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ORIGINAL ARTICLE

Combined hepatoprotective and antidepressant effects of resveratrol in an acute model of depression

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Abstract There are numerous herbal medicines that have been introduced into psychiatric practice because of greater compliance and milder side effects. *Polygonum cuspidatum* is a native Asian plant; known for its medicinal properties and traditionally used in the treatment of neuropsychiatric disorders, such as psychosocial stress, dementia and Parkinson's disease. Resveratrol is the active ingredient of *P. cuspidatum*. Researchers have suggested that the trans-isomer of resveratrol demonstrates a variety of pharmacological activities including antioxidant, anti-inflammatory, hepatic and neuroprotective properties. In this study we examined the hepatoprotective and antidepressant effects of trans-resveratrol against fluoxetine in an acute reserpine model of depression in rats. Main methods: depression-like behaviors were induced by single reserpine intraperitoneal injection (6 mg/kg, i.p.). Trans-resveratrol (15, 30 and 60 mg/kg bwt) and fluoxetine (24 mg/kg bwt) were administered orally for the following 3 days. Behavioral effects namely open field test (OFT) and forced swimming test (FST) and biochemical parameters namely neurotransmitters levels and antioxidant contents were assessed. Liver histopathological examination was performed. Key findings: Results revealed that resveratrol (60 mg/kg bwt) showed a potential hepatoprotective and an antidepressant-like effects compared to those of fluoxetine.

1. Introduction

Depression is a common and invalidating mental illness affecting approximately 2.5% of the general population. It has negative social consequences in terms of reduced employment and psychosocial impairment. Based on the World Health Organization surveys; it has been suggested to become the second leading cause of disability by 2020.[1] Despite a steady increase in the number of antidepressants over the years, the prevalence of the disorder remains stable which may be due to unclear pathophysiology or the inconsistent efficacy of currently available antidepressants with undesirable side effects. However, there is a direct correlation between the catecholaminergic neuronal systems and depression.[2]

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Fluoxetine is a widely prescribed selective serotonin reuptake inhibitor with antidepressant properties.[3] However, it has recently been postulated to induce liver damage and mediates free radical reactions due to its fluorine content.[4]

A variety of consumable plant-derived phytochemicals exhibit nutraceutical properties because they produce physiological benefits and combat disease processes. Emerging evidence suggests that widely accessible and safe organic polyphenolic phytochemicals, in particular, treat depression at much lower concentrations than clinical doses of classical drugs.[5]

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound that has been detected in fruits and some flowering plants. It was first isolated from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) in 1940 and later, in 1963 from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine. Other major dietary sources containing resveratrol include grapes, wine, peanuts, and peanut products. The first real interest in this compound came when in 1992 resveratrol was postulated to explain some of the cardio-protective effects of red wine and was suggested to be an important factor in the French Paradox, a term coined to describe the observation that the French population has a very low incidence of cardiovascular disease, despite a diet high in saturated fat. Five years later, in 1997, resveratrol was reported to work as a chemo-preventive agent, by the ability to inhibit carcinogenesis at multiple stages. Meanwhile, also anti-inflammatory and antioxidant properties were identified for resveratrol.[6–9] Additionally, the protective role of resveratrol against a number of hepatic injuries (e.g. cholestasis) due to oxidative damage of primary rat hepatocytes was reported by several authors.[10–12] Moreover, intraperitoneal administration of resveratrol in rats with ligated bile ducts maintained antioxidant defenses and reduced liver oxidative damage and ductular proliferation.[13] Neuro-pharmacological activities such as amelioration of learning and memory impairment and neuroprotective properties have also been reported.[14–17]

The present study aimed to investigate the combined hepatoprotective and antidepressant effects of trans-resveratrol against fluoxetine in a reserpine model of depression in rats.

2. Materials and methods

2.1. Animals

Adult male Wister rats, weighing 130–150 g each, were purchased from the animal house at the National Research Centre (NRC, Giza, Egypt). All animals received care in compliance with the guidelines of the animal care and use committee of the NRC. Upon arrival, the animals were kept in a quiet place, housed eight per cage and acclimatized to a colony room with controlled ambient temperature (22 ± 1 °C), humidity (50 ± 10%) and a 12 h natural light/dark cycle. They were fed a standard diet, water was provided *ad libitum* and they were acclimated for 7 days before entry into the subsequent study. They were allowed free access to water and food throughout the period of investigation. All the procedures described below were carried out in accordance with the guidelines of the EU Directive 2010/63/EU for animal experiments. The experiments were performed with 8 rats per treatment group according to a randomized schedule. In behavioral tests, animals in every group were intermixed during the observation and the observers were unaware of the treatment conditions.

2.2. Drugs and drug administration

Fluoxetine hydrochloride (Prozac 20 mg dispersible tablets, Lilly, Spain), the tablets were freshly suspended in distilled water prior to oral administration. Trans-resveratrol was provided as a generous gift from Jing Tea LLC, it was provided as Harmoni-T micronized trans-resveratrol capsules for ingestion. The powder in the capsules was freshly dissolved in distilled water just before oral administration. Reserpine was a generous gift from Novartis co. Egypt, it was provided as pure powder for injection and it was freshly dissolved in a DMSO/saline mixture (0.1: 10 ml) before intraperitoneal injection.

2.3. Experimental design

Rats were divided into six different groups (8 rats each) and treated as follows; Group (1): normal control (DMSO/saline group). Group (2): depressed group (reserpine group). Group (3): receiving fluoxetine (24 mg/kg, p.o.).[4] Groups (4, 5 and 6): receiving trans-resveratrol (15, 30 and 60 mg/kg, p.o.).

2.4. Experimental procedure

Groups 2, 3, 4, 5 and 6 were administered reserpine (6 mg/kg, i.p.) once on day one of the experiment. This dose results in depression symptoms that persist for 72 h. after injection.[18] Group (1) was administered DMSO/Saline i.p. injections on the same day. Group (1) was kept in separate cages and had free access to food and water till the end of the experiment. All other groups received the corresponding drugs orally for the following 3 days. On day number 2 behavioral tests, namely open field test (OFT) and forced swimming test (FST) were performed. Twenty-four hours later, the rats were killed by decapitation 30 min after the last drug ingestion. Brain and liver tissues were isolated and each brain or liver was washed with cold sterile physiological saline, blotted between two damp filter papers and stored at −80 °C for further biochemical analysis. Parts of the liver tissues were isolated in formalin and used for the histopathology.

2.5. Behavioral tests

2.5.1. Open field test

The open field test was carried out in a square wooden arena (80 cm × 80 cm × 40 cm high) with red walls and white smooth polished floor divided by black lines into 16 equal squares. The test was performed under white light in a quiet room. Each rat was placed at the same corner square and observed during 5 min. The floor and walls were cleaned after testing each rat. The following parameters were recorded during the 5 min observation period; latency: time taken by each animal till it starts moving in the arena, ambulation frequency: number of squares crossed by the animal, rearing frequency: number of times the animal stood stretched on its hind limbs with or without forelimb support.[19–21]