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Icariin reverses corticosterone-induced depression-like behavior, decrease in hippocampal brain-derived neurotrophic factor (BDNF) and metabolic network disturbances revealed by NMR-based metabonomics in rats

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ABSTRACT

Previously published reports have revealed the antidepressant-like effects of icariin in a chronic mild stress model of depression and in a social defeat stress model in mice. However, the therapeutic effect of icariin in an animal model of glucocorticoid-induced depression remains unclear. This study aimed to investigate antidepressant-like effect and the possible mechanisms of icariin in a rat model of corticosterone (CORT)-induced depression by using a combination of behavioral and biochemical assessments and NMR-based metabonomics. The depression model was established by subcutaneous injections of CORT for 21 consecutive days in rats, as evidenced by reduced sucrose intake and hippocampal brain-derived neurotrophic factor (BDNF) levels, together with an increase in immobility time in a forced swim test (FST). Icariin significantly increased sucrose intake and hippocampal BDNF level and decreased the immobility time in FST in CORT-induced depressive rats, suggesting its potent antidepressant activity. Moreover, metabonomic analysis identified eight, five and three potential biomarkers associated with depression in serum, urine and brain tissue extract, respectively. These biomarkers are primarily involved in energy metabolism, lipid metabolism, amino acid metabolism and gut microbe metabolism. Icariin reversed the pathological process of CORT-induced depression, partially via regulation of the disturbed metabolic pathways. These results provide important mechanistic insights into the protective effects of icariin against CORT-induced depression and metabolic dysfunction.

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1. Introduction

Depression is a serious medical condition and a profound public health concern. Although genetic research has revealed that the vulnerability to depression is partly heritable, there is also strong support for a role of stress in the development and manifestation of this disorder. In response to stress, the hypothalamic–pituitary–adrenal (HPA) axis is activated, which results in a cascade of neuroendocrine events. This cascade includes the release of corticotropin-releasing factor (CRF) from the hypothalamus, which, in turn, causes the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary, culminating in the secretion of glucocorticoids (cortisol in humans and corticosterone [CORT] in rodents) from the adrenal glands into the circulatory system. Under normal conditions, blood glucocorticoid level is tightly regulated by a negative feedback mechanism. However, high concentrations of blood glucocorticoids have been reported in patients with depression due to a dysfunction in the feedback mechanism [1]. Moreover, high levels of glucocorticoids have been shown to induce depression-like behavior in rodents, as indicated by a significant decrease in sucrose consumption and an increase in immobility time in the forced swim

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test (FST) and tail suspension test. These changes are significantly reversed by antidepressants and acupuncture treatment [2,3]. Changes in neurochemistry and brain anatomy related to depression have also been found in animals treated with high doses of glucocorticoids [4,5]. These findings validate a rodent model of glucocorticoid-induced depression as a means of evaluating the efficacy of potential antidepressants and exploring their mechanisms of action [6,7].

Icariin is a major biologically active and most abundant flavonoid isolated from *Epimedium brevicornum* Maxim (Berberidaceae), which is used as a traditional Chinese medicine to nourish the kidney and reinforce *yang* [8]. Previous studies have reported that icariin could shorten immobility time and suppress brain monoamine oxidase A and B activity and serum CRF levels, as well as increase brain monoamine neurotransmitter levels in FST in mice [9]. Icariin also exhibited potent antidepressant-like effects in chronic mild stress (CMS) model of depression in rats via regulation of the HPA axis hyperactivity and the reduced function of the serotonergic system and modulation of neuroinflammation [10–13]. Moreover, icariin remarkably increased the social interaction time in a mouse model of social defeat stress via up-regulation of glucocorticoid receptors [14]. However, the therapeutic effect of icariin in an animal model of glucocorticoid-induced depression remains unknown.

Metabonomics, which focuses on the quantitative measurement of the dynamic multiparametric metabolic response of the living systems to pathophysiological stimuli or genetic modification, has been successfully applied in the fields of disease diagnosis, toxicity evaluation and assessment of drug effectiveness, to name a few [15–19]. However, until now, there have been no reports on the molecular biomarkers for glucocorticoid-induced depression in animals and the efficacy of icariin with a metabonomic approach.

