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Hyperoside protects against chronic mild stress-induced learning and memory deficits

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ABSTRACT

Hyperoside (quercetin-3-O-b-ᴅ-galactosidepyranose) is a plant-derived flavonoid mainly found in fruits, fruit juices (most notably flavanols, flavanones, and anthocyanins) and Chinese traditional medicines. It has been applied to relieve pain and improve cardiovascular functions in clinic. However, the effects of hyperoside on cognitive impairment induced by chronic stress and the underlying molecular mechanisms remain unclear. In the current study, we used chronic mild stress (CMS) rats to investigate the effects of hyperoside on learning and memory and further explore the possible mechanisms. Our results demonstrated that hyperoside reduced the escape latency and the swimming distance of CMS rats in Morris water maze test and reversed depressive symptoms in forced swim test (FST) and sucrose preference test. In addition, hyperoside increased the expression of brain-derived neurotrophic factor (BDNF) in hippocampus of CMS rats without influencing the corticosterone (CORT) level in blood plasma. Furthermore, K252a, an inhibitor of the BDNF receptor TrkB, prevented the protective effects of hyperoside on learning and memory in CMS rats. Taken together, these results indicate that hyperoside reverses the cognitive impairment induced by CMS, which is associated with the regulation of BDNF signaling pathway.

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1. Introduction

Stress is an emotional experience accompanied by predictable biochemical, physiological and behavioral changes. Acute stress can be beneficial, producing a boost that provides the drive and energy to help people get through situations like exams or work deadlines. But chronic stress is an important risk factor in cognitive impairment [1]. For example, a study shows that chronic morbidity is associated with markedly cognitive impairment in over 11 000 individuals from Swedish Twin Registry [2]. Therefore, impaired cognition is regarded as an element of depression and that antidepressant therapy may improve cognitive impairments [3]. Although the stress induced impairment in learning is extensively investigated and cognitive impairment is attenuated by antidepressant therapy, classic antidepressant drugs are associated with a delayed therapeutic response and side effects, limiting their usage [4–6]. Fortunately, a growing percentage of the population uses herbal products for preventative and therapeutic purposes and large quantities of mass-produced drugs have successfully penetrated into the markets of United States and of many European countries [7,8]. As a result, to investigate a novel or higher efficacy and fewer side effects medicine from plant extracts or herbal product is needed and viable.

Hyperoside (also named: quercetin-3-O-b-ᴅ-galactosidepyranose) is a flavonoid compound, which is mainly extracted from hypericum perforatum L (also called St John's wort, SJW). It has a variety of biological effects including anti-inflammatory, anticancer and antioxidant activities [9,10]. In particular, in the central nervous system, hyperoside reduces cerebral ischemia/reperfusion injury through the regulation of nitric oxide signaling pathway and produces antidepressant-like effects [11]. Meanwhile, evidences show that flavonoid compounds Chrysin may represent a new pharmacological approach to alleviate the age-related declines during normal age because it was able to prevent age-associated

memory probably by their free radical scavenger action [12]. In our previous studies, we focused on the neuroprotective effects of flavonoid compounds and proved that flavonoid compounds (breviscapine or baicalein) improved learning and memory by reducing intracelluar Ca^{2+} overload and activating BDNF signal pathway [13,14]. Taken together, these studies suggest that hyperoside reverse cognitive impairment induced by chronic stress, but the underlying mechanisms remain unclear. Therefore, the interest findings strongly attract us to explore whether hyperoside, as the same flavonoid compound, has an effect on improving learning and memory during chronic stress phase.

It is well known that the hippocampus, which is intrinsically linked to both learning and memory, is particularly vulnerable to the effects of glucocorticoids (GCs), as it contains the highest density of GC target receptors within the brain. Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis and increases circulating levels of the stress hormones GCs [15,16]. Therefore, the reduction of CORT level in blood plasma may contribute to protect the hippocampus neuron and improve impairment of learning and memory. BDNF is a neurotrophin that modulates neuronal plasticity, which is frequently associated with the learning and memory [17]. The regulation of the neurotrophin BDNF, whose protein expression and function may be defective in mental disorders, has been extensively investigated in recent years as one of the mechanisms of antidepressants [13,18]. Thus, in our present study, to further explore whether treatment or possible mechanisms with hyperoside in CMS-induced cognitive impairment, we aimed to investigate escape latency and the swimming distance, FST, sucrose preference test, CORT level of blood plasma, and BDNF protein level of hippocampus in CMS-induced rats.

2. Materials and methods

2.1. Animals and treatment

Adult male Sprague-Dawley (SD) rats (160–180 g, 35–38 days old) were obtained from the Experimental Animals Center of Tongji Medical College, Huazhong University of Science and Technology. All animals were housed in groups under standard conditions (12 h light–dark cycle; light on 7 a.m.-7 p.m; temperature of $22 \pm 1\,^{\circ}C$) with free access to water and food, and allowed to acclimate a week. The experimental protocols were approved by the Committee of Animal Care of Jianghan University. According to the previous studies, hyperoside (molecular weight 464.37, purity above 98%, Fig. 1A) was dissolved in dimethyl sulfoxide (0.5% DMSO) and purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China) [10].

