

## Research paper

## Central anti-fatigue activity of verbascoside



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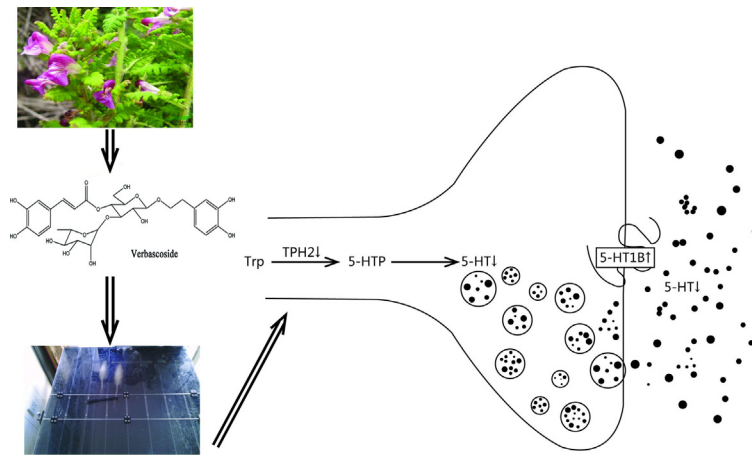
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## HIGHLIGHTS

- Verbascoside could prolong the time to exhaustion in treadmill exercise.
- The mechanism explains the ergogenic effect of verbascoside.
- Verbascoside was as effective as caffeine in these effects.

## GRAPHICAL ABSTRACT



## ARTICLE INFO

## Article history:

Received 16 September 2015

Received in revised form 21 January 2016

Accepted 24 January 2016

Available online 28 January 2016

## Keywords:

*Pedicularis* species

Neurotransmitter

Exercise

## ABSTRACT

In this study, the effects of verbascoside on treadmill exercise endurance, 5-hydroxytryptamine (5-HT) concentrations, the second isoforms of tryptophan hydroxylase (TPH2) and serotonergic type 1B inhibitory autoreceptors (5-HT1B) protein expression in the caudate putamen of exercised rats were investigated. Sixty Sprague-Dawley male rats were randomly divided into six groups: normal group, exercise group, exercise and verbascoside (0.1 mg/kg)-treated group, exercise and verbascoside (1 mg/kg)-treated group, exercise and verbascoside (10 mg/kg)-treated group, exercise and caffeine (10 mg/kg)-treated group. In exercise groups, rats were put on treadmill and forced to run for 30 min once a day for 6 consecutive days. On the 7th day of the experiment, the time to exhaustion in treadmill exercise was determined for the trained groups. Immediately after the determination of the exhaustion time, all rats were sacrificed. 5-HT concentrations were detected by HPLC analysis. TPH2 and 5-HT1B protein expression were measured by western blot analysis. We found that verbascoside could prolong the time to exhaustion in treadmill exercise and suppress the exercise-induced increase of 5-HT synthesis and TPH2 protein expression, and prevent the exercise-induced decrease of 5-HT1B protein expression in the caudate putamen. Verbascoside was found as effective as caffeine in these effects. Verbascoside at 10 mg/kg improved endurance of exercised rats.

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The mechanism of verbascoside's anti-fatigue activity might be related to the inhibition of the exercise-induced synthesis of 5-HT and TPH2 expression, and to the increase of the 5-HT1B expression in the caudate putamen of exercised rats.

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## 1. Introduction

*Pedicularis* plants are herbs widely used in Chinese traditional medicines for treatment of collapse and exhaustion and senility [1]. Previous researches have shown that *Pedicularis tricolor* may possess anti-fatigue effects on exercised mice [2] and the extract of *Pedicularis decora* can exhibit strong effect of promoting physical performance on exercised rats [3]. The *n*-butanol extracts and the remains of *n*-butanol extraction of *Pedicularis densispica* could significantly delay exercise fatigue symptoms and improve exercise capacity of mice [4]. Verbascoside is one of phenylpropanoid glycosides which are characteristic compounds of *Pedicularis* plants [5]. It was isolated from *Pedicularis dolichocymba* by us [6] and showed the effects on reducing oxidative stress in muscle caused by exhaustive exercise [7] and retarding skeletal muscle fatigue in vitro [8]. It has the potential of antagonizing sports anaemia [9] and possible agonistic effect on the hypothalamic regulation of estradiol synthesis [10]. However, the effects of verbascoside on the endurance exercise in relation to central nervous system, which is the most important mechanism, have not yet been clarified.

