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Antidepressant-like effect of *trans*-resveratrol in chronic stress model: Behavioral and neurochemical evidences

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ABSTRACT

Trans-resveratrol is a phenolic compound enriched in *polygonum cuspidatum* and has diverse biological activities. There is only limited information about the antidepressant-like effect of *trans*-resveratrol. The present study investigated whether *trans*-resveratrol has antidepressant-like activity in rats exposed to chronic stress by using two behavioral tasks, shuttle box and sucrose preference tests. The monoamines (5-HT, noradrenaline and dopamine) and their metabolites as well as monoamine oxidase (MAO) enzyme activities in different brain regions were also measured. Compared to unstressed rats, those exposed to chronic stress paradigm showed performance deficits in the shuttle box, reduced sucrose preference, less weight gain and the increase in the ratio of adrenal gland to body weight, which were reversed by chronic treatment with *trans*-resveratrol (40 and 80 mg/kg, i.g.). The neurochemical assay showed that higher dose of *trans*-resveratrol (80 mg/kg) produced a marked increase of 5-HT levels in three brain regions, the frontal cortex, hippocampus and hypothalamus. Noradrenaline and dopamine levels were also increased both in the frontal cortex and striatum. Furthermore, chronic treatment with *trans*-resveratrol was found to inhibit monoamine oxidase-A (MAO-A) activity in all the four brain regions, particularly in the frontal cortex and hippocampus; while MAO-B activity was not affected. These findings indicate that the antidepressant-like effect of *trans*-resveratrol involves the regulation of the central serotonin and noradrenaline levels and the related MAO-A activities.

1. Introduction

Major depression is a highly prevalent mood disorder that affects approximately 20% of the world population (Schechter et al., 2005). There is increasing clinical evidence that depressed patients usually have imbalance or deficiency in brain monoamine neurotransmitters, such as serotonin (5-HT) and noradrenaline (NA) (Blier & de Montigny, 1994). However, the currently available synthetic medicines are commonly associated with unwanted side effects, and their antidepressant mechanisms have not been well elucidated (Xu et al., 2005; Wang et al., 2008). Therefore, the development of safe and effective pharmacotherapeutics remains necessary.

Polygonum cuspidatum is a traditional herbal medicine used widely to treat the neuropsychiatric disorders in Asia, and its efficacy has been reported in many pharmacological and clinical studies (Tredici et al., 1999; Chen et al., 2007). *Trans*-resveratrol is the major active component of *P. cuspidatum*, and it is also enriched in the grapes, red wine and some other dietary products (Bai et al., 2010). The aggressive analysis of this phytocompound has revealed that it has various pharmacological activities, including antioxidant and anti-inflammatory effects (Tredici et al., 1999; Chen et al., 2007; Kumar et al., 2007; Ranney and Petro, 2009). Recently, the neuroprotective effect of *trans*-resveratrol has come to the attention of scientists (Albani et al., 2010). It was reported that resveratrol reverses the Aβ-induced toxicity in the PC12 cells (Jang and Surh, 2003). Furthermore, in a transgenic mouse model of Alzheimer's disease (AD), cognitive improvement was observed after treatment with resveratrol (Wang et al., 2006). Besides AD, the powerful neuroprotective effect of resveratrol has also been confirmed in other neurodegenerative disorders, such as Huntington's disease

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and Parkinson's disease (PD) (Parker et al., 2005; Albani et al., 2009). Previous *in vitro* studies suggested that *trans*-resveratrol inhibits the activity of monoamine oxidase (MAO) in glial cells involved in the pathology of many neurological disorders including depression and anxiety (Mazzio et al., 1998). The MAO enzyme inactivates monoamine neurotransmitters and any change in the enzyme alters the neurotransmitter function (Bortolato et al., 2008). Our pilot study showed that acute treatment with *trans*-resveratrol significantly decreased the immobility time in forced swim and tail suspension tests, indicating a possible antidepressant-like effect (Xu et al., 2010). However, the effect of chronic treatment with *trans*-resveratrol on stress-related depression and the underlying mechanism remain unclear.

