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Antidepressant-like effect of quercetin in bulbectomized mice and involvement of the antioxidant defenses, and the glutamatergic and oxidonitrergic pathways

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ABSTRACT

Olfactory bulbectomy (OB) is an animal model of depression that can mimic symptoms that are characteristic of depressive patients, such as behavioral, neurochemical and neuromorphological changes. Quercetin decreased the immobility time in the forced swimming test and tail suspension test. With the open field test, quercetin did not alter the locomotor activity of mice and in the splash test, quercetin increased the time spent grooming. The repeated treatment with quercetin (25 mg/kg, for 14 days) reversed the behavioral hyperactivity induced by OB in the open field test and was able to prevent depressant-like effects in the forced swimming test and tail suspension test. Regarding oxidative stress, OB reduced the levels of glutathione and increase the activity of superoxide dismutase and lipid hydroperoxide content (LOOH) in the hippocampus. Only the increase in LOOH levels was reversed by treatment with quercetin. In a further series of experiments with non-bulbectomized mice, the antidepressant effect of quercetin in the tail suspension test was reversed by the pretreatment of mice with NMDA, L-arginine or sildenafil. The administration of methylene blue and 7-nitroindazole, in combination with an underactive dose of quercetin (5 mg/kg, p.o.), decreased the immobility time in the tail suspension test compared with the use of drug alone. There was no significant change in locomotor activity in the open field test. Our results suggest that the antidepressant effect of quercetin is dependent on the inhibition of the NMDA receptors and/or synthesis of nitric oxide. In addition, considering the reduction of LOOH levels on the hippocampus, we verify that the antioxidant effects of quercetin also contribute to its antidepressive potential. These data contribute to the understanding of the mechanisms involved in the antidepressant effect of quercetin and reinforce the involvement of the NMDA receptors and the nitric oxide on the pathophysiology of depression.

1. Introduction

Depression has been recorded since ancient times and affects most diverse populations worldwide. This disease is a chronic mental disorder, and in some cases, is a potentially fatal disorder, representing a serious public health problem that generates high costs to society (Fleck et al., 2009) and that strongly affects quality of life of the patients (Larsen et al., 2010; Van Der Feltz-Cornelis et al., 2010). It is well-established that depression involves a reduction in the monoamine system, particularly in the neurotransmission of serotonin, dopamine and norepinephrine, or impaired activity of their receptors (Racagni and Popoli, 2010). In summary, the center of action of current drug therapy is to correct monoamine deficits by increasing synaptic concentrations (Higgins and George, 2010; Bennabi et al., 2015).

In recent years, studies have demonstrated important sex differences in relation to mood disorders (Brunet et al., 2014; Habel et al., 2015; Hiles et al., 2015). Indeed, depression is more prevalent among women than men, and the associated comorbidities also show differences between genders (Kessler, 2003). In addition, it is well-established that women are more susceptible to anxiety and depressive symptoms, especially associated with the reproductive period (Altemusa et al., 2014). Several sex differences in brain function and structure, as well as differences in exposure to reproductive hormones, can explain these findings.

Despite substantial progress achieved with the development of new antidepressants in recent decades, the therapy is not completely effective, and approximately 40% of patients do not respond to treatment (Altomonte et al., 2008). The characterization of the antidepressant-like effect of natural substances is justified by the need to find new compounds that have greater clinical efficacy and fewer adverse effects. Phenolic compounds represent a promising class of natural substances in neuropharmacology, taking into account its antioxidant and neuroprotective properties (Dovichi and Lajolo, 2011). These compounds are found in many foods, such as fruits, vegetables and medicinal plants.

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Indeed, one of them, quercetin, has shown pronounced antidepressant effects in previous studies, which have been able to reduce the immobility time of animals when subjected to the forced swimming test (Anjaneyulu et al., 2003). Moreover, quercetin also attenuated the activation of the hypothalamic–pituitary–adrenal (HPA) axis by suppressing the expression of corticotropin releasing factor (CRF), an important component of the stress response, which is associated with the development of depression (Kawabata et al., 2010).

Olfactory bulbectomy (OB) is an animal model of depression based on the bilateral destruction of the olfactory bulb, which promotes behavioral changes that mimic depressive symptoms, such as learning and memory disorders, psychomotor agitation, apathy and anhedonia, that are typically displayed by depressed patients (Willner et al., 2013). Previous studies showed that the OB model is able to increase reactive oxygen species' (ROS) release in the cerebral cortex and hippocampus (Rinwa and Kumar, 2013). The involvement of oxidative stress in depression has been increasingly highlighted in the literature (Castren et al., 2007; Abdel-Wahaba and Salamab, 2011). Depression can cause susceptibility to oxidative damage by reduced expression of antioxidant enzymes and increased production of ROS (Kim et al., 2008), reinforcing the theory that oxidative stress is closely related to the pathophysiology of mood disorders (Maes et al., 2011).

