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Chrysin promotes attenuation of depressive-like behavior and hippocampal dysfunction resulting from olfactory bulbectomy in mice

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ABSTRACT

Chrysin is a natural flavonoid which is found in bee propolis, honey and various plants, and antidepressant-like effect of chrysin in chronically stressed mice was previously demonstrated by our group. In this work, we investigated the action of chrysin treatment (5 or 20 mg/kg) for 14 days in the depressant-like behavior and in the hippocampal dysfunction induced by olfactory bulbectomy (OB), an animal model of agitated depression. Results demonstrated that OB occasioned a depressant-like behavior in the splash test, open field test and forced swimming test. Chrysin administration, similarly to fluoxetine (positive control), promoted the attenuation of these behavioral modifications. OB also caused the elevation of tumor necrosis factor-α, interferon-γ, interleukin-1β, interleukin-6, kynurenine (KYN) levels and indoleamine-2,3-dioxygenase activity, as well as occasioned the decrease of 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF) levels and increase KYN/tryptophan and 5-hydroxyindoleacetic acid/5-HT ratio in the hippocampus. Chrysin therapy prevented against all these alterations in the hippocampus. In addition, chrysin treatment (20 mg/kg) resulted in the up-regulation of BDNF levels in the control animals, reinforcing our hypothesis that up-regulation of BDNF synthesis play a key role in the antidepressant action of chrysin. In conclusion, this study showed that chrysin, similarly to fluoxetine, is capable of promoting the attenuation of depressant-like behavior and hippocampal dysfunction resulting from OB in mice. These results reinforced the potential of chrysin for the treatment or supplementary treatment of depression, as well as showed that chrysin is also effective with 14 days of therapy in a model of agitated depression.

1. Introduction

Etiology and treatment of depression is one of the most serious challenges to modern medicine. The number of patients suffering from depression is growing [1]. Although various antidepressants have been commercially available for decades, the side effects of these drugs, together with the fact that not all patients respond satisfactorily to treatment, lead to continuous search for new alternatives for the treatment or supplementary treatment of depression [2].

Natural products, especially plant polyphenols, have attracted progressively more attention as supplemental interventions to treat or prevent central nervous system diseases, including depression [2–7]. In this context, chrysin (5,7-dihydroxyflavone, Fig. 1) is a flavonoid which is found in bee propolis, honey and various plants [8]. Research has shown that chrysin has multiple biological activities, such as anti-inflammatory, antineoplastic, hypolipidemic and antioxidant [3,6,9–11]. In addition, recent studies of our group demonstrated the antidepressant potential of chrysin treatment in mice exposed to chronic stress [6,7]. However, we understand that the antidepressant-like effect of chrysin still requires investigations in other animal models of depression.

The bilateral olfactory bulbectomy (OB) creates a chronically altered brain state with complex changes of behavioral and neurochemical parameters, many of which are comparable to those seen in patients with major depression [12]. Thus, OB in rodents has been proposed to represent an animal model that appears to fulfill

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Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
ANOVA	analysis of variance
BDNF	brain-derived neurotrophic factor
CRH	corticotropin-releasing hormone
ELISA	enzyme-linked immune sorbent assay
FST	forced swimming test
HP	hippocampus
HPLC	high pressure liquid chromatography
IDO	indoleamine-2,3-dioxygenase
IFN-γ	interferon-γ
IL-1β	interleukin-1β
IL-6	interleukin-6;
KP	kynureninepathway
KYN	kynurenine
KYNA	kynurenic acid
QUIN	quinolinic acid
S1	supernatant fraction
ST	splash test
TNF-α	tumor necrosis factor-α
TRP	tryptophan
TRYCATs	tryptophan catabolites

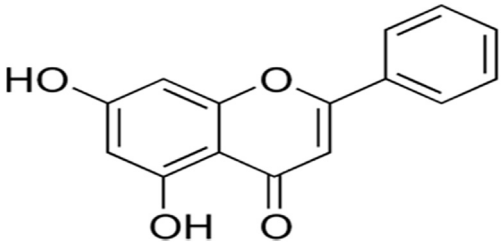

Fig. 1. Chemical structure of chrysin.

many of the necessary criteria for a depression model, especially agitated depression [13–15].

