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Study on antidepressant activity of chiisanoside in mice

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ABSTRACT

The antidepressant-like effect of chiisanoside from the leaves of *Acanthopanax sessiliflorus* was evaluated by using mice models of depression, forced swim test (FST) and tail suspension test (TST). The results showed that treatment with chiisanoside at dose of 5.0 mg/kg significantly decreased immobility time in the FST and TST. Pretreatment with haloperidol (a non-selective D_2 receptor antagonist), bicuculline (a competitive GABA antagonist) and *N*-methyl-D-aspartic acid (NMDA, an agonist at the glutamate site) effectively reversed the antidepressant-like effect of chiisanoside (5.0 mg/kg). Moreover, chiisanoside treatment did not change the locomotor activity. And chiisanoside (5.0 mg/kg) also effectively increased the dopamine (DA) and γ-aminobutyric acid (GABA) levels in mice brains exposed to the FST and TST in the co-treatment groups. Then we designed lipopolysaccharide (LPS)-induced antidepressant behavioral experiment, the results showed that LPS significantly increased immobility duration in the TST and FST. Chiisanoside administration could effectively reduce serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels; at the same time, the changes of related indexes of oxidative stress are improved, such as superoxide dismutase (SOD) and malondialdehyde (MDA). Moreover, chiisanoside effectively down-regulated brain-derived neurotrophic factor (BDNF), tropomyosin-related kinase B (TrkB) and nuclear factor-κB (NF-κB) in hippocampal. In conclusion, chiisanoside displayed significant antidepressant-like effect, which was probably related to the DAergic, GABAergic and glutamatergic systems. And the mechanism of anti-depressant effect of chiisanoside might be via the alterations of animal behaviors, hippocampus inflammation, oxidative stress and neurotrophy, which might be attributed by the BDNF/TrkB/NF-κB pathway.

1. Introduction

Major depression is one of the most prevalent psychiatric disorders; and the main performance is depression, interest drops, pessimism, slow thinking and lack of initiative [1]. There are reports that about 17% of people worldwide suffer from depression, and about 1 million people commit suicide each year because of depression [2]. Despite the rising prevalence of depressive disorders, the available antidepressants could not meet the clinical needs of palliative depression in hospitalized patients, mainly due to side effects and adverse reactions, such as metabolic syndrome, hyperprolactin, sedation, liver dysfunction, sleep disturbance, sexual impotence and body weight gain [3,4]. Therefore, seeking improved treatments of lower side effects and lower adverse reactions is an urgent task. Because of this, many of bioactive compounds from traditional Chinese herbal medicine have been studied for their potential for developing novel antidepressant, which may have lower side effects and better efficacy.

Although a series of hypotheses have been proposed, such as the theory of monoamine neurotransmitters, hypothalamus-hypophysis-adrenal axis (HPA) hyperfunction theory, immune dysfunction theory and neurotrophic deficiency theory, the exact pathophysiological mechanisms of depression remain obscure, which is a complex clinical existence, including different nervous system process [5]. As the current industry recognized mechanism of depression, the monoaminergic hypothesis predicts that the decrease in monoamine neurotransmitters levels in the synaptic cleft is the cause of depression [6]. Accordingly, the chemical drugs, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), which can increase monoamine levels, are the most widely used drugs

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for depression [7]. However, 10 to 30% of depression patients do not respond to existing treatments. Therefore, several other mechanisms, such as inflammatory and neurotrophic, were introduced to understand depression [8]. Studies have shown that the activation of immunoinflammatory pathways, in particular the release of proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, can cause neuroendocrine and neurochemical changes leading to depression [9].

The lipopolysaccharide (LPS) immunoreactive model is a recognized inflammatory-related animal model of depression [10]. LPS can activate innate immune response and secrete proinflammatory cytokines, such as interleukin (IL)-6 and -1β, IL-6 and tumor necrosis factor-α (TNF-α). These cytokines affect neurotransmission and plasticity in the brain, trigger oxidative stress, and inhibit neurogenesis in adults, all of which are thought to be the underlying mechanisms of depression.

Most plants of the *Acanthopanax* species are safe and non-toxic, especially the leaves of *A. sessiliflorus* and *A. senticosus*, which can be eaten as traditional vegetables and tea in China. Chiisanoside, a lupine triterpenoid, is one of the main active ingredients of the leaves of *A. sessiliflorus, A. senticosus*, *A. divaricatus*, *A. subinermis*, *A. koreanus* and so on [11,12]. Chiisanoside exhibits a series of significant pharmacological effects, such as anti-osteoporosis [13], anti-inflammation [14–17], antibacterial [18], anti-platelet aggregating [19], treatment of glycation-associated diseases [20], anti-rotaviral [21], and anti-cancer, the inhibition of lipase [22]. Depression is associated with inflammatory and oxidative stress. In the antidepressant model induced by LPS, the inflammatory cytokines including IL-6 and TNF-α contribute to the pathogenesis of depression and anxiety. Based on all above, it was hypothesized that chiisanoside might have antidepressant activity. In this study, the antidepressant activity of chiisanoside, and the potential mechanisms were studied in mice models.

