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Research report

Antidepressant effects of resveratrol in an animal model of depression

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HIGHLIGHTS

- Resveratrol resulted in antidepressant effect in WKY rat model of depression.
- Resveratrol caused an increase in hippocampal but not frontal cortical BDNF.
- Resveratrol may have potential usefulness in some treatment resistant depression.

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ABSTRACT

Resveratrol (3,4′,5-trihydroxy-trans-stilbene) is a natural non-flavonoid polyphenol antioxidant extracted from red grapes in the processing of wine. Initially it was studied for its potential as anticancer drug, and later was found to reduce cardiovascular disease. More recently resveratrol was shown to alleviate depressive-like symptoms induced by stress or other means in mice and rats. The major purpose of this study was to investigate whether resveratrol would manifest an antidepressant effect in Wistar–Kyoto (WKY) rats, a putative and non-induced animal model of depression, and whether this effect might be associated with an increase in hippocampal and frontal cortical brain-derived neurotrophic factor (BDNF), a protein implicated in chronic effects of many antidepressants. Adult male WKY rats were injected with two doses of resveratrol (10 and 40 mg/kg, i.p.) and their behavior in the open field locomotor activity (LMA), forced swim test (FST: a measure of helplessness), and sucrose preference test (SPT: a measure of anhedonia) was evaluated after a single acute injection or following 7 days of daily treatment. Both acute and chronic administration of resveratrol resulted in a dose-dependent decrease in FST. However, only chronic resveratrol resulted in dose-dependent increase in sucrose consumption. LMA was not affected by any treatment. Parallel to the observed behavioral effects the level of hippocampal, but not frontal cortical, BDNF was also dose-dependently elevated after chronic resveratrol administration. These findings indicate an antidepressant-like effect of resveratrol in an animal model of depression possibly via activation of hippocampal BDNF, and suggest therapeutic potential of resveratrol in at least a subpopulation of depressed patients.

1. Introduction

Depression and other mood affective disorders can be chronic, life threatening, and are widespread throughout the population. For example, major depression, in its many definitions and manifestations, has been reported to have a 12-month prevalence rate of 5.2–10.3% in Western society [1–3]. Numbers vary with age group and population, but reporting of both 12 month and lifetime prevalence appears to be increasing. It is now generally accepted that depression can be caused by one or more changes in the brain, which may or may not be directly related. These changes may include monoamine neurotransmitters (e.g., norepinephrine and serotonin: [4,5]), cellular atrophy, neuronal death or decreased neurogenesis [6–12], and neuroinflammation [13,14]. Traditionally, the first line treatments have used pharmaceuticals that work to stabilize the levels of key biogenic amines (e.g., selective serotonin and/or norepinephrine reuptake inhibitors) or monoamine oxidase inhibitors (MAOI) [5,15]. These drugs act via various pathways, but are limited in their effectiveness, have a long latency to onset, and are often associated with side effects [5,16,17]. The long latency to effectiveness (i.e., need for chronic administration) can be theoretically tied to the neurotrophic effect of antidepressants, and an increase in neurogenesis [12,18,19]. Indeed, converging evidence supports the underlying hypothesis that it is the

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neurotrophic effects of antidepressants that lead to their efficacy and that neurotrophins such as brain-derived neurotrophic factor (BDNF) may play a key role in the pathophysiology of depression, and that antidepressants may in part exert their effects via regulation of BDNF [12,20]. Several clinical studies have even reported that serum BDNF level is decreased in depressed patients, and that can be normalized by antidepressant treatment [21]. However, drugs that act on non-biogenic amine pathways or reduce neuroinflammation may have a faster (e.g., acute) effect. Identification of such therapeutics, with low side effects is needed.

A wide number of natural or traditional Asian medicines have been investigated as potential anti-depressants or general neuoprotectants. Among the most popular have been polyphenols such as curcumin (e.g., [22]), fisetin (e.g., [23]), and resveratrol (e.g., [24,25]). In this study we focused on the anti-depressant potential of resveratrol. A natural non-flavonoid polyphenol antioxidant, resveratrol (3,4,5-trihydroxy-trans-stilbene) is a substance extracted from red grapes in the processing of wine, but it is also found in other fruit skins. Resveratrol was initially studied for its potential for treating cancer [26], but also gained recognition for its ability to reduce cardiovascular disease [27]. More recently resveratrol was shown to alleviate depressive-like symptoms induced by stress in rats [25,28–34], and that at higher doses causes an increase in biogenic amines in the hippocampus and the cortex in mice [24]. In this study we examined the antidepressant-like effect of resveratrol in a non-induced model of depression, the Wistar–Kyoto (WKY) rats. WKY rats are an inbred strain of rats that show depressive-like behavior, decreased BDNF expression, and decreased hippocampal volume in comparison to their control, Wistar rats [35–39]. These rats were initially developed as a normotensive control for the spontaneously hypertensive rats [40], but were later found to demonstrate exaggerated immobility in the forced swim test, a measure of helplessness or depressive-like behavior [41]. Moreover, it was found that these rats are irresponsive to selective serotonin reuptake inhibitors (SSRIs) [42–44]. Therefore, we evaluated the effects of resveratrol on behavioral despair and anhedonia, as well as on hippocampal and frontal cortical BDNF expression in these rats.

