Journal of Ethnopharmacology 123 (2009) 55–60

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

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

Antidepressant effect of Shudihuang on mice exposed to unpredictable chronic mild stress

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ARTICLE INFO

Article history:
Received 25 June 2008
Received in revised form 15 October 2008
Accepted 16 February 2009
Available online 4 March 2009

Keywords:
Rehmannia glutinota Libosch.
Unpredictable chronic mild stress
Depression
Antioxidation
Clomipramine

ABSTRACT

Aim of the study: Depression is a severe mood disorder. It was treated with Shudihuang, the steamed roots of *Rehmannia glutinota* Libosch. (SRG), in traditional Chinese medicine. The present paper was designed to verify its antidepressant effect.

Materials and methods: A mouse model of depression was established though unpredictable chronic mild stress (UCMS). Low and high doses of SRG were administered orally. Fur state, body and organ weight, and gastric ulcers were examined. Locomotion was assayed in open field test. Liver antioxidant indexes were measured spectrophotometrically.

Results: Fur state, body and organ weight were found to be insensitive to UCMS. The locomotion reduced by UCMS was restored by low dose of SRG (2.5 g/kg BW) but not by high dose (5 g/kg BW). UCMS resulted in aggravated gastric ulceration, elevated liver malondialdehyde, together with reduced total antioxidant capability, glutathione content, and superoxide dismutase and catalase activities. The alterations were improved by SRG in a dose-dependent manner. The differences in the activity of glutathione peroxidase were statistically nonsignificant among groups. Clomipramine the positive drug was similar to SRG especially in antioxidation.

Conclusion: SRG is of therapeutic value for depression-like disorders, and antioxidation may be one of the mechanisms underlying its antidepressant action.

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1. Introduction

Rehmannia glutinosa Libosch. (Scrophulariaceae) is one of the medicinal plants distributed in China, Korea and Japan. Its fresh, dried and steamed roots have been used for different medical purposes in traditional Chinese medicine (TCM) for thousands of years. Shudihuang, the steamed roots of *Rehmannia glutinosa* (SRG), are used more widely than the others. It is often included as a primary herb in formulas to treat a great variety of diseases, for example "Liuwei Dihuang Wan", the most famous drug used in the treatment of the Syndrome of Kidney and Yin Deficiency (SKYD) (Hu et al., 2005). The main symptoms of SKYD include lumbar soreness, hot sensation in the palms and soles, irritability, etc. (Jiang et al., 1981). Modern researches have revealed that SKYD characterized by maladjustment of neuroendocrine–immune network (Jiang et al., 1981; Shen, 1990), which is similar to the responses evoked by chronic stress to a great extent (Black, 2002). Some researchers in China have established animal stress models for SKYD research (Fan et al., 2001; Wang et al., 2006).

Stress is an everyday burden, endured by most living creatures. The failure of successful adaptation during stressful situations will result in stress-related diseases including depression (Maes et al., 2000; Michel et al., 2007). Unpredictable chronic mild stress (UCMS) has been widely used in animals to model depression-like disorders, and is regarded as being close to the unexpected stressors of everyday life (Willner et al., 1987). Initially, UCMS functions as a stimulant, increasing metabolic rates and increasing the production of reactive oxygen species (ROS). The generation of appropriate ROS would be an effective way to induce organism's adaptability (Parsons, 1996). However, if the concentration of the ROS exceeds the body's capacity to neutralize them, the superfluous ROS begin to harm cells, tissues and organs, and result in oxidative stress.

Oxidative stress has been proposed to impair the antioxidant defence system, leading to oxidative damage by changing the balance between oxidant and antioxidant factors (Fontella et al., 2005; Yu and Chung, 2006). UCMS-induced oxidative damage has been postulated to be involved in the etiopathogenesis of a diverse variety of diseases, ranging from psychiatric disorders such as depression and anxiety, immunosuppression, endocrine disorders including diabetes mellitus, impotence, cognitive dysfunctions, peptic ulceration, to hypertension and ulcerative colitis (Bhattacharya and Muruganandam, 2003). Importantly, nearly all of these diseases manifest SKYD during their development, which can

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doi:10.1016/j.jep.2009.02.029

be treated with SRG in TCM (Jiang et al., 1981; Zhang et al., 2008a). Clinical investigations have revealed that the antioxidant capacity has been severely damaged in patients with SKYD (Chen and Jiang, 1989; Ding et al., 1996; Li and Zheng, 1998), and formulas containing SRG have been successfully applied to treat depression accompanied by SKYD (Jiang, 2000; Liu, 2004; Ge, 2006). In addition, many patients have been shown to exhibit both anxious and depressive symptoms, this comorbidity was explained by a sequential relationship, and high anxiety may be a risk factor for the occurrence of mood disorders (Fava et al., 2000; Ducottet and Belzung, 2005). SRG has been proved to have an anxiolytic action (Cui et al., 2006), so it is likely that SRG plays a major role in the effectiveness of the drugs used against depression and hence antioxidation might be one of its therapeutic mechanisms.

In the present paper, a six-week UCMS protocol was applied to mice to model depression-like disorders, high and low doses of SRG were orally administrated during the last three weeks, and clomipramine was used as a positive drug. Fur state, body and organ weight, locomotion, gastric ulceration were assayed to assess the effects of SRG on the mice exposed to UCMS, and the antioxidant indexes were determined to discuss its mechanism.

