing anxiolytic and antidepressant activities in acute animal models (Sousa et al., 2007; Teixeira et al., 2013). The antidepressant-like effect seems to be mediated by an interaction with the dopaminergic (D1 and D2 receptors), noradrenergic (α1 receptor) and serotonergic (5-HT_{1A} receptor) systems (Teixeira et al., 2013).

Given the current importance of the neurotrophic hypothesis of depression, we investigated the effects of RIP II on BDNF levels and also on oxidative stress parameters in a corticosterone-induced depression model.

2. Materials and methods

2.1. Animals

The experiments were conducted using female *Swiss* mice (22–25 g) which were maintained at 22–25 °C with free access to water and food, under a 12:12 h light/dark cycle (lights on at 7:00 a.m.). Animals were randomly distributed into specified experimental groups. All experiments were carried out between 12:00 p.m. and 4:00 p.m. The procedures in this study were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH, 1996) and approved by the Ethics Committee of the Institution. All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

2.2. Drugs and treatment

To conduct the chronic treatment mice were divided into six groups: (1) vehicle + vehicle; (2) vehicle + riparin II; (3) vehicle + fluvoxamine; (4) corticosterone + vehicle; (5) corticosterone + riparin II; (6) corticosterone + fluvoxamine. For the treatments, corticosterone (CORT, 20 mg/kg, Sigma-Aldrich, St Louis, MO, USA) was dissolved in a saline solution containing 0.1% dimethyl sulfoxide and 0.1% Tween 80 and administered subcutaneously (between 9:00 a.m. and 10:30 a.m.), for 21 consecutive days. Fluvoxamine (FLU, 50 mg/kg, Luvox®, Abott, New Jersey, USA) was dissolved in distilled water and riparin II (RIP II, 50 mg/kg) was dissolved in distilled water containing 2% of Tween 80. RIP II was isolated from the green fruits of *Aniba riparia*. This substance was deposited in the Bank of Standards of Natural and Synthetic Products of the Laboratory of Pharmaceutical Technology of the Federal University of Paraiba, and for use in this work, it was repurified by thin-layer chromatography. FLU and RIP II were orally administered, after CORT, during the last 7 days of treatment. On the 21st day, 1 h after the last treatment, the animals were submitted to the behavioral tests. On the 22nd day, the groups (1) vehicle + vehicle; (4) corticosterone + vehicle; (5) corticosterone + riparin II; (6) corticosterone + fluvoxamine; which presented significative results, were dissected and submitted to biochemical evaluations. Fig. 1 shows an experimental design of the treatments, behavioral and biochemical analysis.

The dosage and route of administration for drugs were selected based on previous studies (Zhao et al., 2008; Teixeira et al., 2013; Vasconcelos et al., 2015).

2.3. Behavioral assessment

2.3.1. Open field test

This test evaluates the influence of drugs on the locomotor activity of the animal (Archer, 1973). An acrylic apparatus was used (transparent walls and black background, dimensions 30 × 30 × 15), divided