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Antidepressant-like effect of *trans*-resveratrol: Involvement of serotonin and noradrenaline system

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Abstract

The antidepressant-like effect of *trans*-resveratrol, a phenolic compound present in polygonum cuspidatum, was evaluated through behavioral and neurochemical methods. *trans*-Resveratrol (20, 40 and 80 mg/kg, via gavage) significantly decreased the immobility time in mouse models of despair tests, but did not influence locomotor activity. Two behavioral models and neurochemical assays suggested that *trans*-resveratrol produced a significant increase in serotonin and noradrenaline levels at 40 or 80 mg/kg in brain regions. In addition, *trans*-resveratrol dose dependently inhibited MAO-A activity. These findings indicate that the antidepressant-like effect of *trans*-resveratrol might be related to serotonergic and noradrenergic activation.
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1. Introduction

Affective disorders are a major cause of morbidity and mortality in children and adolescents, with an estimated prevalence rate in the United States of 8.3% (Skaer et al., 2009). Patients with major depression have symptoms that are reflected by changes in brain monoamine neurotransmitters, specifically noradrenaline (norepinephrine, NE) and 5-hydroxytryptamine (serotonin, 5-HT) (Blier and De Montigny, 1994; Dhingra and Sharma, 2006). The first-line option in the management of depressive illness is pharmacotherapy. At present, there are several types of classical antidepressants used in clinical practice, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and serotonin and noradrenaline reuptake inhibitor (SNRI), that exert their

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antidepressant effects by increasing the levels of monoamines, such as serotonin and/or noradrenaline (Deniker, 1984). Many of these drugs can produce undesirable side effects and the mechanism of action has not been satisfactorily resolved (Xu et al., 2006); thus, identification of potent and safe therapeutic agents is still a significant need.

There are numerous herbal medicines that have been introduced into psychiatric practice because of greater compliance and milder side effects (Thachil et al., 2007). *Polygonum cuspidatum* is a plant used historically in Asia, known for its medicinal properties and traditionally used in the treatment of neuropsychiatric disorders, such as psychosocial stress, dementia and Parkinson's disease (Tredici et al., 1999; Chen et al., 2007). The *trans*-isomer of resveratrol is the active ingredient of *P. cuspidatum* and is also found abundantly in the skin of red grapes and red wine (Bai et al., 2010). Researchers have suggested that *trans*-resveratrol demonstrates a variety of pharmacological activities including antioxidant, anti-inflammatory, neuroprotective properties and amelioration of learning and memory impairment (Tredici et al., 1999; Chen et al., 2007; Kumar et al., 2007; Ranney and Petro, 2009). Previous studies indicated that *trans*-resveratrol inhibits monoamine oxidase (MAO) isoform activity in C6 glial cells (Mazzio et al., 1998). MAOs are mitochondrial bound isoenzymes which catalyze the oxidative deamination of dietary amines and monoamine neurotransmitters, such as 5-HT, noradrenaline, dopamine and other trace amines. The development of MAO inhibitors has led to important breakthroughs in therapies for several neuropsychiatric disorders ranging from mood disorders to Parkinson's disease (Bortolato et al., 2008). Recent studies showed that resveratrol is an inhibitor of noradrenaline and 5-HT uptake activity in rats (Yáñez et al., 2006a). However it remains unknown whether the antidepressant-like effects of *trans*-resveratrol are due to neurotransmitter changes and MAO inhibition.

In this study we examined the antidepressant-like effect of *trans*-resveratrol in mouse behavioral despair tasks. As the monoaminergic system is one of the most important targets in the pathophysiology and therapy of depression (Blier and De Montigny, 1994), we investigated the possible role of monoaminergics in the antidepressant-like effect of *trans*-resveratrol through various behavioral paradigms. In addition, the brain monoamine levels and MAO activity were also tested by neurochemical and biochemical assays to confirm the participation of monoamine transmitters in treatment involving *trans*-resveratrol.