Firstly, in the effects of hyperoside on Morris water maze (MWM) test without non-stress, rats were randomly divided into five groups (n = 12, per group), i.e., control group, vehicle (equal volume of DMSO) group, fluoxetine (15 mg/kg) group hyperoside (1 mg/kg) and hyperoside (10 mg/kg) groups. The rats with administration were conducted for 34 days (Fig. 1B). In the effects of hyperoside on antidepressant behavior tests, rats with CMS were randomly divided into five groups (n = 12, per group), i.e., control group (equal volume of vehicle), model (equal volume of vehicle) group, fluoxetine (15 mg/kg) group, hyperoside (1 mg/kg) group, hyperoside (10 mg/kg) group and the rats with administration were conducted for 34 days (Fig. 1C). Then, in the effects of hyperoside on MWM test with CMS, we again got new rats and randomly divided them into five groups (n = 12, per group), i.e., control group (equal volume of vehicle), model group (equal volume of vehicle), fluoxetine (15 mg/kg) group, hyperoside group (1 mg/kg), hyperoside (10 mg/kg) group (Fig. 1D). At last, in the effects of hyperoside with K252a on MWM test with CMS, the rats were randomly divided into seven groups (n = 12, per group), i.e., control group (equal volume of vehicle), model group (equal volume of vehicle), fluoxetine (15 mg/kg) group, 10 mg/kg hyperoside group, K252a group, K252a with hyperoside (1 mg/kg) group and K252a with hyperoside (10 mg/kg) group (Fig. 1E). All the animals were administrated intraperitoneal injection (i.p.) once daily for 34 d (except for K252a administration, K252a 25 mg/kg, i. p., daily for 14 days) and were administered their respective
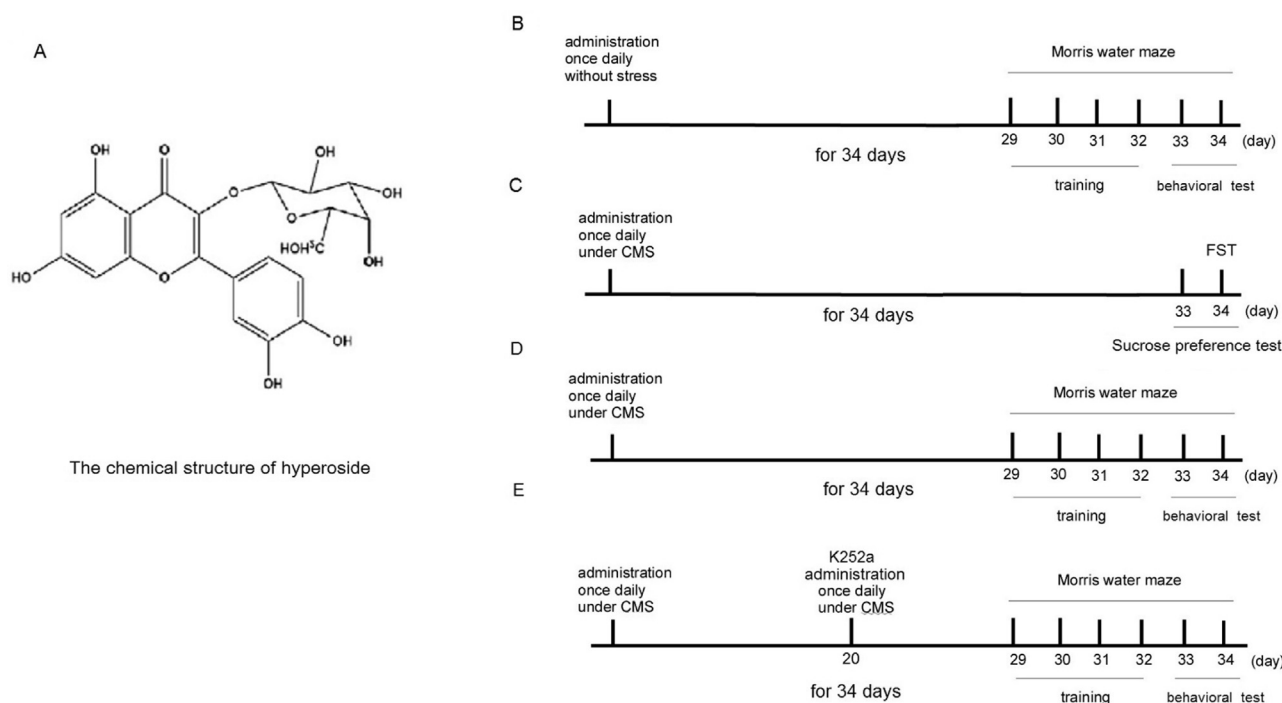

Fig. 1. Chemical structure and administrative procedure.