



Behavioural pharmacology

Apigenin reverses depression-like behavior induced by chronic corticosterone treatment in mice



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ABSTRACT

Previous researches found that apigenin exerted antidepressant-like effects in rodents. However, it is unclear whether the neurotrophic system is involved in the antidepressant-like effects of apigenin. Our present study aimed to explore the neurotrophic related mechanism of apigenin in depressive-like mice induced by chronic corticosterone treatment. Mice were repeatedly injected with corticosterone (40 mg/kg) subcutaneously (s.c) once daily for consecutive 21 days. Apigenin (20 and 40 mg/kg) and fluoxetine (20 mg/kg) were administered 30 min prior to the corticosterone injection. The behavioral tests indicated that apigenin reversed the reduction of sucrose preference and the elevation of immobility time in mice induced by chronic corticosterone treatment. In addition, the increase in serum corticosterone levels and the decrease in hippocampal brain-derived neurotrophic factor (BDNF) levels in corticosterone-treated mice were also ameliorated by apigenin administration. Taken together, our findings intensively confirmed the antidepressant-like effects of apigenin and indicated that the antidepressant-like mechanism of apigenin was mediated, at least partly by up-regulation of BDNF levels in the hippocampus.

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1. Introduction

Major depressive disorder is a serious mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and a loss of interest or pleasure in normally enjoyable activities. Until recently, the pathophysiology of depression has not been well characterized. Monoamine deficiency, hypothalamic–pituitary–adrenal axis hyperactivity and neurotrophin reduction are involved in the pathophysiology of depression. The neurotrophin hypothesis of depression, which was proposed by Duman et al. (1997), has attracted increased attention in the areas of depression and antidepressants. As a key member of the neurotrophin family of growth factors, brain-derived neurotrophic factor (BDNF) is currently at the center of research in many areas of basic and clinical neuroscience (Bramham and Panja, 2014). Moreover, BDNF plays a confirmed, crucial role in the antidepressant treatment (Lee and Kim, 2010); thus, BDNF is considered an important target for antidepressants.

Flavonoid intake has alleviated depression-like symptoms in both clinical trials and experimental models (Volz, 1997; Ekeanyanwu and Njoku, 2015). Apigenin (4',5,7-trihydroxyflavone), a flavonoid widely presents in many plants, has various

pharmacological effects, including antioxidant, antitumor, anti-inflammatory and nephroprotective activities. Previous studies found that apigenin exerted the antidepressant-like effects in forced swimming test, tail suspension test and chronic mild stress in rodents (Nakazawa et al., 2003; Yi et al., 2008). Recently, studies demonstrated that apigenin produced antidepressant-like effects due to its anti-inflammatory properties (Li et al., 2015a,b). However, it is unclear whether the neurotrophic system is involved in the antidepressant-like effects of apigenin. Therefore, our present study was aimed to investigate whether the antidepressant-like effect of apigenin was mediated by BDNF expression.

2. Materials and methods

2.1. Animals

Male ICR mice (24 ± 2 g) were purchased from Laboratory Animal Centre, Fujian Medical University, Fujian Province, China. Animals were single-housed under a normal 12-h/12-h light/dark cycle with the lights on at 07:00 a.m. Ambient temperature and relative humidity were maintained at 22 ± 2 °C and at 55 ± 5%, and animals were given a standard chow and water ad libitum for the duration of the study. The animals were allowed to acclimatize to these conditions for 1 week before any experimental procedure was initiated. All procedures were approved by College Committee

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and performed in accordance with the published guidelines of the China Council on Animal Care.

2.2. Chemicals and reagents

Corticosterone was purchased from TCI Development Co., Ltd. (Tokyo, Japan). Apigenin (purity > 98% by HPLC) was purchased from Shanxi Huike Botanical Development Co., Ltd. (Xi'an, China). Fluoxetine hydrochloride was purchased from Changzhou Siyao Pharmaceuticals Co., Ltd. (Changzhou, China).

2.3. Drugs treatment

Mice were randomly divided into five groups ($n=8$): control-vehicle group, corticosterone-vehicle group, fluoxetine group (20 mg/kg) and apigenin groups (20 and 40 mg/kg). All groups except the control-vehicle group received a corticosterone injection for 21 days. The corticosterone was dissolved in physiological saline containing 0.1% dimethyl sulfoxide (DMSO) and 0.1% Tween-80, and injected subcutaneously (s.c) once daily at a dose of 40 mg/kg (Ali et al., 2015). The control-vehicle group was injected with the same volume of physiological saline containing 0.1% DMSO and 0.1% Tween-80. Apigenin and fluoxetine were suspended in physiological saline and administered by oral gavage 30 min prior to the corticosterone injection for the following 21 days.

