Physiology & Behavior 169 (2017) 184–188

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Elevation of synaptic protein is associated with the antidepressant-like effects of ferulic acid in a chronic model of depression

Ya-Min Liu [a], Chun-Yue Hu [a], Ji-Duo Shen [a], Su-Hui Wu [a], Yu-Cheng Li [a,*], Li-Tao Yi [b]

[a] College of Pharmacy, Henan University of Traditional Chinese Medicine, Zhengzhou 450046, Henan province, PR China
[b] Department of Chemical and Pharmaceutical Engineering, College of Chemical Engineering, Huaqiao University, Xiamen 361021, Fujian province, PR China

HIGHLIGHTS

- Ferulic acid increases sucrose preference and decreases immobility time in CUMS.
- Ferulic acid up-regulates BDNF signaling.
- Ferulic acid promotes synaptic protein levels.

ARTICLE INFO

Article history:
Received 28 September 2016
Received in revised form 7 November 2016
Accepted 2 December 2016
Available online 07 December 2016

Keywords:
Ferulic acid
Brain-derived neurotrophic factor
Synaptic protein
Depression
Chronic unpredictable mild stress

ABSTRACT

Ferulic acid is a hydroxycinnamic acid that widely presents in plant cell wall components. It has been demonstrated that ferulic acid can reverse depressive-like behaviors in both forced swimming test and tail suspension test. However, it is unclear whether chronic ferulic acid treatment can ameliorate the depressive-like behaviors in chronic unpredictable mild stress (CUMS). Because of the putative relationship between neurotrophic system and antidepressant-like activity, we also investigated the effects of chronic ferulic acid on the brain-derived neurotrophic factor (BDNF), postsynaptic protein PSD95, presynaptic protein synapsin I in both prefrontal cortex and hippocampus. The results showed that ferulic acid significantly alleviated CUMS-induced depressive-like behaviors in sucrose preference test and forced swimming test. In addition, ferulic acid significantly up-regulated the levels of BDNF, PSD95 and synapsin I in the prefrontal cortex and hippocampus. The present data indicated that ferulic acid exerted the antidepressant-like effects on behaviors by increasing neurotrophin-related synaptic protein levels in CUMS mice.

1. Introduction

Depression is a common but serious mood disorder impacting human's life. Generally, antidepressants are used as a major medication for depression treatment. Although monoamine hypothesis has ever promoted the development of antidepressants in the last fifty years, some clinical and experimental phenomenon don't really support this hypothesis. Recently, a new neurotrophic hypothesis is proposed that depression results from decreased neurotrophic support, leading to neuronal atrophy, decreased hippocampal synaptic proteins synthesis and neurogenesis, and that antidepressants improve this neurotrophic factor deficit, and thereby reverse the cell loss [1].

Ferulic acid, a hydroxycinnamic acid, widely present in plant cell wall components, has been found to possess a lot of potential improved effects related to different diseases. Besides its classical antioxidant activity, ferulic acid can also prevent trimethyltin-induced cognitive deficits in mice [2], attenuate the symptom of Alzheimer's disease induced by chronic neuroinflammation and oxidative stress in rats [3] and protect rats brain after nerve injury induced by cerebral ischemia [4]. In addition to above bioactivities, some papers indicated that ferulic acid produced the antidepressant-like effects in tail suspension test or forced swimming test. These papers indicated that serotonergic and noradrenergic systems, as well as PKA, CaMKII, PKC, MAPK/ERK and PI3K signaling pathways were involved in the antidepressant-like effects of ferulic acid [5–8]. However, it is unclear whether chronic ferulic acid can improve depressive-like behaviors in chronic depressive-like animals, and whether its long-term antidepressant-like effects are mediated by neurotrophic systems.

Here, we investigated whether ferulic acid possessed antidepressant-like effect in a chronic depression-like model of chronic unpredictable mild stress (CUMS). Behavioral analyses including sucrose preference test and forced swimming test were performed. In addition, brain-derived neurotrophic factor (BDNF) and its downstream targets synaptic proteins were also detected in the present study. This study

* Corresponding author.
E-mail addresses: Liyucheng@hactcm.edu.cn (Y.-C. Li), litao.yi@yahoo.com, litaoyi@hqu.edu.cn (L.-T. Yi).

http://dx.doi.org/10.1016/j.physbeh.2016.12.003
0031-9384/

aimed to explore the role of ferulic acid and its corresponding neurotrophic mechanism, and may provide experimental evidence leading to the clinical treatment of depression.

2. Materials and methods

2.1. Animals

Male ICR mice (20 ± 2 g, 6 weeks old for original experiment; 26 ± 1 g, 10 weeks old for supplementary experiment) were purchased from the Beijing Vital River Laboratory Animal Technology Co., Ltd. Animals were housed eight per cage (320 × 180 × 160 mm) under a normal 12 h/12 h light to dark schedule with lights on at 07:00 a.m. Animals were allowed to adjust to the housing conditions before experiments began. Ambient temperature and relative humidity were maintained at 22 ± 2 °C and at 55 ± 5%, respectively. Throughout the study, animals were given standard chow and water ad libitum. All procedures were performed in accordance with the published guidelines of the China Council on Animal Care (Regulations for the Administration of Affairs Concerning Experimental Animals, approved by the State Council on 31 October 1988 and promulgated by Decree No. 2 of the State Science and Technology Commission on 14 November 1988), and were approved by the Committee of Animal care of Henan University of Traditional Chinese Medicine.

