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Reversal effect of Riparin IV in depression and anxiety caused by corticosterone chronic administration in mice

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ABSTRACT

Mental disorders have a multifactorial etiology and stress presents as one of the causal factors. In depression, it is suggested that high cortisol concentration contributes directly to the pathology of this disease. Based on that, the study aims to evaluate the potential antidepressant effect of Riparin IV (Rip IV) in mice submitted to chronic stress model by repeated corticosterone administration. Female Swiss mice were selected into four groups: control (Ctrl), corticosterone (Cort), Riparin IV (Cort + Rip IV) and fluvoxamine (Cort + Flu). Three groups were administrated subcutaneously (SC) with corticosterone (20 mg/kg) during twenty-one days, while the control group received only vehicle. After the fourteenth day, groups were administrated tested drugs: Riparin IV, fluvoxamine or distilled water, by gavage, 1 h after subcutaneous injections. After the final treatment, animals were exposed to behavioral models such as forced swimming test (FST), tail suspension test (TST), open field test (OFT), elevated plus maze (EPM) and sucrose preference test (SPT). The hippocampus was also removed for the determination of BDNF levels. Corticosterone treatment altered all parameters in behavioral tests, leading to a depressive- and anxious-like behavior. Riparin IV and fluvoxamine exhibit antidepressant effect in FST, TST and SPT. In EPM and OFT, treatment displayed anxiolytic effect without alteration of locomotor activity. Corticosterone administration decreased BDNF levels and Riparin IV could reestablish them, indicating that its antidepressant effect may be related to ability to ameliorate hippocampal neurogenesis. These findings suggest that Riparin IV improves the depressive and anxious symptoms after chronic stress and could be a new alternative treatment for patients with depression.

1. Introduction

Depression is a chronic and complex disorder with an enormous impact on society and is associated with functional impairment and high morbidity and mortality. The prevalence of major depression is high and is still increasing. Data confirmed that women are more vulnerable than men and are more frequent in young people and in the elderly (Silva et al., 2014; World Health Organization, 2017). According to The World Health Organization (WHO), by 2020 depression is estimated to be the second leading global burden of illness.

Depression symptoms include depressed mood, irritability, lack of concentration, psychomotor retardation or agitation, anhedonia (reduced ability to experience pleasure from natural rewards), and abnormalities in appetite and sleep (American Psychiatric Association, 2014; Anisman and Matheson, 2005). Anxiety disorders have substantial comorbidity with depression and could combine, in addition to regular depressive symptoms, nervous dread of the future, hypervigilance, increased heart rate and blood pressure (Gregus et al., 2005; Grillo, 2016; Miller and Hen, 2015).

Most depression occurs idiopathically, but some risk factors could trigger depressive symptoms, such as some types of cancers, endocrine abnormalities, side effects of drugs, stressful life events, among many

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others (Wager-Smith and Markou, 2011). Stress is presented as one of the causal factors of many mental disorders (Anisman and Matheson, 2005; Wang et al., 2008) and it is suggested that hypersecretion of cortisol contributes directly to the pathology of anxiety and depression (Du and Pang, 2015; Rohleder et al., 2010; Skórzewska et al., 2006).

During depression, disturbs in the limbic system may result in alterations in the hypothalamus-pituitary adrenal (HPA) axis where the hippocampus appears to be involved in negative feedback control of the glucocorticoid levels (Gogos et al., 2009; Krishnan and Nestler, 2008; Schoenfeld and Cameron, 2015; Sterner and Kalynchuk, 2010; Warner-Schmidt and Duman, 2006).

This inhibition appears to be dependent on the hippocampal integrity. Studies suggest that depressed patients show hippocampal volumetric reductions (Chattarji et al., 2015; Lorenzetti et al., 2009) and neurogenesis in rodent hippocampus is reduced by stress and increased by various types of antidepressant treatments (Miller and Hen, 2015; Sahay and Hen, 2007; Warner-Schmidt and Duman, 2006). The neurotrophic alterations observed in the hippocampus of depressed patients may be attributed in part to the reductions of the brain-derived neurotrophic factor (BDNF) (Autry and Monteggia, 2012).

Many strategies can take advantage of the molecular diversity of natural products in the designing of combinatorial synthesis collections. Structural modifications of the skeleton of an existing bioactive natural product are intended to promote improvements in their inherent biological activity or pharmacological properties at a reasonable cost. This can be achieved by means of semi-synthetic modifications of the molecule or by synthetic methods (Haustedt et al., 2006; Koehn and Carter, 2005).

Riparin IV is a synthetic alkamide drug analogue to *Aniba riparia*'s natural compounds (Fig. 1). The synthesis involves the condensation between acyl chlorides and *O*-methyltyramine in a very high yield (Barbosa-Filho et al., 1990). Studies conducted by Dias (2012) and Nascimento et al. (2016) evidenced that Riparin IV has an antinociceptive and anti-inflammatory activity in the model of nociception induced by acetic acid, formalin and carrageenan.