2.4. Sucrose preference test

The sucrose preference test was carried out at the end of corticosterone treatment according to the previous report (Mao et al., 2014). Briefly, before the test, the mice were trained to adapt to 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 24 h. The test was conducted at 9:30 a.m. in which the mice were housed in individual cages and had free access to two bottles containing sucrose solution and water, respectively. After 24 h, the weights of the consumed sucrose solution and water were recorded.

2.5. Forced swimming test

The forced swimming test was performed after 24 h of sucrose preference as described in detail elsewhere (Porsolt et al., 1977), with some modification. Briefly, mice were individually placed in a glass cylinder (20 cm in height, 14 cm in diameter) filled with 10-cm high water (25 ± 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 those movements necessary to keep its head above the water. The test sessions were recorded by a video camera and scored by an observer blind to treatment.

2.6. Blood and tissue sampling

Animals were killed by decapitation one day after the forced swimming test. To avoid fluctuations on hormone levels due to circadian rhythm, animals were bled at 10:00 a.m. to 12:00 p.m. on the day of sacrifice. The brain region of hippocampus was isolated immediately, and then stored at -80 °C for later analysis of BDNF measurement.

2.7. Serum corticosterone assay

Blood was immediately collected on ice and separated in a

refrigerated centrifuge at 4 °C. Serum was stored at -20 °C until assays were performed. Serum corticosterone levels were measured using an enzyme immunoassay kit (Enzo Life Sciences, Plymouth Meeting, USA).

2.8. RT-PCR

Total RNA was isolated from hippocampus using Trizol reagent following the manufacturer's instructions. Reverse transcription was performed using moloney murine leukemia virus reverse transcriptase for complementary DNA synthesis. Real-time PCR reactions were performed using a SYBR Premix Ex Taq Kit in ABI-7500 system. The BDNF (forward 5'-TTATTTTCATACTTCGGTTGC-3'; reverse 5'-TGTCAGCCAGTGATGTCG-3') and the internal control GAPDH (forward 5'-TGAGCCGGTGCTGAGTATGT-3'; reverse 5'-CAGTCTTCTGGGTGGCAGTGAT-3') primers were used. The fluorescence signal was detected at the end of each cycle. Melting curve analysis was used to confirm the specificity of the products. The results were analyzed by the $2^{-\Delta\Delta CT}$ method.

2.9. Hippocampal BDNF protein levels

Each hippocampus tissue was weighed and homogenized in 20 μ l/mg tissue of lysis buffer containing 137 mM NaCl, 20 mM Tris-HCl (pH 8.0), 1% NP40, 10% glycerol, 1 mM PMSF, 10 μ g/ml aprotinin, 1 μ g/ml leupeptin, 0.5 mM sodium vanadate. The homogenate was centrifuged at 16,000g for 30 min at 4 °C, and the supernatant was collected and stored at -80 °C until assay. Protein levels of samples were measured using the Lowry Method. BDNF protein was measured using BDNF ELISA kit (Boster, China) according to the protocol of the manufacturer.

2.10. Statistical analysis

Data are presented as mean \pm S.E.M. and analyzed by one-way ANOVA followed by post-hoc Dunnett's test. A value of $P < 0.05$ was considered statistically significance.

3. Results

3.1. Effects of apigenin on sucrose preference induced by corticosterone

Chronic exposure to corticosterone induced a significant decrease [$F(1,14)=8.66$, $P < 0.05$] on the sucrose preference (Fig. 1). Treatment with apigenin (40 mg/kg) and fluoxetine (20 mg/kg) significantly increased the sucrose preference in mice exposed to corticosterone treatment ($P < 0.05$, $P < 0.05$, respectively).

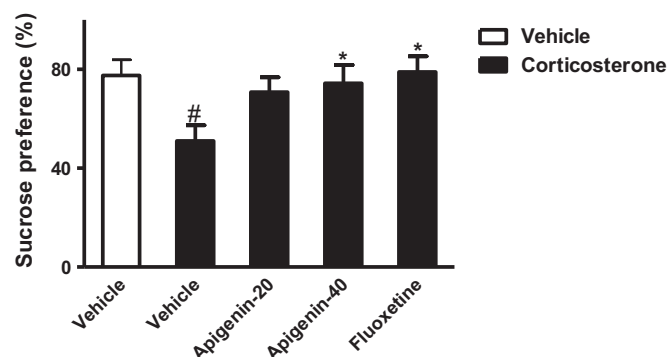


Fig. 1. Effects of apigenin and fluoxetine on sucrose preference in mice exposed to repeated corticosterone injection. ## $P < 0.01$ vs control-vehicle group. * $P < 0.05$ and ** $P < 0.01$ vs corticosterone-vehicle group.

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