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Antidepressant Effects of Resveratrol in an Animal Model of 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.

Keywords

Resveratrol; Depression; Animal Model; BDNF; Hippocampus

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Conflict of interest
The authors state no conflict of interest.

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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% to 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 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 levels are decreased in depressed patients, and that they 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,

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we evaluated the effects of resveratrol on behavioral despair and anhedonia, as well as on hippocampal and frontal cortical BDNF expression.

2. Methods

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 × 20.5 × 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 animals 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. 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 hours 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 Figure 1 for details of paradigm).

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 x 27 x 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

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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 hours 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 hours after day 7 injection. Tests were repeated one week later without any treatment injections, to test the potential of lasting behavioral effects.

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 the 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 protease inhibitors (Sigma-Aldrich, St. Louis, MO). The protein concentration in each sample was determined using a BCA protein Assay Kit (Pierce Biotechnology Inc., IL), and equal protein amount (as confirmed by β-actin) was loaded in each immunoblot. The proteins were separated using the SDS-PAGE gel and transferred onto a nitrocellulose membrane. The membranes were blocked with a blocking reagent (5% nonfat milk in TBS buffer) for 30 minutes and incubated at 4°C overnight with the primary antibody BDNF (1:200, Santa Cruz Biotechnology Inc., Santa Cruz, CA). The membranes were washed with TBST (TBS buffer with 1% Tween-20) and blocked with the blocking reagent. Membranes were then incubated for 1 hour at room temperature in Goat Anti-Rabbit-HRP conjugated secondary antibody (1:3000 in TBS, Bio-rad Laboratories, CA). The membranes were then washed in the TBST washing solution and then visualized using enhanced chemiluminescent kits (Bio-rad Laboratories, CA). The intensity of the protein bands on the gel was quantified using ChemiDoc XRS system (Bio-rad Laboratories, CA).

5. Statistics

All data were analyzed using one-way analysis of variance (ANOVA) with repeated measures, followed by Tukey HSD post hoc test when significant main effects were indicated. All analyses were two-tailed and $*p<0.05$ was considered significant a priori.

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3. Results

3.1. Acute

Acute treatment of resveratrol resulted in a significant dose-dependent reduction of helplessness as measured by FST (Figure 2: $F(2, 15) = 22.18$, $p<0.038$ for 10mg/kg and $p<0.001$ for 40mg/kg). There was no significant effect on locomotor activity (Figure 3: $F(2, 15) = 2.59$, $p>0.05$), or sucrose preference (Figure 4. $F(2, 15)= 0.089$, $p> 0.05$).

3.2. Chronic

Chronic treatment of resveratrol resulted in a similar significant dose-dependent reduction of helplessness as measured by FST (Figure 2: $F(2, 15) = 27.96$, $p<0.004$ for 10mg/kg and $p<0.001$ for 40mg/kg). There was no significant effect on locomotor activity (Figure 3), but a significant dose-dependent effect was observed in sucrose preference test (Figure 4: $F(2, 15) = 8.32$, $p<0.05$ for 10mg/kg and $p<0.01$ for 40mg/kg).

3.3. One-week post chronic injections

The effect of resveratrol on FST immobility as well as on sucrose preference had disappeared one week after stopping the injections (Figure 2 and 4: $F(2, 15) = 1.95$, $p>0.05$). Locomotor activity also was not different among the treatment groups (Figure 3).

3.4. BDNF expression after chronic resveratrol

Western blot quantification and analysis showed that chronic resveratrol treatment resulted in a dose-dependent increase in hippocampal BDNF level (Figure 5c). Thus, parallel to the behavioral effects, both 10 and 40 mg/kg doses of reveratrol resulted in significant increases $F(2, 15) = 10.52$ in hippocampal BDNF (17% increase with 10 mg/kg, $p<0.05$ and 24% increase with 40 mg/kg, $p<0.01$). As depicted in Figure 5d the level of frontal cortical BDNF was not affected by any dose of resveratrol $F(2, 15) = 2.06$, $p>0.05$).

4. Discussion

The results of the current study, while confirming the antidepressant-like effects of resveratrol, extend those findings to include its effectiveness in a non-induced and SSRI resistant animal model. Hence, resveratrol may be of particular use in at least a subtype of depressed patients. Moreover, the data suggest a role for hippocampal neurotrophic factor in antidepressant effects of resveratrol.