Due to the similarity with the tyramine chemical structure, a sympathomimetic amine, and central effects of riparins I, II, and III, it becomes relevant to investigate the pharmacological potential of Riparin IV in anxiety and depression models. Based on these findings, the goal of this study is to evaluate the potential antidepressant effect of Riparin IV in mice submitted to a chronic stress model through repeated corticosterone injections.

2. Materials and methods

2.1. Animals

Female Swiss mice (22–25 g, age: 8–10 weeks) were used in this study. The animals were maintained on a 12/12 h light/dark cycle, with access to water and food *ad libitum*, randomly distributed into specified experimental groups. All experiments were performed at 23 ± 2 °C room temperature and were carried out between 12:00 and 16:00 h. Experiments were performed in accordance with the current laws and the National Institute of Health Guide for the Care and Use of Laboratory Animals and under the consent and surveillance of the Ethics Committee from the Department of Physiology and Pharmacology of Federal University of Ceará (Protocol number 112/2014).

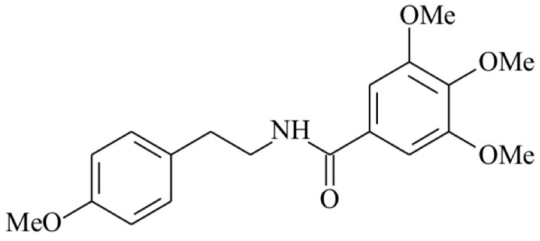

Fig. 1. Chemical structure of Riparin IV.
Adapted from Barbosa-Filho et al. (1990).

2.2. Drugs

Corticosterone (Sigma®, St Louis, MO, USA) was dissolved in a 0.9% saline solution containing 0.1% polysorbate (Tween®) 80 (VETEC™, USA) and 0.1% dimethyl sulfoxide (DMSO) (VETEC™, USA) and it was administered in a dose of 20 mg/kg, subcutaneously (SC).

The Riparin IV, a total of three batches, was provided by Laboratory Chemistry of Bioactive Natural and Synthetic Products, Federal University of Piauí, Teresina, PI, Brazil. Riparin IV was emulsified with 2% Tween® 80 and administered intragastric (oral gavage) doses of 50 mg/kg. Fluvoxamine (Abott®, New Jersey, USA), in a 50 mg/kg dose were dissolved in distilled water and given by oral gavage.

2.3. Experimental procedure

The study design was based on a depression mouse model involving exogenous corticosterone administration (Zhao et al., 2008), where repeated corticosterone injections increase depression-like behavior in mice after up to 1 week.

The animals were divided in four experimental groups (n = 10 animals/group, on average): (1) control; (2) corticosterone (Cort); (3) corticosterone + Riparin IV (Cort + Rip IV) and (4) corticosterone + fluvoxamine (Cort + Flu). Groups (1), (2) and (3) were administrated subcutaneously (SC) with 20 mg/kg corticosterone in a saline vehicle for twenty-one days, while the control group was administrated only with saline vehicle. In the last seven days of treatment, each group was administrated with tested drugs Riparin IV (50 mg/kg) (group 3), fluvoxamine (50 mg/kg) (group 4) or distilled water vehicle (distilled water emulsified with 2% Tween® 80) (groups 1 and 2), per gavage, with a 1 hour interval between corticosterone treatment injections (Fig. 2).

Behavioral determinations were registered 60 min after the last drug administration and the hippocampus was removed for BDNF levels evaluation. One group of 40 animals, divided in 4 groups was tested in OFT, FST and SPT behavioral tests. Other group of 40 animals, divided as explained above, was submitted to other behavioral tests and their hippocampus used to BDNF analysis.

2.4. Behavioral tests

2.4.1. Forced swimming test

The procedure used was based on that described by Porsolt et al. (1977) with a minimum modification. Mice were placed individually in the cylinders tank filled with water (25 °C ± 1 °C) to a depth of 25 cm, dimensions the mice will not be able to touch the bottom of the tank, either with their feet or their tails, during the swimming test. Animal behavior was analyzed by an independent researcher who did not know the experimental groups. The immobility time during a five minute period was recorded. Immobility was defined as the animal floating in the water with the absence of any movement except for those necessary for keeping the nose above water. An increase in the duration of immobility is indicative of depressed-like behavior (Yankelevitch-Yahav et al., 2015).

2.4.2. Tail suspension test

The procedure followed in this study was previously described by Steru et al. (1985). Mice were suspended 50 cm above the floor by adhesive scotch tape placed around 1 cm from the tip of the tail. Immobility time was measured using a chronometer by an observer during a six minute period.