2. Materials and methods

2.1. Drugs

SRG was purchased from Jinan Jianlian Decoction Pieces Factory (batch number: 20070936). It was produced by steaming the dried roots for 24 h in the GMP workshop of the factory according to Pharmacopoeia of China. During processing, stachyose the primary constituent was decomposed into manninotriose, most of the iridoid glycosides including catalpol were broken down, and a series of new pentanoid monoterpenes and norcarotenoids have been formed (Liu et al., 2007; Zhang et al., 2008a).

The crude drug was authenticated by Professor Yong-lin Chen (Institute of Pharmacognosy, Shandong University), and a sample was deposited in the herbarium of the laboratory. SRG (250 g) was extracted three times (1 h, each time) with boiled water (1500, 1000 and 1000 ml). The extract was filtrated and concentrated under reduced pressure, then, freeze-dried to yield a black powder, and preserved for use at −18 °C. The yield of extract was 64.5%.

2.2. Animals

Male Kunming mice (23 ± 3 g) were obtained from the Center for New Drug Evaluation of Shandong University. The animals were housed 5 per cage matched for their weights, and maintained for two weeks under laboratory conditions with controlled ambient temperature (22 ± 2 °C), humidity (45 ± 10%) and a 12-h light/dark cycle (light on at 7 am), on *ad libitum* food (standard rodent pellets from the above center) and water before the start of the stress protocol.

Forty mice received unpredictable chronic mild stress, and ten mice were not exposed as normal control (CK). Three weeks later, the stressed mice were divided into four subgroups, and orally administered with vehicle (distilled water, UCMS), SRG of low (equivalent to crude drug of 2.5 g/kg BW, L-SRG) and high concentration (5 g/kg BW, H-SRG), and clomipramine hydrochloride (Nhwa Pharmaceutical Group Co., Ltd., 15 mg/kg BW, CLOM) for another three weeks. CK animals only received distilled water in the same volume used for drug administration (0.1 ml/10 g BW). The experimental procedure was conducted in conformity with the instructive notions with respect to caring for laboratory animals issued by Ministry of Science and Technology of the People's Republic of China in 2006.

2.3. Stress protocol

The protocol was slightly modified from those used by others (Monleon et al., 1995; D'Aquila et al., 1997), which included one 16 h period of water deprivation, two periods of continuous overnight illumination, two periods (7 and 17 h) of 45° cage tilt, two periods (7 and 17 h) in a soiled cage (100 ml water in sawdust bedding), two periods (2 h) of dark in day time, two periods (3 and 5 h) of noise (30 dB, 10 Kc/s), three times of confinement for 1 h (in a 10 cm × 5 cm plastic tube). The fourteen stressors were scheduled in a semi-random order, so that they were unpredictable for the animal. On average, two stressors were applied daily. The schedule was repeated weekly.

2.4. Behavioral and physiological assay

2.4.1. Physical state

The state of the fur was scored in seven body areas (face, nose, ears, eyes, back, belly and tail), the normal areas were scored 0, and the damaged, dirty or piloerected areas were scored 1. The sum of scores was used to reflect the mice global fur state (Ducottet and Belzung, 2005). It was evaluated three times, i.e., before the stress protocol, and three and six weeks later.

2.4.2. Open field test

In the open field test, a white rectangular plastic box (42 cm × 28 cm × 12 cm) was used, the bottom of which was divided into 24 equal squares. The mice were placed at the centre of the bottom and monitored for 2 min by a video camera. The visited square number (with at least three paws on one square) and the rearing number (defined as standing upright on its hind legs) were recorded, and the sum was used as open field activity. The apparatus was cleaned thoroughly before the next animal test (Harro et al., 1999).

2.4.3. Body and organ weight

Body weight was measured weekly throughout the experiment. 24 h after the last stressor exposure, mice were sacrificed by decapitation, and liver, spleen, thymus and adrenal were quickly removed and weighted. The livers were frozen in liquid nitrogen and then stored at −80 °C until assay.

2.4.4. Gastric ulceration

After mice were sacrificed, the stomach was removed, opened along the greater curvature, and thoroughly rinsed with physiological saline. After being fixed in 10% formol saline solution for 20 min, the stomach was inspected for ulcer. The damage degree was assessed by the number (N) of small ulcers (the ulcer diameter < 0.5 mm) together with the diameter (D) of the damaged part according to the technical standard issued by Ministry of Health of the People's Republic of China in 2003. It was scored as follows: 0, no ulceration; 1, $N < 4$; 2, $N = 4$–8 or $D = 0.5$–1.0 mm; 3, $N = 9$–16 or $D = 1.0$–2.0 mm; 4, $N > 16$ or $D > 2.0$ mm.

2.5. Antioxidant assay

Oxidative stress includes disturbed redox reactions and structural and functional alterations caused by free radicals and other reactive species. It is much severe in metabolically active tissues (Fisher et al., 1981; Yu and Chung, 2006), therefore, the concentration of malondialdehyde (MDA) and glutathione (GSH), the total antioxidant capability (TAOC), and the activities of antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) in the livers were determined in the present study.

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