Involvement of neurotrophic factors in general, particularly BDNF, in mood regulation and/or effectiveness of antidepressants has been amply documented [12, 50-52]Although the exact circuitry controlling mood is far from clear, several areas including the hippocampus and to some extent the frontal cortex have been shown to play a key role. Thus, resveratrol was shown to alleviate depressive-like symptoms in mice, and that at higher doses cause an increase in serotonin and noradrenaline in the hippocampus, and noradrenaline, dopamine, and serotonin in the frontal cortex[24]Whether these changes ultimately lead to neurotrophic alteration in these regions and whether alterations in neurotrophic pathways may be the common denominator in effectiveness of all antidepressants remains to be elucidated.

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However, it is of relevance to note that we did not see any alteration in frontal cortical BDNF following resveratrol administration. Thus, possible role of frontal cortex and the underlying neurobiological substrates associated with antidepressant effects of resveratrol in this area remain to be investigated. It is noteworthy that chronic administration of ketamine also results in antidepressant effects in WKY rats, which is associated with an increase in hippocampal BDNF [45]

In addition to manipulation of the neurotrophic factors, observed here by us and others [31, 33], at least part of resveratrol's antidepressant properties may be related to its modulation of the inflammatory process whose role in mood dysregulation has been recently highlighted [14, 53]. Thus, it was shown that at least in primary cortical neurons, resveratrol significantly inhibited LPS-induced microglial activation, and hence production of pro-inflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and nitric oxide [54]. In this regard it would be of considerable interest to investigate possible interactions between the inflammatory and neurotrophic factors, particularly following long-term resveratrol treatment. Moreover, the established antioxidant effects of resveratrol as well as its interaction with the hypothalamic-pituitary axis [29] may be also contributing to its mood regulating effects. A further advantage of resveratrol may involve its prevention of cognitive decline that might also be associated with chronic unpredictable mild stress [30]. Thus, it has been proposed that resveratrol may be of therapeutic potential not only in age-related depression, but also the associated cognitive decline [25].

It has to be noted that in our paradigm resveratrol was administered intraperitoneally. Although resveratrol is available over the counter as supplementary diet and is advertised as antioxidant and possible neuroprotective agent, the dose-equivalency of an orally administered resveratrol has to be established before effectiveness of such claims can be verified. Finally, our data does not provide sufficient evidence that resveratrol alone might be able to fully normalize the depressive characteristics. In this regard possible additive or synergistic effects of resveratrol with other antidepressants (e.g. curcumin: [22]) should be investigated.

5. Conclusions

The results of this study indicate an interaction of resveratrol with hippocampal neurotrophic factor and suggest its potential usefulness in at least a subpopulation of treatment resistant depression.

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Research Highlights

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

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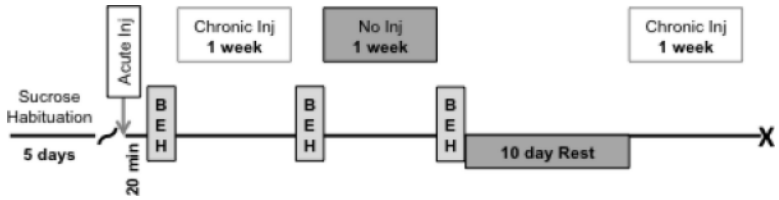

Fig 1.

Schematic of drug treatment and behavioral testing. Sucrose habituation occurred the week before testing began. BEH – Behavioral testing occurred 20 min after acute injection, after one week of daily chronic injections, and again one week after chronic injections were stopped. Animals where then rested 10 days before receiving another week of chronic injections before sacrifice for brain collection, denoted by **X**.

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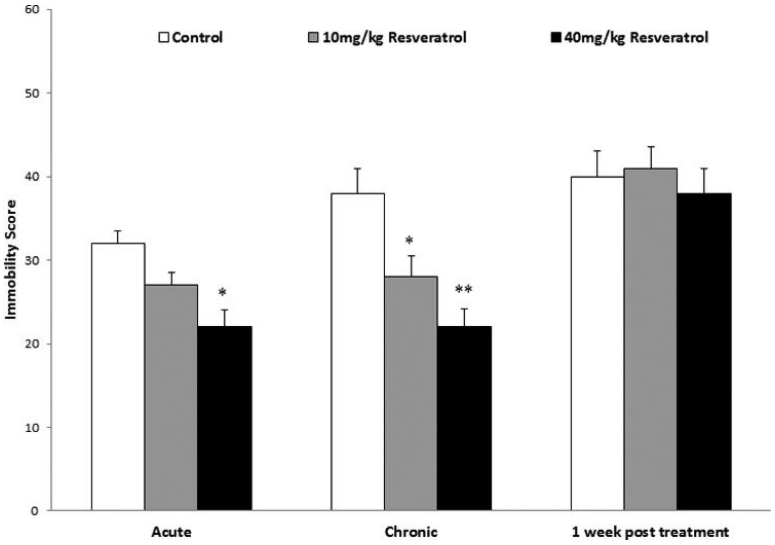

Fig 2.