2. Materials and methods

2.1. Animal

SPF (specific pathogen free) grades, adult male ICR mice, weighing 20 ± 2 g, were obtained from the Changchun Yisi experimental animal technology Co., Ltd. Mice were maintained on standardized laboratory conditions (temperature 23 ± 2 °C, 55% ± 5% humidity on a 12-h light/dark cycle). And mice were provided with diet and water ad libitum during the experimental period. After one week of acclimatization, all mice were randomly divided into different groups. All experiments were carried out in accordance with the Guide for Animal Experimentation of Jilin Agricultural University. The protocol was approved by the Jilin Agricultural University Institutional Animal Care and Use Committee.

2.2. Drugs and reagent

Chiisanoside was prepared by ourselves. The air-dried leaves of *A. sessiliflorus* were extracted with 70% ethanol. The extract was filtered and concentrated under reduced pressure, and then passed through a D101 macroporous resin column, chromatographed on a silica gel column with chloroform–methanol (5:1) to afford chiisanoside (28.5 g). The purity of chiisanoside was determined by HPLC (purity > 98%), and the structure was identified by NMR [23].

Antidepressant drugs: fluoxetine (an antidepressant drug belonging to SSRIs), reboxetine (an antidepressant drug belonging to noradrenaline reuptake inhibitors) were obtain from Sigma (St. Louis, MO, USA). Receptor antagonists and agonist: haloperidol (a non-selective D_2 receptor antagonist), prazosin (a α_1-adrenoceptor antagonist), *N*-methyl-D-aspartic acid (NMDA, an agonist at the glutamate site) and bicuculline (a competitive GABA antagonist) were also from Sigma. LPS were produced by Sigma-Aldrich (St. Louis, USA). The detecting ELISA kits including GABA, Noradrenaline (NA), DA, Glutamic (Glu), TNF-α, IL-6, superoxide dismutase (SOD) and malondialdehyde (MDA) were supplied by Nanjing Jiancheng Bioengineering Institute (Nanjing, China). All other reagents used in the study were of analytical grade.

2.3. Behavioral evaluation methods

2.3.1. Spontaneous locomotors activity test (SLT)

The goal of SLT is to exclude the possibility of the alteration in the immobility time in the tail suspension test (FST) and forced swimming test (TST), which is due to interference with autonomous activities [24,25]. The SLT was done in an open filed experimental video analysis system placed in a darkened and sound attenuated testing room. The spontaneous activity time of each mouse was measured within 5 min.

2.3.2. Tail suspension test (TST)

The TST was performed according to a previous research [26]. This test was also used as a standard rodent test for screening of antidepressant activity. Mice were suspended 75 cm above the floor by taping 1 cm from the tip of the tail. Each mouse was suspended for 6 min, and each mouse was considered immovable only when it absented of escape-oriented behavior. The total duration of immobility was assayed during the last 4 min.

2.3.3. Forced swimming test (FST)

The FST was similar to the traditional method [27]. This test was used as a standard rodent test for screening of antidepressant activity. Mice were separately placed in an open cylindrical container (diameter 14 cm, height 25 cm), containing 20 cm of water (depth) at 24 ± 2 °C. Each mouse was forced to swim for 6 min, and only when it stopped struggling and floated on the water, the mouse was considered immovable. The total duration of immobility was assayed during the last 4 min.

2.4. Drug treatments and experimental design

Chiisanoside and other medicine were dissolved in physiological saline (0.9% NaCl aq) immediately before test. The mice in the blank group were given the same volume of physiological saline. All mice were administered chiisanoside and other medicine by intraperitoneal (i.p.) injection. The administration operators were blind to the drugs including the vehicles, the tested materials, antidepressant drugs and receptor antagonists and agonists. The observers were also blind to the drug treatment. Specific tests were arranged as follows.

2.4.1. Effect of chiisanoside on locomotor activity in the SLT and antidepressant effect in the TST and FST

The mice of blank control group, chiisanoside groups (125 μg/kg, 500 μg/kg, 2.5 mg/kg and 5 mg/kg, respectively) and fluoxetine group (20 mg/kg) were administered. After 30 min of a single-dose administration, spontaneous locomotor activity of each mouse was observed in a ZZ-6 mouse autonomic activity test instrument (Shanghai benefits of the medical equipment Development Co., Ltd., Shanghai, China). The TST and FST were carried out after 60 min of the administration. The animals were allowed to rest for 1 h between the TST and FST.

2.4.2. Antidepressant effect of co-administration of chiisanoside and antidepressant drugs in the TST and FST

Positive drug groups (sub-effective doses): the mice were administered with a single-dose fluoxetine (5 mg/kg) and reboxetine (2.5 mg/kg) 60 min prior to the TST and FST, respectively. Positive drug + chiisanoside groups (sub-effective doses): the mice were administered with a single-dose fluoxetine (5 mg/kg) and reboxetine (2.5 mg/kg) immediately after the administration of a single-dose chiisanoside (125 μg/kg) 60 min prior to the TST and FST, respectively. The animals were allowed to rest for 1 h between the TST and FST.