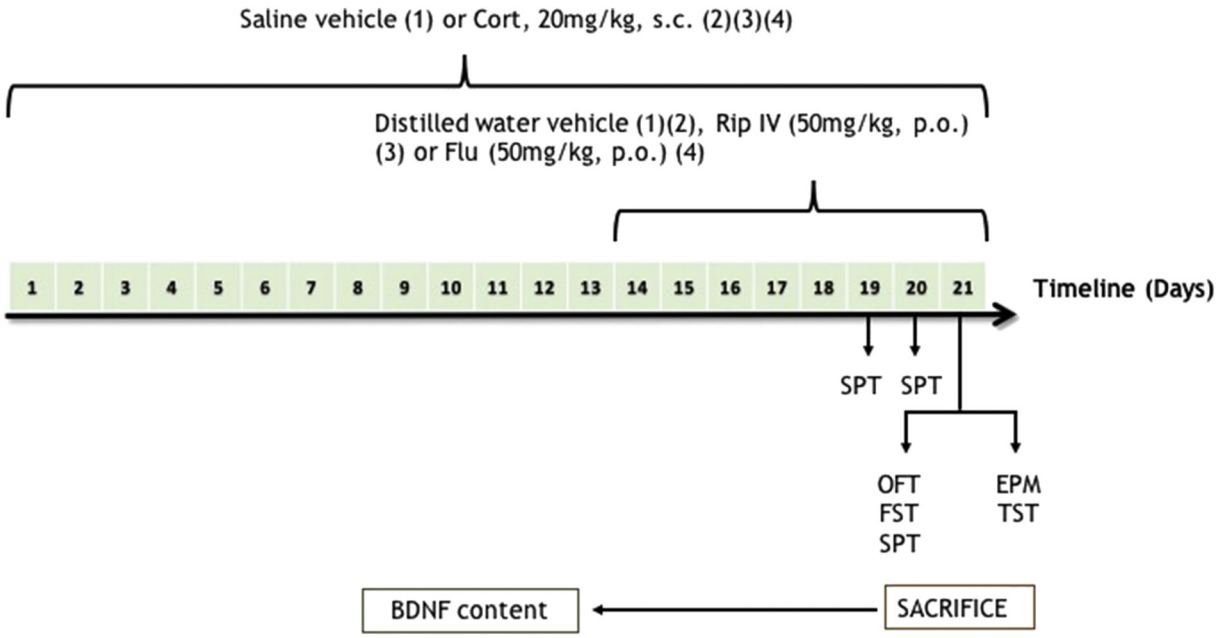

Fig. 2. Schematic overview of the experimental design. SC: subcutaneous; PO: per oral gavage; FST: forced swimming test; TST: tail suspension test; OFT: open field test; EPM: elevated plus maze test; SPT: sucrose preference test; BDNF: brain-derived neurotrophic factor.

2.4.3. Open field test

The test was performed in a soundproof in an air-conditioned chamber under dim light. The apparatus used was a cube of transparent acrylic with a black floor (30 × 30 × 15 cm) and divided into nine equal square grids clearly drawn on the surface. After 60 min of treatment, the animals were placed on the central quadrant to begin the test. The outcome measured during the 5 minute test was: number of line crosses contacted with all four legs (spontaneous movement), number of grooming (licking the paws, washing movements over the head, fur licking and/or tail/genitals cleaning) and rearing, which is the number of times an animal stood erect on its hind legs with forelegs in the air against the wall (Archer, 1973).

2.4.4. Elevated plus maze

The elevated plus maze is a plus-shaped apparatus with four arms at right angles to each other as described by Handley and Mithani (1984). Sixty minutes after oral treatment, the animal was placed at the center of the plus maze facing one of the enclosed arms, and observed for 5 min, according to the following parameters: number of entries into the open and closed arms and time of permanence in each of them. The criterion for arm visit was considered only when the animal decisively moved all its four limbs into an arm. The percentage of time spent in the arms was calculated by time in open arms or closed arms / total time × 100, the number of entries into the arms was calculated using the number of entries into open or closed arms / total number of entries.

2.4.5. Sucrose preference test

Sucrose preference is considered to be an index of anhedonia (Wang et al., 2014). The test was performed as described previously by Strekalova et al. (2004), with minor modifications. In this model, a mouse is given free choice between two solutions to drink: water or a sucrose solution. Usually, mice show a clear preference for the sweetened water, while depressed animals demonstrate less interest. Before the test, on the 19th day of the experiment, the mice were habituated to 2% (w/v) sucrose solution by placing two bottles of 2% sucrose solution in each cage. On the 20th day, sucrose solution in two bottles was replaced with tap water. After adaptation, for SPT mice were housed in individual cages for 18 h and were given free access to two identical bottles, one filled with 2% sucrose solution and the other filled with tap water. The beginning of the test started with the onset of the dark (active) phase of the animals' cycle and no previous food or water deprivation was applied before the test. After 18 h, sucrose and water consumption were recorded and the sucrose preference was calculated by the following formula:

$$\text{Sucrose preference (\%)} = \frac{\text{Sucrose consumption}}{\text{Water consumption} + \text{Sucrose consumption}} \times 100$$