Effects of acute and chronic (7day) treatment with two doses of resveratrol on immobility in the forced swim test. The animals were tested 20 min after the acute injection and 18-20 h after the last chronic injection. The animals were tested again after one week of rest (post treatment). Values are mean ± SEM. N = 6/group. *p<0.05, **p<0.01 compared to control.

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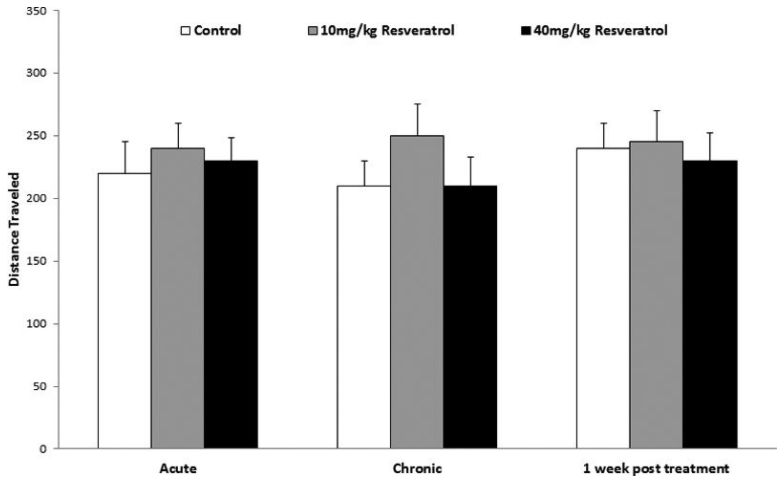

Fig 3.

Effects of acute and chronic (7day) treatment with two doses of resveratrol on open field locomotor activity (distance travelled cm). The animals were tested 20 min after the acute injection and 18-20 h after the last chronic injection. The animals were tested again after one week of rest (post treatment). Values are mean ± SEM. N = 6/group.

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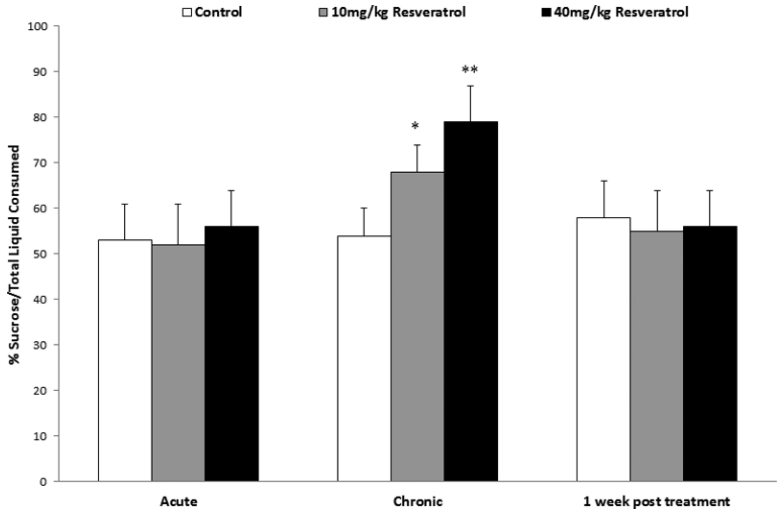

Fig 4.

Effects of acute and chronic (7day) treatment with two doses of resveratrol on sucrose preference (% sucrose/total liquid consumption). The animals were tested for 12 h after acute or chronic injections. The animals were tested again after one week of rest (post treatment). Values are mean ± SEM. N = 6/group. *p<0.05, **p<0.01 compared to control.