2.2. Drugs and reagents

Ferulic acid ((E)-3-(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid, CAS No. 1135-24-6) and BDNF primary antibody were purchased from Santa Cruz Biotechnology, Inc. Fluoxetine hydrochloride was purchased from Sigma-Aldrich Co., Ltd. Synapsin I, PSD-95 and GAPDH primary antibodies were purchased from Cell Signaling Technology.

2.3. Drug administration

Animals were divided into responding groups after sucrose training: the Control-vehicle group, the CUMS-vehicle group, the CUMS-fluoxetine group (20 mg/kg of fluoxetine dissolved in 0.9% saline containing 0.3% carboxymethyl cellulose, p.o.) and the CUMS groups that received 20 or 40 mg/kg ferulic acid (dissolved in 0.9% saline containing 0.3% carboxymethyl cellulose, p.o.). Vehicle groups were administrated with 0.9% saline containing 0.3% carboxymethyl cellulose. The drugs were administrated once a day for successive four weeks. The timeline for our present study was provided as Fig. 1 and Fig. S1.

According to the previous study, ferulic acid (40 or 80 mg/kg) exerted antidepressant-like effects in both mouse tail suspension test and forced swimming test after acute treatment [6]. However, 20 mg/kg ferulic acid did not decrease immobility time in tail suspension test. Considering that the goal of our present study was to evaluate the effects after chronic treatment, we decided to use 20 and 40 mg/kg ferulic acid.

2.4. CUMS

The CUMS procedure was obtained and followed from previous literature [9]. Briefly, the weekly stress paradigm consisted of food and water deprivation, exposure to an empty water bottle, exposure to a soiled cage, light/dark succession every 2 h, space reduction, a 45° cage tilt, overnight illumination, and predator sounds. All stressors were applied individually and continuously throughout the day and night. The control animals were housed in a separate room and had no contact with the stressed animals. To prevent habituation and to ensure the unpredictability of the stressors, all stressors were randomly scheduled over a 1-week period and were repeated throughout the duration of the experiment. On the basis of their sucrose preference following 4 weeks of CUMS, both stressed and control mice were divided into matched subgroups.

2.5. Sucrose preference test

Before the test, mice were trained to adapt to a sucrose solution (1%, w/v): two bottles of sucrose solution were placed in each cage for 24 h and then one bottle of sucrose solution was replaced with water for 24 h. After the adaptation, the mice were deprived of water and food for 12 h. After 24 h, the weights of the consumed sucrose solution and water were recorded. Sucrose preference was calculated using the formula as described below: Sucrose preference = Sucrose consumption/(Water and Sucrose consumption) × 100%.

2.6. Forced swimming test

The forced swimming test was performed according to the method described by Porsolt et al. with some modifications [10]. After 24 h of the SPT, the forced swimming test was conducted. Briefly, mice were individually placed in a glass cylinder (25 × 12 × 25 cm) filled with water at 15 cm high (23 ± 2 °C). All animals were forced to swim for 6 min, and the duration of immobility was recorded during the final 4 min interval of the test. The immobility period was regarded as the time spent by the mouse floating in the water without struggling and making only the necessary movements to keep its head above the water. Each animal was used only once in this test. The test sessions were recorded by a video camera and scored by a blinded observer.

2.7. Protein extraction and western blotting

Mice were sacrificed by decapitation after the forced swimming test. Whole brains were rapidly removed and chilled in an ice-cold saline solution. Prefrontal cortex and hippocampus tissues were dissected on a cold surface and were immediately frozen in liquid nitrogen. The tissue samples were stored at −80 °C until assay.

Tissue samples were homogenized in modified RIPA buffer followed by centrifugation at 1000 ×*g* for 5 min at 4 °C to remove nuclei and intact cells. The supernatant was then centrifuged at 12,000 ×*g* for 20 min at 4 °C and the resulting supernatant was collected. The protein concentration in the final supernatant was determined by a Bradford protein assay using bovine serum albumin as a standard. The proteins were separated by SDS-polyacrylamide gel electrophoresis and transferred to PVDFs membranes. The membranes were blocked with 5% (w/v) non-fat dried milk in Tris-buffered saline containing 0.1% Tween 20 (TBST) and were incubated with the following antibodies in TBST containing 5% milk. After incubation, the membranes were washed with TBST and were then incubated with a horseradish peroxidase-conjugated anti-rabbit or anti-mouse IgG secondary antibody in 5% non-fat dried milk in TBST. After washing, the immunocomplexes were detected using Chemiluminescence Imaging System. The images were subsequently subjected to densitometric analysis.

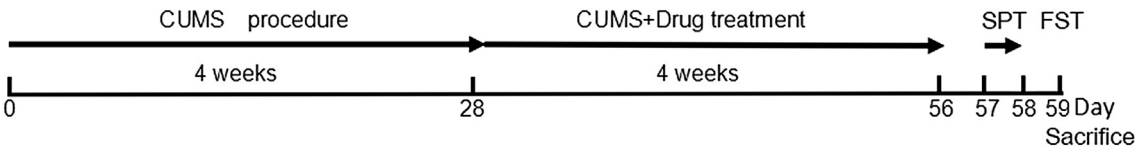

Fig. 1. The timeline for CUMS, drug treatment and behavioral tests.