2.5. Neurochemical tests

2.5.1. BDNF

After twenty-one days of treatment, the animals were euthanized by decapitation to remove the skulls. The hippocampi were dissected and stored in a freezer at −80 °C for posterior biochemical analysis. The content of BDNF protein was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, Minnesota) according to the manufacturer's instructions. The amount of BDNF was determined by absorbance in 450 nm and expressed as pg per g of wet tissue. The standard curve demonstrates a direct relationship between optical density and BDNF concentration.

2.6. Statistical analysis

The data were analyzed with GraphPad Prism 7.0a (San Diego, CA, USA). Statistical analysis of the data was performed by one-way ANOVA, followed by Student-Newman-Keuls post-hoc test. Data are expressed as mean ± SEM and differences were considered significant when $p \leq 0.05$.

3. Results

Mice were treated with subcutaneous corticosterone injections at a dose of 20 mg/kg, daily, and behavioral tests were assessed on the twenty-first day by using the forced swimming test (FST), tail suspension test (TST), sucrose preference test (SPT), elevated plus maze (EPM) and open field test (OFT).

Results have showed that exogenous corticosterone administration

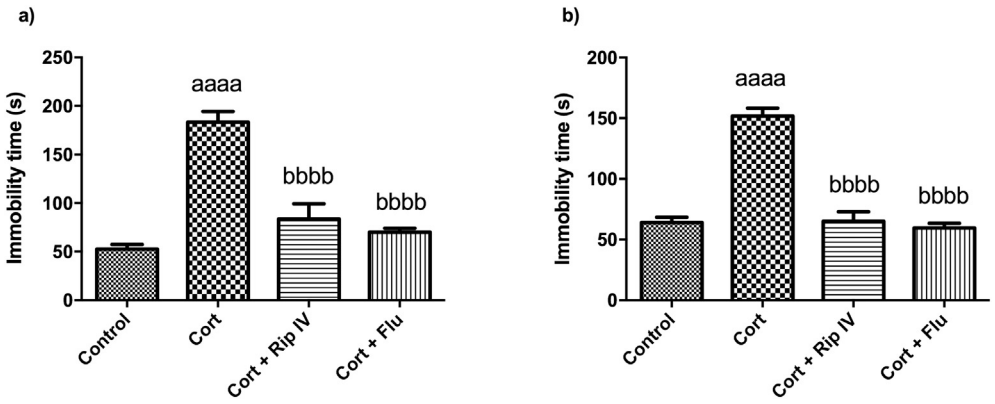

Fig. 3. Immobility time analysis in forced swimming test (a) and tail suspension test (b) after chronic corticosterone injections (20 mg/kg) and 7 days of oral administration of tested drugs Riparin IV (50 mg/kg) or fluvoxamine (50 mg/kg). Data are expressed as mean ± SEM of immobility time (n = 10 per group). Statistical analysis was performed by one-way ANOVA, followed by Student-Newman-Keuls post-hoc test. $^{aaaa}p < 0.0001$ *vs* control; $^{bbbb}p < 0.0001$ *vs* stressed group.

for twenty-one days can produce depressive-like behavior in the forced swimming and tail suspension tests (Fig. 3). Administration of Riparin IV or fluvoxamine for 7 days has decreased immobility time compared to corticosterone administration only ($p < 0.0001$).

It was also studied the effect of Riparin IV in the open field and elevated plus maze, two sensitive tests to evaluate anxious-like behavior (Korte and De Boer, 2003). In the OFT, groups treated orally with Riparin IV and fluvoxamine decreased the number of rearing and grooming as compared to Cort group. No alteration was observed in the number of crossings (Fig. 4).

In the elevated plus maze (EPM), the number of entries and the time spent in the open arms were taken as indexes of anxiety. The treatment significantly increased in number and time spent in the open arms compared to the Cort group. When comparing percentage time spent in the open arms to the closed arms, the animals treated with Riparin IV ($p < 0.0001$) and fluvoxamine ($p < 0.01$) spent significantly more time in the open arms than compared to Cort and control groups. These parameters were expressed as a percentage of the total entries and the total time spent within any arm during the 5 minute test session (Fig. 5).

In the evaluation of the sucrose preference parameter (Fig. 6), the Cort-treated group had a lower sucrose consumption when compared to other groups ($p < 0.001$), while Riparin IV ($p < 0.01$) and fluvoxamine ($p < 0.0001$) treatment was able to recover the sucrose preference after the corticosterone exogenous administration.