2. Experimental procedures

2.1. Animals

Male ICR mice (20–22 g) were obtained from the Animal Center of Shanghai Branch, Chinese Academy of Sciences. Upon arrival, the mice were housed eight per cage and acclimatized to a colony room with controlled ambient temperature (22 ± 1 °C), humidity (50 ± 10%) and a 12 hour natural light/dark cycle. They were fed a standard diet, water was provided *ad libitum* and they acclimated 7 days before entry into the subsequent study. The experiments were performed with 10 mice per treatment group according to a randomized schedule. In behavioral tests, animals in every group were intermixed during the observation (10:00 h and 14:00 h) and the observers were unaware of the treatment conditions. All experiments were conducted in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985), and approved by the Wenzhou Medical College Committee on Animal Care and Use.

2.2. Drugs and drug administration

trans-Resveratrol, imipramine hydrochloride, *p*-chlorophenylalanine HCl (PCPA, an inhibitor of serotonin synthesis), apomorphine hydrochloride, kynuramine dihydrobromide, 4-hydroxyquinoline, clorgyline, deprenyl, 5-hydroxytryptamine, noradrenaline, dopamine, 5-hydroxyindoleacetic acid (5-HIAA) and 4-dihydroxyphenylacetic acid (DOPAC) were purchased from Sigma Chemical Co. (USA). Moclobemide hydrochloride and sodium carboxymethyl cellulose were provided by the Beijing Institute of Pharmacology and Toxicology (China). For oral administration (via gavage, i.g.), *trans*-resveratrol was dissolved in 0.5% sodium carboxymethyl cellulose and moclobemide was dissolved in redistilled water on the day of testing. For intraperitoneal injection, imipramine and fluoxetine were dissolved in redistilled water.

The plasma and brain concentrations of *trans*-resveratrol peak at 20–30 min and maintain their levels up to 60 min after oral administration in mice (Sale et al., 2004). Accordingly, the behavioral and neurochemical tests were conducted 30 min after *trans*-resveratrol treatment. The effects of positive antidepressants such as moclobemide (20 mg/kg, i.g.), imipramine (10 mg/kg, i.p.) and fluoxetine (10 mg/kg, i.p.), were tested 1 h (meclobemide) and 30 min (imipramine and fluoxetine) respectively, after administration of the drugs as previously described (Xu et al., 2005b; Wang et al., 2008).

2.3. Forced swimming test

The forced swimming test employed was similar to that described previously (Porsolt et al., 1977; Porsolt et al., 1978) with minor modification (Xu et al., 2005a). Briefly, mice performed a swimming-stress session for 15 min (pre-test), 24 h before being individually placed in glass cylinders (height: 25 cm; diameter: 10 cm; containing 10 cm of water at 24 ± 1 °C) for 6 min (test). A mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only small movements necessary to keep its head above water. The duration of observed immobility was recorded during the last 4 min of the 6-min testing period.

2.4. Tail suspension test

The tail suspension test was based on the method of Steru et al. (1985) as our previous work (Xu et al., 2005b). Animals were suspended 50 cm above the floor by means of an adhesive tape, placed approximately 1 cm from the tip of the tail. The time during which mice remained immobile was quantified during a test period of 6 min. Mice were considered immobile only when they hung passively and completely motionless.

2.5. Locomotor activity

The assessment of locomotor activity was carried out on mice using a slightly modified method (Xu et al., 2005b). Briefly, the locomotor activity of the mice was measured by an ambulometer with five activity chambers (JZZ98, Institute of Materia Medica, Chinese Academy of Medical Sciences, China). Mice were placed in the chambers and their paws contacted or disconnected the active bars producing random configurations that were converted into pulses. The pulses, which were proportional to the locomotor activity of the mice, were automatically recorded as the cumulative total counts of motor activity. Mice were placed in test chambers 5 min prior to the