

Antidepressant-like effect of asiaticoside in mice

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Received 11 July 2007; received in revised form 17 January 2008; accepted 25 January 2008

Available online 5 February 2008

Abstract

In the present study, the potential antidepressant properties of asiaticoside were investigated in male mice in three tests—splash test in the unpredictable chronic mild stress (CMS) model, tail suspension test (TST), forced swimming test (FST)—with clomipramine being a positive control. In the splash test, asiaticoside (10 mg/kg, PO) and clomipramine (50 mg/kg, PO) significantly augmented the frequency of grooming behavior in stressed mice. In the tail suspension test, asiaticoside (10, 20 mg/kg, PO) and clomipramine (50 mg/kg, PO) significantly decreased immobility time. In the forced swimming test, asiaticoside (10, 20 mg/kg, PO) and clomipramine (50 mg/kg, PO) significantly decreased immobility time. These results suggest that asiaticoside may have antidepressant-like action.

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Keywords: Asiaticoside; Clomipramine; Antidepressant; Mice; Splash test; Unpredictable chronic mild stress (CMS) model; Tail suspension test; Forced swimming test

1. Introduction

Asiaticoside, a major pentacyclic triterpenoid saponin component of *Centella asiatica* (L.) Urh, has been described to have wound healing, antiulcer, antioxidant and anti-inflammatory activities (Fig. 1). Guo et al. (2004) reported that the mechanisms by which asiaticoside exerted its antiulcer and anti-inflammatory effects may be associated with inhibition of NO synthesis by its inhibitory effect on inducible nitric oxide synthase (iNOS). In our previous studies, asiaticoside was shown to present an anxiolytic-like effect (Si Wei Chen et al., 2006).

Chronic mild stress (CMS) suppresses rewarded-related behaviors in rats and mice. The CMS has a reasonably high degree of validity (Willner, 1984; Willner et al., 1992), and its prolonged duration makes it suitable to examine the effects of

chronic treatment with antidepressant drugs. It has been reported that the CMS regimen decreases the consumption of or preference for a sucrose solution (Willner et al., 1987) and induces a degradation of the physical state of the coat (Ducottet et al., 2003; Ducottet and Belzung, 2004). Chronic treatment with antidepressant drugs reverses the hedonic deficits caused by chronic mild stress (Willner et al., 1992). In the context of screening for potential antidepressive agents, mice may be preferable to rats on grounds of cost, size and social organization (Santiago and Paolo, 1995). In the present study we used two parameters: the state of the coat was used to evaluate grooming behavior indirectly whereas the splash test was used to determine this behavior directly (Santarelli et al., 2003).

We also used the tail suspension test (TST) and forced swimming test (FST) to evaluate the antidepressant-like activity of asiaticoside. The TST and FST are well established screening paradigms for antidepressants. A variety of antidepressants are known to reduce immobility time in TST (Steru et al., 1985). The FST, as originally described by Porsolt et al. (1977a,b), is the most widely used pharmacological model for assessing antidepressant activity (Weiss and Kiltz, 1998). This is largely due to its ease of use, reliability across laboratories, and ability

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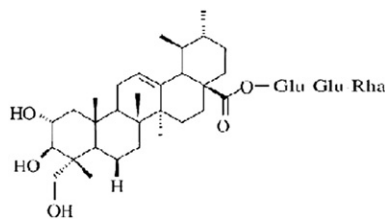


Fig. 1. The structure of asiaticoside.

to detect a broad spectrum of antidepressants (Borsini and Meli, 1988; Weiss and Kilts, 1998).

2. Animals and methods

2.1. Experiment 1

2.1.1. Animals

Male Swiss mice (bred at the Experimental Animal center of Shenyang Pharmaceutical University) Weighing 16–18 g was used in this study. They were kept in the laboratory for two weeks before treatment. In the unpredictable chronic mild stress (CMS) model the stressed mice were individually housed and the non-stressed mice were kept in groups of five in polycarbonate cages (cage size: 25 × 14 × 12 cm) and kept in a 12 h light/dark cycle (lights on at 19:00). Food and water were freely available.

