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Original article

Antidepressant-like activity of icariin mediated by group I mGluRs in prenatally stressed offspring

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Abstract

Objective: The present study was performed to identify antidepressant-like activity of icariin in prenatally stressed male rats.

Methods: The effects of icariin on PRS-induced depression were examined using sucrose preference test (SPT) and forced swimming test (FST) in male offspring, and measuring protein and mRNA expressions of group I mGluRs receptors and EAAT2 via western blotting and quantitative real-time PCR assays.

Results: The results indicated that prenatal restraint stress (PRS) resulted in several behavioral anomalies. Treatment with icariin relieved the elevated protein and mRNA levels of group I mGluR receptors as well as the diminished protein and mRNA levels of EAAT2 in the PRS male offspring.

Conclusions: Collectivity, the data support that icariin ameliorates PRS-induced depressive-like behavior via regulating expression of mGluR1, mGluR5 and EAAT2 in the hippocampus.

Keywords: Depression; Icariin; Prenatal restraint stress; Group I mGluR receptors; EAAT2

1. Introduction

Depression is one of the most common psychiatric disorders, affecting nearly 350 million people of the population worldwide as per the statistics of the World Health Organization (WHO), and more than half of the suicides are accompanied by depression [1]. In China, the estimated lifetime prevalence for major depressive disorder is 13.2%, while the current prevalence is 4.9% according to an epidemiology study at traditional Chinese medicine hospital in Shanghai [2].

Most of the widely clinically prescribed drugs for the treatment of depression are selective serotonin reuptake inhibitors (SSRIs) and noradrenaline reuptake inhibitors. However, SSRIs are fully effective in only approximately 40% of depressed patients [3,4]. In addition, there is 3–8 weeks latency to achieve therapeutic effects, which complicates optimization of medication and delays symptomatic relief. Therefore, more studies are urgently needed to find a new, more effective therapy to examine the pathophysiology of depression.

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Icariin is a major constituent of flavonoids isolated from Herba epimedium, a traditional Chinese medicinal herb, and has been demonstrated to display a wide range of pharmacological activities [5]. According to previous works reported, epimedium exerts clinical therapeutic effects on patients with chronic obstructive pulmonary disease [6], kidney deficiency syndrome of ischemic cardio-cerebral vascular diseases [7], osteoporosis [8] and hemodialysis maintenance [9]. In addition, epimedium was used against diseases of eye and kidney, impotence, asthma, arthritis and hypertension; besides being used as analeptic, expectorant, antibacterial, hypoglycemic, vasodilator and refrigerant [10]. The pharmacokinetic results demonstrated that pretreated with/without epimedium extract for three consecutive days did not significantly alter the pharmacokinetics of dapoxetine in rats and the oral bioavailability of dapoxetine was about 75% in rats [11]. However, the effect of epimedium on mental disease is still on the animal models. A large number of literatures manifested that there was remarkable remission effect of epimedium on depression model animal [12–14]. The underlying mechanism may be associated with the promotion of cell proliferation and peripheral nerve regeneration and improvement of the function of damaged nerves regulation [15,16]. Previous studies have shown that intragastric administration of icariin exerts antidepressant-like effects in mice exposed to social defeat stress and chronic unpredictable mild stress, mainly via modulation of glucocorticoid receptors and decreased brain monoamine neurotransmitter levels [17,18]. However, few studies have investigated the antidepressant-like effects of icarrin in prenatally stressed offspring rats, and whether this is associated with modulation of glutamate systems, remain unknown.

Metabotropic glutamate receptor 1 and 5 (mGluR1 and mGluR5) are members of the group I mGluRs family, which couple to G-proteins [19], and are important regulators of postsynaptic excitability and synaptic plasticity. Additionally it has been confirmed that mGluR1 and mGluR5 are involved in depression [20]. But due to conflicting evidence, the role of mGluR5 in modulation of depression remains unclear. Some studies have demonstrated stress induced an increase in mGluR5 protein levels in the prefrontal cortex, and that mGluR5 antagonism contributed to antidepressant-like effects in rats [21,22]. However, one study indicated lower mGluR5 expression in the prefrontal cortex of postmortem brains of individuals with major depression [23]. Furthermore, another study demonstrated mGluR5$^{-/-}$ mice revealed more severe depressive-like behaviors than control mice when both groups were exposed to diverse stressful stimuli, as well as displayed more obvious social withdrawal, learned helplessness and anhedonia [24]. Excitatory amino acid transporter 2 (EAAT2) is a member of EAATs, which play the predominant role in the reuptake of glutamate in the brain and maintain the proper concentration of glutamate levels in the synaptic cleft, and is responsible for up to 80–90% of total extracellular glutamate uptake activities [25]. Recently, many researchers have begun to focus on the potential use of EAAT2 as a therapeutic target for neurological and psychiatric disease. For example, Zink and colleagues, using an animal model of depression, found that treatment with fluoxetine significantly promoted EAAT2 expression in hippocampus in comparison with saline injections showed the effects of antidepressant treatment upon EAAT2 expression [26]. The dysfunction or dysregulation of EAAT2 can lead to excessive glutamate-mediated toxicity. These findings drove us to focus on group I mGluRs and EAAT2 to verify the mechanism underlying offspring depressive-like behavior induced by PRS. The aim of the present study was to identify the molecular mechanism underlying of icariin as an antidepressant.

2. Materials and methods

2.1. Animals

Sprague–Dawley rats were kept in an animal house with maintained temperature (22–26 °C) and humidity level (60%) for a 12 h dark/light cycle. The animals were allowed uncontrolled access to food and water for the duration of the experiment. Nulliparous female and male Sprague-Dawley rats were purchased from Institutional Animals Care and Use Committee at Xi'an Jiaotong University, Shaanxi, China. All animals were raised for one week to adapt to the environment before mating. Afterwards, three virgin female rats (230–250 g) were brought together with an adult male rat (280–350 g) for mating (3:1). Vaginal smear was performed on the next morning, and the positive vaginal smear of sperm was determined as day zero of gestation. Each pregnant female rat was then fed individually. All manipulations were implemented on the basis of USA Public Services Health Guide for Care and Use of Laboratory Animals and were recognized by the Institutional Animals Care and Use Committee at Xi'an Jiaotong University.

2.2. Prenatal restraint stress (PRS)

The PRS model we used is restraint stress model. The restraint apparatus was a transparent plastic cylinder (6.8 cm in diameter), and the length of plastic cylinder was adjustable in accordance with rats size, allowing for restriction of animal activities. At the two closed ends of cylinder, some air holes were drilled for breathing. The pregnant rats were randomly assigned to the control group or the PRS group. The pregnant rats of control group don't subject to any disposal in their cage.