In the neurochemical analysis, Fig. 7 shows the significant effect of Riparin IV and fluvoxamine treatment on BDNF protein levels in the hippocampus. Corticosterone administration significantly decreased BDNF protein levels in the hippocampus of mice, as compared to control. Riparin IV and fluvoxamine treatment significantly increased the BDNF protein levels when compared to stressed animals.

4. Discussion

Stress induced by repeated corticosterone administration was chosen to induce chronic depression because it can control over increases in circulating glucocorticoids, different than other stress models such as chronic mild stress exposure and repeated restraint stress (Gregus et al., 2005; Herrera-Pérez et al., 2016). Animals can differ in stress responses (quality and quantity) and HPA axis stimulation and this may result in differentiating corticosterone levels between different animals exposed to the same stressor, which in turn could lead to increased experimental variability (Marks et al., 2009; Zhao et al., 2008).

Animal models of depression are typically based on exposure of animals under a stressful condition (a real or a potentially dangerous situation) and on the use a specific test for measuring behavioral and physiological reactions. The forced swimming and tail suspension tests are two of the most widely used models for assessing antidepressant-like activity in mice (Bai et al., 2018; Bergner et al., 2016; Can et al., 2012; Cryan et al., 2005, 2002; Krishnan and Nestler, 2011; Palanza, 2001) and they are highly sensitive to all major classes of antidepressant drugs and treatments including MAO inhibitors, tricyclics, serotonin-specific reuptake inhibitors, atypical antidepressants, and electroconvulsive shock (Castagné et al., 2011). The increased immobility behavior in the FST and TST is considered to be an indicator of despair and is widely used to investigate the acute and chronic effects of antidepressant drugs (Bergner et al., 2010).

Depression is one the leading cause of disability for both males and

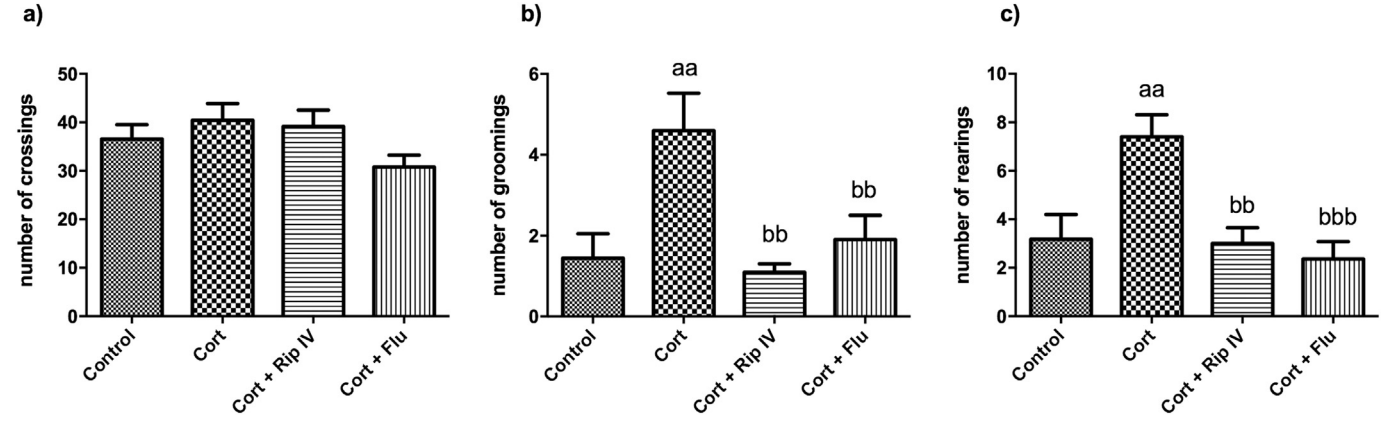

Fig. 4. Number of squares crossed (a), grooming (b) and rearing (c) of animals in the open field test after chronic corticosterone injections (20 mg/kg) and 7 days of oral administration of tested drugs Riparin IV (50 mg/kg) or fluvoxamine (50 mg/kg). Data are expressed as mean ± SEM during 5 min' test (n = 10 per group). Statistical analysis was performed by one-way ANOVA, followed by Student-Newman-Keuls post-hoc test. Significant values: $^{aa}p < 0.01$ *vs* control; $^{bb}p < 0.01$ and $^{bbb}p < 0.001$ *vs* Cort group.