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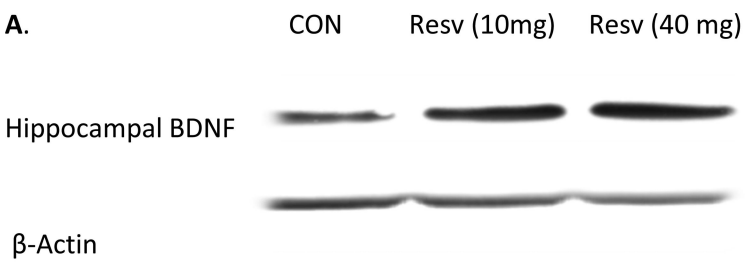

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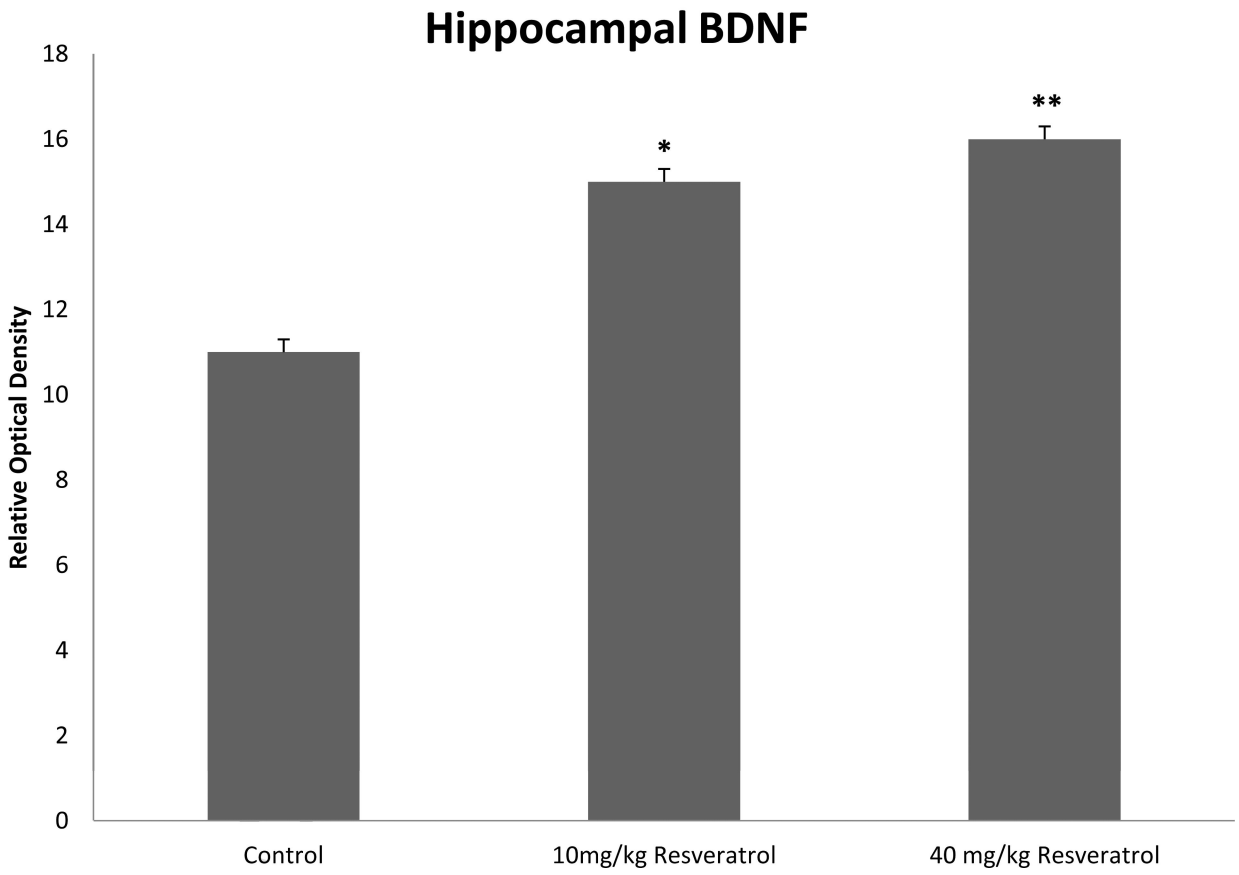

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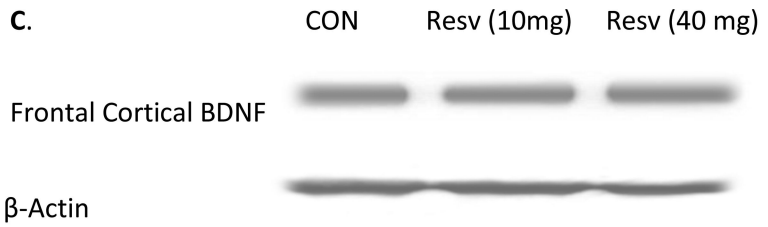