2. Methods

2.1. Animals

In this study, adult male WKY rats (14–15 weeks old) were obtained from Harlan Laboratories (Indianapolis, IN). Animals receiving the same treatment were pair-housed through the duration of the experiment in a standard polypropylene shoebox cages (42 cm × 20.5 cm × 20 cm) on chip bedding. Animals were subjected to a 1-week acclimatization period upon their arrival, during which hey were handled daily to minimize any handling related stress. Throughout the study, with the exception of behavioral tests, animals had free access to food (Harlan Tek Lab) and water. The room was maintained at 24–26 °C at 55–66% relative humidity, on a reverse light cycle (lights on 7:00 PM–7:00 AM) to allow convenient behavioral evaluations during the animal's active period. Acclimatization to reversed dark cycle was done over a one-week period where the light hours were shifted by approximately 2 h daily. All behavioral testing and injections occurred between 8:00 A.M. and 12:00 P.M. during the animal's active phase as described previously [37,38,45,46]. All experiments were carried out in accordance with NIH guidelines, as approved by the Institutional Animal Care and Use Committee of the Howard University.

2.2. Injections

Animals were divided into three groups ($n = 6$/group), and received intraperitoneal (i.p.) injection of either saline (control) or 10, or 40 mg/kg dose of resveratrol [*trans*-1,2-(3,4′,5-trihydroxydiphenyl)ethylene: TCI America, USA)]. Acute behavioral tests were conducted 20 min after first injection. For chronic behavioral tests the same animals continued receiving daily injection for 7 days, and behavioral tests were carried out 18–20 h after the last injection. Following 1 week of rest after the last chronic injection animals were tested again for possible lasting behavioral effects. Following this behavioral test, the animals were rested for 10 days before receiving another 7 days of chronic injection. In this case, however, the animals were sacrificed by decapitation, 18–20 h after last injection, without any behavioral tests to collect brains for neurochemical evaluations. Thus, the same animals were used to assess the behavioral and neurochemical effects of resveratrol (see Fig. 1 for details of paradigm).

2.3. Behavioral tests

Three behavioral tests were conducted. First, open field locomotor activity was measured for each animal during a 5 min period. An open field activity-monitoring cage (27 cm × 27 cm × 20.3 cm, Med Associates, Inc., St. Albans, VT) was used to assess activity. Ambulatory counts, representing the number of infrared beam interruptions were automatically recorded. Second, to assess helplessness, a hallmark of depressive-like behavior, a modified, 5 min forced swim test (FST) was used to measure immobility of the rats [47]. Essentially, rats were individually placed into a cylinder filled with ~30 cm water (25 ± 1 °C) to ensure that animals could not touch the bottom of the container with their hind paws or their tails. A time-sampling scoring technique was used whereby the predominant behavior – immobility or swimming – in each 5-s period of the 300-s test was recorded as previously described [38]. It is of relevance to indicate that WKY rats exhibit spontaneous immobility in the forced swim test; hence, there is no need to have a pretest exposure to forced swimming the day before as is customary in inducing helplessness in other strains [35,37,38,43]. Moreover, it is our experience that the immobility of the rats in the FST is maintained albeit at slightly higher level, provided the test is carried out after one week of rest. Third, anhedonia was tested using sucrose preference test (SPT). To do this, rats were habituated to 1% sucrose solution for 5 days (6 h/day) prior to experimental start. On day of test, rats were singly housed with ad libitum food and 2 bottles – one with water and one with a 1% sucrose solution – for the 12 h dark cycle following drug treatment. Bottles were reversed halfway through the time to avoid side preference. The preference for the sucrose solution was calculated as a percentage of total liquid consumed [45]. Sucrose preference below 65% is usually taken as the criterion for anhedonia, and is based on the ≥65% sucrose preference of control animals [48].

Acute locomotor and FST tests were performed 20 min after first injection, and 18–20 h after day 7 injection. Tests were repeated one week later without any treatment injections, to test the potential of lasting behavioral effects.

2.4. Tissue collection and biochemical analysis

Twenty-four hours after last chronic (7 days) injection animals were sacrificed by decapitation. The brains were rapidly removed, frozen on dry ice and stored at −80 °C. Each frozen brain was later thawed on ice and hippocampus (bilateral) and frontal cortex up to the genu of corpus callosum was dissected as described previously [49]. Homogenate of each sample was made in lysis buffer (10 mM Tris-buffer, 5 mM EDTA, 150 mM NaCl, 0.5% Triton X-100 (v/v) with