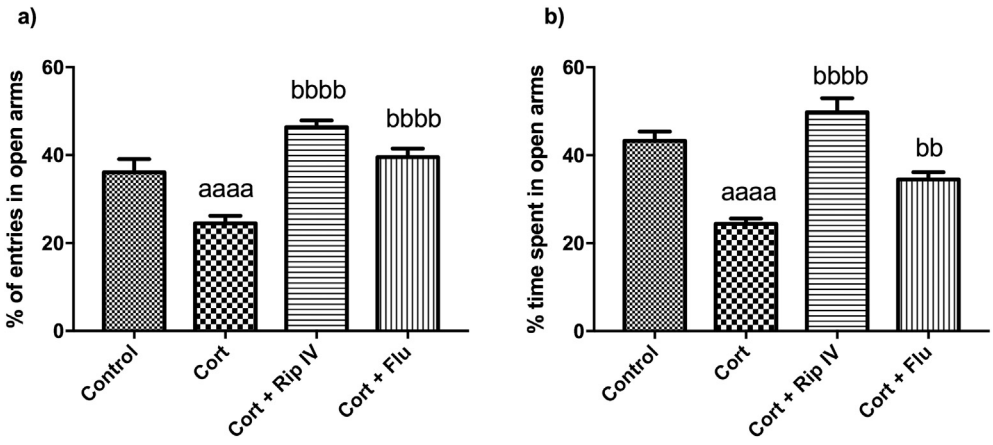

Fig. 5. Percentage of the total entries (a) and the total time spent (b) in open arms analysis of animals in the elevated plus maze after chronic corticosterone injections (20 mg/kg) and 7 days of oral administration of tested drugs Riparin IV (50 mg/kg) or fluvoxamine (50 mg/kg). Data are expressed as mean ± SEM during 5 minutes' test (n = 10 per group). Statistical analysis was performed by one-way ANOVA, followed by Student-Newman-Keuls post-hoc test. Significant values: $^{aaaa}p < 0.0001$ *vs* control; $^{bb}p < 0.01$ and $^{bbbb}p < 0.0001$ *vs* Cort group.

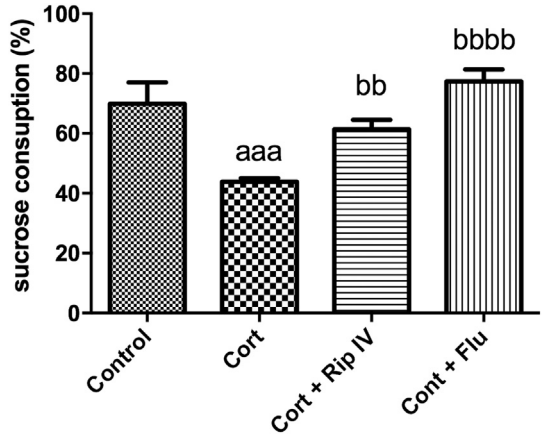

Fig. 6. Percentage of sucrose consumption analysis of animals in the sucrose preference test after chronic corticosterone injections (20 mg/kg) and 7 days of oral administration of tested drugs Riparin IV (50 mg/kg) or fluvoxamine (50 mg/kg). Data are expressed as mean ± SEM (n = 10 per group). Statistical analysis was performed by one-way ANOVA, followed by Student-Newman-Keuls post-hoc test. Significant values: $^{aaa}p < 0.001$ *vs* control; $^{bb}p < 0.01$ and $^{bbbb}p < 0.0001$ *vs* Cort group.

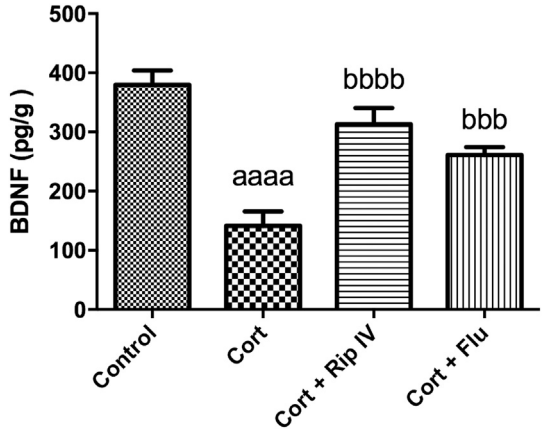

Fig. 7. Brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus of animals after chronic corticosterone injections (20 mg/kg) and 7 days of oral administration of tested drugs Riparin IV (50 mg/kg) or fluvoxamine (50 mg/kg). Data are expressed as mean ± SEM (n = 8 per group). Statistical analysis was performed by one-way ANOVA, followed by Student-Newman-Keuls post-hoc test. Significant values $^{aaaa}p < 0.0001$ *vs* control; $^{bbb}p < 0.001$ and $^{bbbb}p < 0.0001$ *vs* Cort group.