In parallel to the increased oxidative stress caused by OB, previous studies showed that bulbectomized mice demonstrated an increase in glutamate release in the striatum (Hoa et al., 2000). Glutamate is the main excitatory neurotransmitter in the brain and its presence in most synapses is involved in various functions, such as memory formation, cognitive processes, learning, and the training of neural networks. However, excessive stimulation of N-methyl-D-aspartate (NMDA) receptors by glutamate can cause various forms of damage, such as a massive influx of calcium and the release of nitric oxide (NO) (Bishop and Anderson, 2005). Additionally, several studies have also shown that inhibition of nitric oxide synthase and/or soluble guanylate cyclase and the consequent reduction of cyclic guanosine monophosphate (cGMP) can produce an antidepressant-like effect (Zomkowski et al., 2010; Moretti et al., 2011; Zeni et al., 2011).

In view of the above, this study aimed to investigate the effects of repeated administration of quercetin in some behavioral changes induced by OB in female mice: anhedonic behavior in the splash test, the antidepressant-like effect of the forced swimming test and tail suspension test and hyperactivity in the open-field test (Fig. 1). We also investigated the involvement of oxidative stress, NMDA receptors and the L-arginine-NO-cGMP pathway on the antidepressant effect of quercetin.

2. Materials and methods

2.1. Animals

Considering that several epidemiological studies demonstrate that mood disorders are at least twice as common in women as in men (Herzog et al., 2009), this work was performed using female Swiss mice (25–30 g, 3 months) obtained from the Animal Center of UNIVALI. The animals were housed at a temperature of 22 ± 2 °C under a 12:12 h light:dark cycle, with free access to food and water, except during the experimental procedures. All experiments were previously approved by the Institutional Ethics Committee of UNIVALI, Itajaí, SC, Brazil, under approval certificate number 021/13, and were carried out in accordance with the international standards and ethical guidelines on animal welfare. After 14 postoperative days (recovery period), the mice were assigned to the following 14-day treatment groups: (I) SHAM-vehicle, (II) SHAM/quercetin, (III) SHAM/fluoxetin (IV) bulbectomized/vehicle, (V) bulbectomized/quercetin and (VI) bulbectomized/fluoxetine.

2.2. Drugs and treatment

Quercetin and fluoxetine (Sigma Chemical Co, USA) were dissolved in saline and administered orally, once daily, for 14 days. The solutions were prepared daily. Controls received an equal volume of saline (vehicle). The administration route and the dose of the drug used were chosen based on a pharmacological screening performed in our laboratory, and on the literature data (Bhutada et al., 2010). To investigate the involvement of the NMDA receptors and L-arginine-NO-cGMP pathway on the antidepressant effect of quercetin, the following drugs were used: L-arginine, methylene blue, NMDA, 7-nitroindazole (Sigma Chemical Co, USA), and sildenafil (Pfizer). These drugs were dissolved in saline with a few drops of Tween 80, and were administered using the intraperitoneal (i.p.) route, at a constant volume of 10 ml/kg body weight, except for the NMDA, which was administered using the intracerebroventricular (i.c.v.) route (Laursen and Belknap, 1986; Zomkowski et al., 2010).

2.3. Induction of depression by OB

The procedure was carried using the suction method previously described by Leonard and Tuite (1981). The animals were previously randomly separated into two experimental groups: fake operated (sham) and bulbectomized. The mice were anesthetized with xylazine (6 mg/kg, i.p.) and ketamine (100 mg/kg, i.p.) diluted in saline. An incision was made in the skin to expose the skull, and holes were drilled in both sides of the midline. The olfactory bulbs were then bilaterally sucked through a hypodermic needle (1.0–1.2 cm long with a rounded tip 0.80 to 1.2 mm in diameter) attached to a syringe (10 mL), with care used to avoid damaging the frontal cortex, as standardized by Machado et al. (2012). Any bleeding was ceased and the holes were cleaned with gauze and covered with dental resin. The sham animals underwent the same procedure, but without the suction of the olfactory bulbs. After surgery, the animals underwent a recovery period of 14 days until the start of the treatments.

2.4. Investigation of the effect of repeated treatment (14 days) with quercetin and/or fluoxetine in animals subjected to OB

To verify the best dosage of quercetin for the treatment of bulbectomized mice, a dose–response curve was initially performed. For this purpose, the animals received increasing doses of quercetin (10, 25 and 50 mg/kg, p.o.) for a period of 14 days. Then, 24 h after the last treatment, the mice were evaluated in the forced swimming

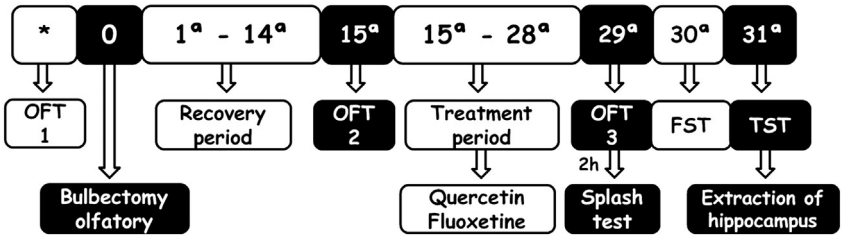

Fig. 1. Experimental schedule of the protocol, with the treatment period and behavioral tests period (OFT: open-field test, splash test, FST: forced swimming test and TST: tail suspension test). After completion of behavioral testing, mice were sacrificed by decapitation and hippocampus were dissected and stored at −80 °C for subsequent biochemical analysis.