People encounter various stressors in everyday life, which might contribute to some degree, to the development of depression. Chronic administration of various uncontrollable stresses, a procedure known as "chronic unpredictable stress", is an appropriate model for the pre-clinical evaluation of antidepressants (Bhutani et al., 2009). Therefore, we decided to explore whether long-term *trans*-resveratrol treatment could affect behavioral and neurochemical aspects of depressive like state of chronically stressed rats. Due to the importance of the monoaminergic system in the pathophysiology and therapy of depression, we investigated the involvement of monoamine neurotransmitters and the related enzyme activities in the antidepressant-like effect of *trans*-resveratrol by various behavioral and neurochemical methods.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley (SD) rats (190–200 g) were obtained from the Animal Center of Shanghai branch, Chinese Academy of Sciences. The rats were housed six per cage under standard colony conditions, with a 12-h light/dark cycle and had free access to food and water. They were allowed to acclimatize to the colony for 5 days before any experiment. All experiment procedures were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985), as approved by the Wenzhou Third Hospital and Wenzhou Medical College Committee on Animal Care and Use.

2.2. Drugs and drug administration

Trans-resveratrol, imipramine hydrochloride and fluoxetine were purchased from Sigma (USA). For oral administration (via gavage, i.g.), *trans*-resveratrol was dissolved in 0.5% sodium carboxymethyl cellulose on the day of testing. For intraperitoneal injection, imipramine and fluoxetine were dissolved in redistilled water. *Trans*-resveratrol, imipramine and fluoxetine were administered 30 min before the chronic stress for 21 days. Behavioral tests were performed 24 h after the last stressful event (Murua et al., 1991).

2.3. Unpredictable chronic stress protocol

The rats were subjected to the following conditions used by Molina et al. (1990) and Xu et al. (2006, 2012) with minor modifications. Stress was administered once a day over a period of 21 days. The order of the stressors used was as follows:

Days	1	2	3	4	5	6	7	8	9	10
Stressors	Shaking (high speed, 45 min)	Cold swim (10 °C, 5 min)	Restraint (1.5 h)	Tail pinch (1 min)	Water deprivation (24 h)	Foot shock (30 min; 1 mA, 1 s duration, average 1 shock/min)	Cold swim (1 °C, 8 min)	Food deprivation (24 h)	Restraint (2 h)	Shaking (high speed, 1 h)
11	12	13	14	15	16	17	18	19	20	21
Tail pinch (1 min)	Water deprivation (24 h)	24 h social isolation (mice were individually placed in 30 × 15 × 10 cm cages in another room)	Foot shock (45 min; 1 mA, 1 s duration, average 1 shock/min)	Cold swim (8 °C, 10 min)	Shaking (high speed, 1.5 h)	Restrain (2.5 h)	Tail pinch (2 min)	Food deprivation (24 h)	Restraint (3 h)	Water deprivation (24 h)

On day 22, 23 and 24, the stressed rats were subjected to behavior tests between 8:00 am to 2:00 pm. Following behavioral testing, mice were sacrificed to assess any neuroendocrine changes that may have occurred.

2.4. Shuttle-box testing

At the beginning of the shuttle box session, rats were allowed to habituate to the test environment for 5 min and then submitted to 30 escape trials (30 s inter-trial interval). A white noise signal was presented 4 s prior to each trial, followed with a 4 sec 0.8 mA shock. Failure to respond before or during the shock delivery was designated as escape failure, and the number of escape failure was recorded (Xu et al., 2006).

2.5. Sucrose preference test

Rats were exposed to both the test solution (1% sucrose) and tap water for a 24 h period. During the test, sucrose preference was evaluated for 1 h by utilizing two bottles of 1% sucrose and tap water and the position of the bottles was switched after 30 min. The rats were food and water deprived for 14 h prior to the start of the experiment. The sucrose preference was calculated as the ratio of the consumed sucrose solution to the total amount of liquid consumed.

2.6. Determination of monoamines and metabolites

Rats were decapitated and their brains were rapidly removed and placed on an ice-chilled glass plate. Different brain regions, including hippocampus, prefrontal cortex, hypothalamus and striatum, were obtained according to the reported protocol. The tissue samples were weighed and stored at −80 °C until homogenization. The contents of serotonin, noradrenaline, dopamine and 5-HIAA (the metabolites of 5-HT) were measured as described