The experiments were performed following approval of the committee of Experimental Animal Administration of the University and were in accordance with the National Institutes of Health Guide of the care and use of Laboratory Animals.

2.1.2. Drugs and treatments

Asiaticoside was purchased from Guangxi Changzhou Natural Products Development Co. Ltd (Nanning, China), clomipramine from Jiangsu Nhwa Pharma. Corporation (Jiangsu, China), Tween-80 from Shenyang dongxing Reagent Factory (Shenyang, China).

At the end of two weeks of a drug-free stress exposure mice were assigned to the different groups in a semi-randomized manner, so that the initial coat state and body weight were equivalent in all the groups. The drugs were given daily at 13:30. Asiaticoside (5, 10, 20, 40 mg/kg) and clomipramine (50 mg/kg) were both ultrasonically dispersed in distilled water containing Tween-80 (0.5%), and were prepared freshly on test days and administered PO two weeks after the beginning of the unpredictable chronic mild stress regimen in a volume of 10 ml/kg. Control animals were administered with the corresponding vehicle. The non-stressed mice were also administered PO at the same time with the stressed mice in a volume of 10 ml/kg.

2.1.3. Unpredictable chronic mild stress model (CMS)

The CMS was based on the procedure originally designed by Willner et al. (1992) and adapted to mice (Ducottet and Belzung, 2004). Mice were subjected several times a day for six weeks to one of the following stressors such as damp sawdust, sawdust changing, placement in an empty cage, placement in an

empty cage with water on the bottom, switching cages, cage tilting (45 °C), a period of intensity stroboscopic illumination (150 flashes/min), predator sounds for 15 min, inversion of light/dark cycle, lights on for a short time during the dark phase (Ipek and Fazilet, 2005). To prevent habituation and to provide an unpredictable feature to the stressors, all the stressors and/or sequences were administered at different time points every week (see Table 1).

2.1.4. Coat state and body weight

The coat state and body weights of the animals were recorded every Monday before and during the CMS. The evaluation of the coat state was carried out by the assessment of eight different body parts: head, neck, dorsal coat, ventral coat, tail, forepaws, hindpaws and genital region (Ducottet et al., 2003; Ducottet and Belzung, 2004). A score of 0 for a coat in a good state or a score of 1 for a dirty coat were given for each of these areas. Total score was obtained from the sum of the score of each body parts. We presented the total score that we obtained the last week of the stress regimen. The observers who scored the state of the coat were unaware of the treatment of the mice.

2.1.5. Splash test

After 3 weeks of treatment (beginning the sixth week) the splash test was performed. This test was used to evaluate the grooming behavior of both stressed and non-stressed mice. 10% sucrose solution was squirted on the dorsal coat of mice in their homecage (0.35 ml per mouse). Grooming is cleaning the fur of animal by licking or face grooming (strokes along the snout), head washing (semicircular movements over the top of the head and behind the ears), body grooming (body fur licking). The frequency of grooming refers to the number of licking during 5 min. The frequency of grooming was recorded during 5 min after the vaporization of sucrose solution (Ducottet and Belzung, 2004). The observer was unaware of the treatment conditions.

2.1.6. Open-field test

Locomotor activity was studied in mice by open-field test, each animal was placed in the center of a square arena (60 × 60 × 35 cm) with a black floor which was divided into 16 equal squares with white line. The apparatus was illuminated with red bulbs (25 w) on the ceiling. The drugs were administered P.O. 60 min prior to testing. The total number of squares entered was recorded for 5 min (Si Wei Chen et al., 2005). We presented the total squares entered that we obtained the last week of the stress regimen. The observers were unaware of the treatment of the mice.

2.2. Experiment 2

2.2.1. Animals

Male Swiss mice (bred at the Experimental Animal center of Shenyang Pharmaceutical University) Weighing 16–18 g were used in this study. Mice were housed in groups of five in polycarbonate cages for at least 10 days prior to testing under a

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