Monoamine levels in central nervous system have been associated with exercise performance and fatigue [11]. Physical exercise is often terminated due to the muscle fatigue and to the increase in serotonin (5-hydroxytryptamine, 5-HT) concentrations in the brain during prolonged exercise [12,13]. Increased concentrations of brain 5-HT during sustained physical activity could hasten the onset of fatigue [14], while decreasing 5-HT concentration could delay the time to fatigue [15]. The second isoform of tryptophan hydroxylase (TPH2) is considered the rate-limiting enzyme in 5-HT synthesis [16]. Serotonergic type 1B (5-HT1B) inhibitory autoreceptors upon stimulation, inhibit local synthesis and release of 5-HT [17]. Since it is difficult to control the exercise intensity of each mouse in swimming, we used the method of treadmill running to research the effects of verbascoside on treadmill exercise endurance, 5-HT, TPH2, 5-HT1B expression in the caudate putamen which is one of the important areas in movement and fatigue [18] of exercised rats.

## 2. Materials and methods

### 2.1. Animals

Adult male Sprague-Dawley rats of grade SPF, weighing  $217 \pm 13.32$  g and aged 5 weeks were used in this study. They were obtained from Hunan Lake King of laboratory animal Co. Ltd, Changsha, Hunan, China. Ten animals were housed per cage under the controlled conditions of temperature (25 °C–26 °C), humidity (40%), a light/dark cycle (12 h/12 h) with the access to food and water at will. Animals were allowed to acclimatize to the laboratory before the commencement of the experiment. The rodent license of the laboratory (no.SCXK (Xiang) 2011-0003) was issued by the Hunan Province Laboratory Animal Care and Use Committee. Procedures were approved by the Guidance Suggestions for the Hunan Province Laboratory Animal Care and Use Committee.

### 2.2. Drugs

*Pedicularis dolichocymba* was collected in Zhongdian, Yunnan, China in August 2003 and identified by Prof. Hong Wang, Kunming Institute of Botany, Chinese Academy of Sciences. The dried whole plants of *P. dolichocymba* were extracted by 95% ethanol and then concentrated under reduced pressure. The residue was dissolved in hot water and successively extracted by EtOAc. The EtOAc portion was eluted by CHCl<sub>3</sub>-MeOH (20:1) over silica gel column to give verbascoside [6]. Verbascoside was stored at 4 °C.

### 2.3. Experimental design

Sixty rats were randomly divided into six groups (n = 10 in each group): normal group (A), exercise group (B), exercise and verbascoside (0.1 mg/kg)-treated group (C), exercise and verbascoside (1 mg/kg)-treated group (D), exercise and verbascoside (10 mg/kg)-treated group (E), exercise and caffeine (10 mg/kg)-treated group (F). Rats in the exercised groups were made to run in a treadmill with 0° of inclination for 30 min once a day for 6 consecutive days, whereas those of normal group were left on the treadmill for 30 min without forced running. The exercise duration consisted of forced running at a speed of: 10 m/min for 10 min, 13 m/min for another 10 min, and 16 m/min for the last 10 min from the first day to the third day, and 15 m/min for 10 min, 18 m/min for another 10 min, and 23 m/min for the last 10 min from the fourth day to the sixth day.

### 2.4. Drug administration

Rats in verbascoside-treated groups (C, D and E) were given verbascoside (dissolved in saline) 0.1, 1 and 10 mg/kg respectively for six days by the intragastric gavage once per day. Rats in exercise and caffeine-treated group (F) were given caffeine (dissolved in saline) 10 mg/kg respectively for six days by the same method. Rats in normal group (A) and exercise group (B) were administered with saline for six days by the same method. The volume of each intragastric gavage was 2 ml per rat which was performed 2 h before the start of treadmill running.

### 2.5. Determination of exhaustion time and collection of the caudate putamen sample

On the 7th day of the experiment, the time to exhaustion in treadmill exercise was determined for the trained groups. Time to exhaustion is defined as the time between the commencement of exercise and the first occurrence of the experimental animals failing to keep up with the treadmill machine for a period of 3 min or more. The speeds used for measurement of the time to exhaustion were 18 m/min for 2 min, 21 m/min for 2 min, 24 m/min for 2 min, and then 26 m/min until exhaustion. Immediately after the determination of the exhaustion times all rats were sacrificed to remove the caudate putamen tissues (–0.92 to –1.80 mm posterior to bregma) for further processing.

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