In the present study, the effects of icariin on behavior and brain-derived neurotrophic factor (BDNF) level were evaluated in a rat model of depression induced by CORT, a principal glucocorticoid. A nuclear magnetic resonance (NMR)-based metabonomic study was then performed to characterize the metabolic signature of CORT-induced depression in rats and to explore the antidepressant-like effects and the underlying mechanisms of icariin treatment.

2. Materials and methods

2.1. Chemicals and reagents

Water was produced by a Milli-Q ultra-pure water system (Millipore, Bedford, MA, USA). Icariin was purchased from Shanghai Ronghe Medical Science Co., Ltd. (Shanghai, China). The purity of icariin was at least 98%, as verified by high-performance liquid chromatography (HPLC). CORT and D_2O were obtained from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals used were of analytical grade made in China.

2.2. Animal experiments

Male Sprague-Dawley (S.D.) rats (weighing 160 ± 20 g) were commercially obtained from the Experimental Animal Center of Sun Yat-Sen University (Guangdong, China). The rats were maintained under standard laboratory conditions ($22 \pm 2\,^{\circ}$C, $50 \pm 10\%$ humidity, and 12/12 h light/dark cycle) with food and water freely available. Experimental protocols used in the present study were approved by the Committee on the Ethics of Animal Experiments of Guangdong Pharmaceutical University. All efforts were made to minimize animal suffering and to reduce the number of animals used.

After one week of adaptation, the rats were randomly allocated into three groups of 12 rats each: control group (vehicle), model group (CORT plus vehicle) and icariin treatment group (CORT plus icariin). Rats in the model and icariin treatment groups were subcutaneously injected with CORT (40 mg/kg, suspended in saline containing 0.1% dimethyl sulfoxide and 0.1% Tween-80) once daily for 21 days, while those in the control group received a subcutaneous injection of an equal volume of vehicle. The treatment group was treated with icariin (60 mg/kg, suspended in saline) by gastric instillation 1 h prior to CORT injection once a day for 21 days, while the control and model groups the same volume of vehicle via oral gavage. The dose of CORT and icariin were chosen based on previous reports [7,11]. After the last dose on day 21, half of the animals from each group were used for behavioral tests and to determine hippocampal BDNF levels and the other animals were used for metabonomic study.

2.3. Sucrose preference test

Rats were trained to sweet taste as described previously [19] with minor modifications. Briefly, single housed rats were introduced to 1% sucrose solution supplied in two drinking bottles 48 h prior to the test. After a 24-h period of water and food deprivation, the sucrose preference test was carried out by providing rats with two bottles filled with either 1% sucrose solution or tap water. The ratio of the amount of sucrose solution to that of total solution ingested within 1 h represented hedonic behavior.

2.4. Forced swim test (FST)

The procedure used was the same as described in detail elsewhere [13]. Briefly, rats were individually placed in a glass cylinder (50 cm in height, 18 cm in diameter) filled with water to a height of 30 cm ($25 \pm 2\,^{\circ}$C). All animals were forced to swim for 15 min for the first section and 5 min for the second section after 24 h. The immobility time was recorded in seconds by two expert observers who were blinded to the groups. Immobility period was regarded as the time spent by the rat floating in the water without struggling and making only those movements necessary to keep its head above the water.

2.5. Measurement of BDNF levels in the rat hippocampus

Twenty-four hours after completion of the FST, the rats were sacrificed by decapitation. The entire hippocampus was quickly dissected out on a cold plate and immediately frozen in liquid nitrogen and stored at $-80\,^{\circ}$C until assayed. The hippocampus samples were homogenized in ice-cold 0.1 M phosphate buffer (pH 7.4) containing a protease inhibitor cocktail (Biotool, Munich, Germany) and were then centrifuged at 14,000*g* for 15 min at $4\,^{\circ}$C to remove cellular debris. BDNF content in the hippocampus was measured using a sandwich ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Total protein from the supernatant was measured by Bardford method using bovine serum albumin as a standard. The results are expressed as pmol/mg protein.

2.6. Sample collection and preparation for metabonomic analysis

A 24-h urine sample from each animal was collected into ice-cooled vessels containing 0.5 ml of 2% sodium azide as an antibacterial agent on day 21 and centrifuged at 6000*g* for 10 min at room temperature to remove particle contaminants. Then, rats were anesthetized by diethyl ether inhalation and blood was collected from the retroorbital plexus, allowed to clot for 1 h at $4\,^{\circ}$C and serum was obtained by centrifugation at 3500*g* for 15 min at $4\,^{\circ}$C.

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