A hyperactivity response, the major behavioral change in OB, can be reversed by chronic treatment with antidepressants, mimicking the slow onset of antidepressant action reported in clinical studies [14]. Studies have analyzed self-care, motivational and/or anhedonic behavior associated with hyperactivity in bulbectomized rodents [14,16]. Moreover, OB in rodents has been associated with chemical alterations in the hippocampus (HP), including pro-inflammatory cytokines production [17], serotonin (5-HT) system [12], and brain-derived neurotrophic factor (BDNF) levels [12,17].

Thus, the aim of this work was to investigate the effect of treatment with chrysin in an animal model of depression induced by OB, comparing it to the effect of fluoxetine, a positive control [14,18]. Our working hypothesis is that chrysin may promote the attenuation of depressive-like behavior and hippocampal changes induced by OB in mice.

2. Materials and methods

2.1. Animals

Experiments were realized with male C57B/6J mice (20–25 g, 90 days old). Animals were maintained at 22–25 °C, with free access to water and food, under a 12:12 h light/dark cycle, with lights on at 7:00 a.m. The procedures of this study were conducted according to the guidelines of the Committee on the Care and Use of Experimental Animal Resources.

2.2. Drug solutions and administrations

Chrysin and fluoxetine were purchased from Sigma (St. Louis, MO, USA), with a purity of 97% and 99%, respectively. All other chemicals used were obtained from standard commercial suppliers.

Chrysin was dissolved in a distilled water/propyleneglycol solution (80:20). Fluoxetine was dissolved in distilled water. Both drugs were administered per oral (p.o.) in the volume of 10 ml/kg.

2.3. Bilateral olfactory bulbectomy (OB) surgical procedure

After a 2-week acclimatization period, OB was performed according to the procedure described by Leonard and Tuit [19]. Briefly, mice were anesthetized with xylazin (20 mg/kg) in combination with ketamine (100 mg/kg) diluted in saline (0.9% NaCl) administered intraperitoneally (i.p., 10 ml/kg body weight). The skull covering the olfactory bulbs was exposed by skin incision, and two burr holes were drilled using a dentist drill. The olfactory bulbs were bilaterally aspirated using a blunt hypodermic needle (1.0–1.2 cm long and with a rounded tip of 0.80–1.2 mm in diameter) attached to a 10 ml syringe, taking care not to cause damage to the frontal cortex. Finally, the burr hole was filled with acrylic resin to avoid bleeding and contamination of the surgical site. SHAM-operations were performed in the same way, but the olfactory bulbs were left intact. After surgery, all animals were allowed to recover in a post-operative cage (maintained at 24 °C) for 3 h. After this time period, the mice were returned to their home cage. After behavioral testing, all animals were sacrificed and the presence of lesions was verified. The bulbectomized animals that showed incomplete removal of olfactory bulbs or damage to other brain areas were excluded from the subsequent analysis following the previously described criteria [15,20,21].

2.4. Drug treatments and experimental design

After exposed to open field test (OFT), all animals were submitted to surgery to remove their olfactory bulbs or only to surgery (SHAM). The animals had 14 days of recovery and were then again subjected to an OFT after exposure to treatments.

Mice were treated with chrysin at doses of 5 or 20 mg/kg [6,7], or fluoxetine (positive control) at the dose of 10 mg/kg [6,7,14,18,22], daily for 14 days. Thus, the mice were divided into eight groups (n = 4–6) [1]: Control (SHAM + vehicle) {V} [2], Fluoxetine 10 mg/kg (SHAM + fluoxetine 10 mg/kg) {F10} [3], Chrysin 5 mg/kg (SHAM + chrysin 5 mg/kg) {C5} [4], Chrysin 20 mg/kg (SHAM + chrysin 20 mg/kg){C20} [5], OB (OB + vehicle) {V} [6], OB + fluoxetine 10 mg/kg {F10} [7], OB + Chrysin 5 mg/kg {C5} and [8] OB + Chrysin 20 mg/kg {C20}.

After the treatments, the animals were subjected to splash test (ST) and after 24 h were exposed to OFT and subsequently to forced swimming test (FST). After 24 h the animals were euthanized by decapitation and HP was dissected for hippocampal determinations (Fig. 2).