females, however the burden of depression is two to three times more common in women than in men (World Health Organization, 2017) and the female gender is considered to be a risk factor for treatment-resistant depression (Kornstein and Schneider, 2001). It remains unclear whether this prominent sex difference in depression pathophysiology and treatment is caused by cultural aspects or is based on biological differences between the sexes. One of the major hypotheses is that females are more sensitive in the hypothalamic-pituitary-adrenal axis (HPA) related hormones than males (Albert, 2015; DeSantis et al., 2011; Palanza, 2001). Indeed, estrogen administration to ovariectomized females enhances corticosterone secretion following stress (Herman et al., 2003; Soares, 2017). In this light, Cheslack-Postava et al. (2015) indicated that women using oral contraceptive showed reduced rates of major depression and anxiety compared with non-users. Taken together, these studies suggest that moderating of the estrogen cycle may have an important effect (possibly protective) on the pathology that underlies depression and that decreases in estrogen may raise the risk for depression. In addition, recent preclinical studies in depression by our group have been conducted using all female animals (Lopes et al., 2018; Silva et al., 2016, 2013; Sousa et al., 2015; Vasconcelos et al., 2015). Thus, our results are in line with those found in the literature that show the precipitation of depressive-like behavior in female rodent induced by chronic stress.

High cortisol levels could also be associated to psychotic depression, where people with severe depression may also develop psychotic symptoms (hallucinations and/or delusions), most commonly thematically consistent with the negative, self-blaming cognitions, low mood, suicidal ideation and neuropsychological impairment. This subtype of depression proves difficult to treat and the pharmacotherapy includes the combination of antidepressants and antipsychotics associated with many adverse effects (Bajor et al., 2011; Furuse and Hashimoto, 2009; Iijima et al., 2010).

Clinical studies proved that monotherapy using the fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), was effective against both the psychotic and depressive symptoms of this disorder (Furuse and Hashimoto, 2009). Zanardi et al. (2000) conducted a double-blind study comparing fluvoxamine and venlafaxine monotherapy for six weeks. In twenty-eight hospitalized patients diagnosed with major depression and severe psychotic features, fluvoxamine showed efficacy as the treatment of psychotic depression. These results motivated the choice of fluvoxamine as the reference drug for this work. In addition, studies conducted in our laboratory showed the effect of fluvoxamine in this model (Lopes et al., 2018; Vasconcelos et al., 2015).

The stress response is meant to maintain the stability or the homeostasis of the organism. Long-term activation of the stress system can cause pathological states, or exacerbate pre-existing or latent morbid states such as obesity and cardiovascular diseases (Pereira-Figueiredo et al., 2017; Rohleder et al., 2010). Stressful events also

underlie various pathophysiological processes associated with mood disorders, such as unipolar or bipolar depression, as well as posttraumatic stress disorder (PTSD) (Morris et al., 2012) or anxiety (Kiyohara and Yoshimasu, 2009).

More than half of individuals with depression are also diagnosed with an anxiety disorder (Wu and Fang, 2014) and it was crucial to evaluate the anxiolytic-like effect of Riparin IV. The open field test is used to measure not only anxiety-like behaviors but also activity or even sedation (Prut and Belzung, 2003). Our findings show that the corticosterone, Riparin IV and fluvoxamine treatment didn't change the locomotor activity in animals. However chronic corticosterone administration increased grooming and rearing, and the treatment with tested drug significantly decrease these parameters demonstrating also an anxiolytic effect.

According to van Erp et al. (1994) and Kalueff and Tuohimaa (2004), stress can induce grooming in rodents and this innate behavior might be related to endocrine hypothalamus-pituitary adrenal axis. Riparin IV was able to decrease grooming suggesting that treatment may alter cortisol homeostasis. Treatment with Riparin IV was able to decrease mice immobility time caused by chronic stress and also preserved locomotor activity in OFT, suggesting that its antidepressant effect in this predictive model is specific and not related to an increase in motor activity of the animals.

In the animal's models, the results found by Iijima et al. (2010) showed a different conclusion. Rats received corticosterone injections (20 mg/kg, subcutaneously), once a day for 21consecutive days prior to the forced swimming test. A day prior to the behavior test, animals orally received fluvoxamine (3 mg/kg), imipramine (10.0 mg/kg) and a combination of risperidone (0.1 mg/kg) and fluvoxamine (3.0 mg/kg). Acute treatment with fluvoxamine and imipramine monotherapy failed to decrease the immobility time but a combination of antidepressant and antipsychotic drugs could decrease immobility time in the forced swimming test when administered once. Our behavioral findings show that fluvoxamine also reversed stress symptoms associated with depression and anxiety in a higher dosage (50 mg/kg) and after several days of administration.