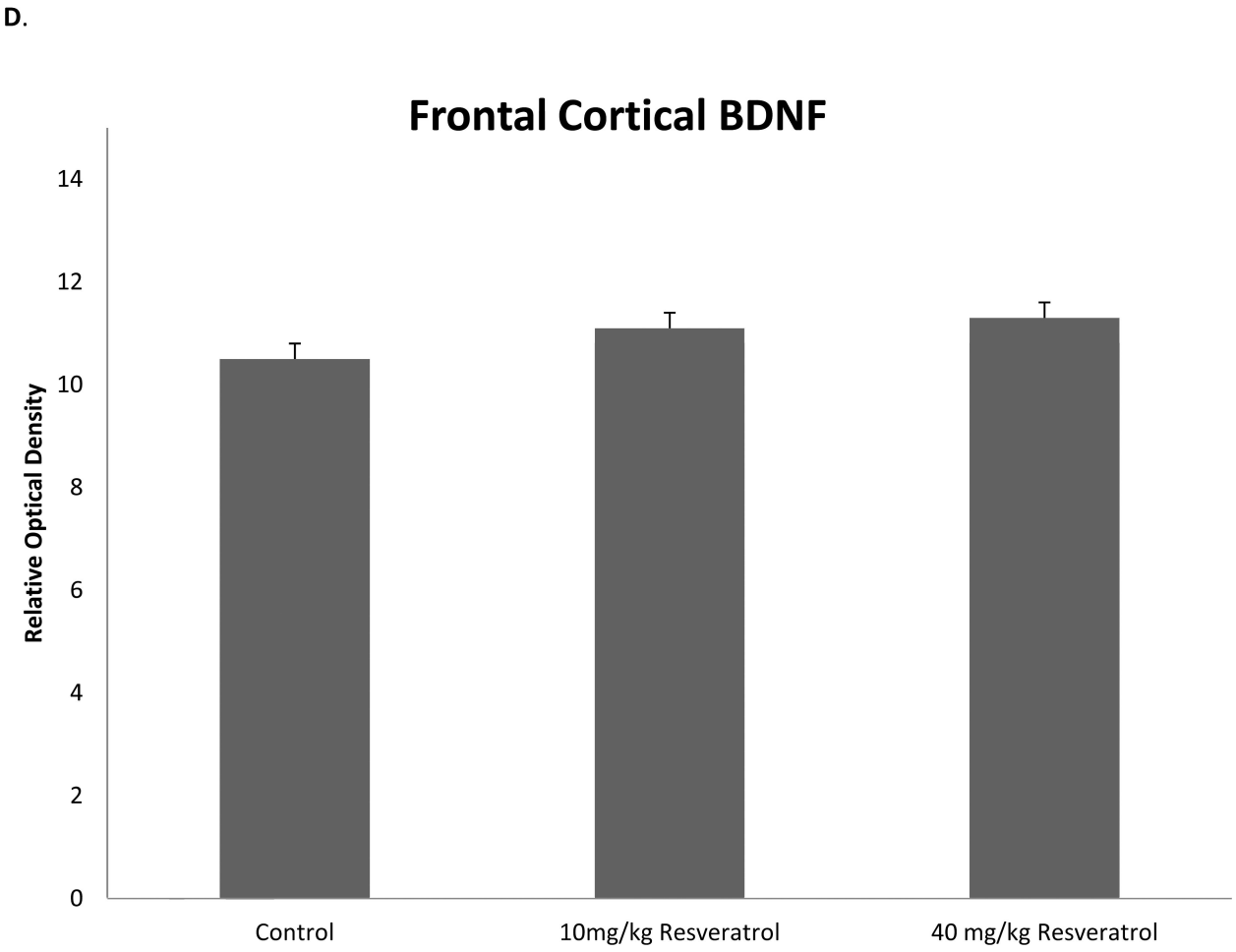

Fig 5.

Effects of chronic (7day) treatment with two doses of resveratrol on BDNF levels in the hippocampal and frontal cortex. The animals were sacrificed 18-20 h after the last injection. The upper panel depicts the immunoblots in Western assay. Values are mean ± SEM. N = 6/ group. *p<0.05, **p<0.01 compared to control.