Results from several previous studies have indicated that repeated corticosterone treatments can influence rodent behavior and induce depressive symptoms (Iijima et al., 2010; Lussier et al., 2013; Marks et al., 2009; Murray et al., 2008; Silva et al., 2016; Skórzewska et al., 2014; Zhao et al., 2009, 2008), including anhedonia (Abelaira et al., 2013; Bai et al., 2018; Gupta et al., 2015; Levinstein and Samuels, 2014; Li et al., 2015; Lopes et al., 2018; Pizzagalli, 2014; Vasconcelos et al., 2015). Anhedonia is a key symptom of all forms of depression and it can influence many of its symptoms (American Psychiatric Association, 2014; Bogdan and Pizzagalli, 2006). The reduction of the ability to experience pleasure caused by stressful events tends to be long-lasting and its operationally defined by a decreased preference for sweetened solutions (Strekalova et al., 2004).

Studies indicate that anhedonia arises from dysfunctional interactions between stress and brain reward systems, related to dysfunction in mesolimbic dopamine pathways (Pizzagalli, 2014). This information corroborates with the ability of Riparin IV, in acute studies, in causing changes in monoaminergic systems, including increased levels of dopamine with involvement of D1 and D2 receptors (unpublished data). Corticosterone administration led to a reduction of sucrose consumption and a seven-day treatment with Rip IV normalize sucrose intake similar to fluvoxamine. This finding is very relevant because some types of antidepressants and anxiolytics drugs are ineffective in reversing chronic stress-induced anhedonia (Patel, 2016; Treadway and Zald, 2011; Willner et al., 1992).

Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth factor family. BDNF, signaling in the mesolimbic pathway, plays a role in survival mechanism in the central nervous system, such as neurogenesis, neuronal growth, cellular differentiation and survival of neurons. This type of neurotrophin also influences dendritic connectivity and neuroplasticity (Banerjee et al., 2014; Bramham and Messaoudi, 2005; Castrén and Rantamäki, 2010a).

However, under stress, the gene for BDNF is repressed, leading to atrophy and possible apoptosis of neurons in the hippocampus. These events, in turn, lead to depression and susceptibility to social anhedonia followed by social stress (Huang and Lin, 2015; Kiyohara and Yoshimasu, 2009; Kupferberg et al., 2016). Furthermore, the hippocampus is particularly susceptible to the damaging effects of prolonged stress, (Ihara et al., 2016; Novkovic et al., 2015) evidenced by decreased hippocampal neurogenesis and hippocampal glucocorticoid receptor (GR) mRNA expression (Brummelte and Galea, 2010; Sterner and Kalynchuk, 2010). This GR decrease could lead to a stimulation of the HPA axis and increase glucocorticoid serum levels and creating even more hippocampal damage.

Many antidepressant drugs acutely increase monoamine levels, but in order to achieve success in therapy it is necessary to lead long-term adaptation such as regulation of neurotrophins, as BDNF (Kozisek et al., 2008). Studies have shown, in depressed patients and animal models of stress, that the efficacy of antidepressants in causing alterations behavioral symptoms of depression depends on their ability to increase BDNF levels (Banerjee et al., 2014; Castrén and Rantamäki, 2010b; Deltheil et al., 2008; Sousa et al., 2015).

Data suggests that chronic corticosterone administration reduces BDNF levels in the hippocampus (Gregus et al., 2005; Jacobsen and Mørk, 2006; Sousa et al., 2015; Vasconcelos et al., 2015; Warner-Schmidt and Duman, 2006) and Riparin IV shows a significant effect in BDNF levels which is not a regular finding in all antidepressant treatment.

Jacobsen and Mørk (2004) found different changes in antidepressant treatment in BDNF protein level, where escitalopram (a selective serotonin reuptake inhibitor [SSRI]) decreased BDNF protein in the hippocampus and desipramine (a tricyclic antidepressant that inhibit the reuptake of noradrenaline) did not affect the BDNF protein level. Thus, the antidepressant effect of Riparin IV may be related to the ability to increase hippocampal neurogenesis.

As previously mentioned, chronic stress induced by corticosterone is a model of depression involving psychotic symptoms and turn into a persistent kind of depression (Lorenzetti et al., 2009). Psychotic depression is difficult to treat and normally involves the administration of the combination of an antidepressant and an antipsychotic, which increases the risk of adverse effects (Hamoda and Osser, 2008). The evidence that Riparin IV could reverse the psychotic depression induced in animals as a monotherapy incites its importance in depression management.

5. Conclusion

Depression is a common mental disorder associated with debilitating symptoms; it can also co-exist with other mental disorders such as anxiety and psychosis and affect populations around the globe. There is a lack of effective pharmacological treatments and 10–30% of patients did not respond to regular antidepressant treatments (Al-Harbi, 2012). Treating a resistant depression causes socioeconomic impact and the development of new strategies is extremely necessary.

Animal models are utilized to provide knowledge of the neurobiological basis of several disorders, which could ultimately produce improved treatment options for the patient with depression. We have reviewed the findings of preclinical research demonstrating that Riparin IV prevents the effects of corticosterone induced stress on behavior. The ability to increase BDNF levels is also a critical finding and could lead to Riparin IV as a potential treatment strategy in the future.

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