Resveratrol exerts anti-inflammatory and neuroprotective effects to prevent memory deficits in rats exposed to chronic unpredictable mild stress

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HIGHLIGHTS

• Resveratrol attenuates the deficits in cognition seen in stressed rats.
• Resveratrol decreased proinflammatory cytokine concentrations in plasma.
• Resveratrol improved neurotrophic factor expression in hippocampus and amygdala.
• Resveratrol have a role in reversing the deleterious effects of stress on cognition.

ABSTRACT

A number of studies have recently focused on the neuroprotective and anti-inflammatory effects of resveratrol. In prior studies, we described its beneficial effects on scopolamine-induced learning deficits in rats. The aim of this study was to investigate the effects of resveratrol on emotional and spatial cognitive functions, neurotropic factor expression, and plasma levels of proinflammatory cytokines in rats exposed to chronic unpredictable mild stress (CUMS), which is known to induce cognitive deficits. Resveratrol (5 or 20 mg/kg) was administered intraperitoneally for 35 days. Rats in the CUMS group and in the 5 mg/kg resveratrol + CUMS group performed poorly in tasks designed to assess emotional and spatial learning and memory. The 20 mg/kg resveratrol + CUMS group showed improved performance compared to the CUMS group. In addition, the CUMS procedure induced lower expression of brain-derived neurotrophic factor and c-Fos in hippocampal CA1 and CA3 and in the amygdala of stressed rats. These effects were reversed by chronic administration of resveratrol (20 mg/kg). In addition, plasma levels of tumor necrosis factor-alpha and interleukin-1beta were increased by CUMS, but were restored to normal by resveratrol. These results indicate that resveratrol significantly attenuates the deficits in emotional learning and spatial memory seen in chronically stressed rats. These effects may be related to resveratrol-mediated changes in neurotrophin factor expression in hippocampus and in levels of proinflammatory cytokines in circulation.

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1. Introduction

Chronic stress is an unavoidable life experience that can induce depression [1], impair spatial cognition [2], and cause abnormalities in neuroendocrine function [3] and plasticity [4]. Based on these observations, an animal model of chronic unpredictable mild stress (CUMS) has been developed to mimic the development and progress of stress-associated clinical depression [5] and cognitive deficits [6].

It has been proposed that the learning and memory deficits associated with chronic stress may be alleviated using novel therapeutics such as dietary and medicinal phyto-antioxidants. One such nutraceutical is resveratrol. It is a dietary polyphenol found in a wide variety of foods such as berries, nuts, grape skins, and red wine. An increasing research effort is aimed at identifying potential therapeutic roles of resveratrol in human health given its various, and potentially beneficial, antioxidant, anti-inflammatory, and neuroprotective activities [7,8]. Recent studies focusing on the neuroprotective effects of resveratrol have shown that it attenuates amyloid beta peptide- (9,10) and kainic acid-induced toxicities.
was applied 4
nine stressors were randomly applied for 35 days, and each stressor
tail for 1 min, and inversion of the light/dark cycle for 24 h. These
with another stressed animal for 48 h, level shaking for 10 min, nip
water for 5 min, swimming in 45 °C hot water for 5 min, pairing
cage tilting for 24 h, wet bedding for 24 h, swimming in 4 °C cold
jected to nine different types of stressors, as listed: restraint for 4 h,
CUMS was applied as described previously by Yazir and co-workers
– 5 times during this period. A rat received only one of
2.2. Unpredictable chronic mild stress procedure
CUMS was applied during CUMS at a dose of 5 mg/kg/day or 20 mg/kg/day.
prevent animals from predicting the occurrence of
water deprivation. The control groups receiving no stress had free
2.3. Locomotor activity test
Locomotor activity was measured with a computerized system
(May Commat, Ankara, Turkey; in a 40 cm × 40 cm × 35 cm box).
Total locomotor activity was measured before the cognitive behavioral
tests and was expressed as the sum of the stereotypic, ambulatory,
and vertical activities of the animals. Locomotor activity was evaluated
over a 5-min period.
2.4. Passive avoidance test
A one-trial, light–dark passive avoidance apparatus (Ugo Basile
model 7551, Italy) was used for the evaluation of emotional memory
based on contextual fear conditioning[21]. In this test, the animal learns
to avoid a specific place associated with an aversive event. The reduction
of latency to avoid was used as a learning index. The apparatus consisted
of two compartments, each measuring 22 × 21 × 22 cm. An illuminated
white box was connected to a dark box equipped with an electrifiable
grid floor. An inescapable electrical shock could thus be delivered to the
animal’s feet via a shock generator. The two boxes were separated by a
flat-box partition, including an automatically operated sliding door at
floor level.
A training trial was carried out as described by Monleon and co-
workers[22]. A preacquisition trial was performed on the first day
of training in which the rats were placed individually into the light
compartment and allowed to explore the boxes. The door between
the two boxes was opened after 30 s and the animal was able to
move freely into the dark compartment. Fifteen minutes after the
preacquisition trial, an acquisition (training) trial was performed.
Rats were again placed in the light compartment of the passive
avoidance apparatus. After 30 s of familiarization with the apparatus,
the door between the compartments was opened. When the animal
entered the dark compartment completely, the sliding door between
the chambers was closed automatically and an electric foot-shock
(0.5 mA) of 3-s duration was delivered through the grid floor. The time
taken to enter the dark compartment was recorded as the training laten-
cy. If the animal failed to cross over from the illuminated to the dark
compartment within 300 s, it was excluded from the experiment. The
animals were then removed from the dark box and put back in their
home cages. Both compartments of the box were cleaned thoroughly
between each training session to remove any confounding olfactory
cues.
Twenty-four hours after the acquisition trial, a retention trial was
performed. Recall of the shock stimulus was evaluated by returning
the animals to the light compartment and recording their latency to
enter the dark compartment (four paws in). No foot shock was applied
in this trial. If the animal did not enter the dark compartment within
300 s, it was returned to its home cage and a latency of 300 s was
recorded. This latency served as a measure of the retention performance
of the passive avoidance response.
2.5. Morris water maze test
Performance in the Morris task was assessed in a water tank (150 cm
in diameter) as previously described[23]. The rats underwent three
trials during five daily sessions. During the first four days, the platform,
which was situated in the center of the southwest quadrant, was
submerged 1.5 cm below the surface of water, and small black pieces
of plastic were placed on the water surface. The plastic was invisible
to the rats due to its placement, and it was used to monitor spatial
learning. The platform position remained unchanged over 4 days, and
latency to find the platform was assessed. A trial was started by placing
a rat into the pool, facing the wall of the tank. Each of three starting
positions (north, east, and west) was used once in a series of three randomly ordered trials. Each trial was terminated as soon as the rat had climbed onto the escape platform or at the end of 60 s. A rat was allowed to stay on the platform for 20 s, after which it was taken from the platform, and the next trial was started. Rats that did not find the platform within 60 s were put on the platform by the experimenter and were allowed to stay there for 20 s. After completion of the 3rd trial, rats were gently dried with a towel, kept warm for an hour, and returned to their home cage. Twenty-four hours after the last acquisition session (on day 5), a ‘probe trial’ was used to assess the rat’s spatial retention of the location of the hidden platform. During this trial, the platform was removed from the maze and the rat was allowed to search the pool for 60 s before being removed. During this time, animals that have learned the task were expected to spend more time searching in the quadrant that previously contained the hidden platform than in the other three quadrants.

2.6. Immunohistochemistry
Paraffin sections were prepared from rat brains fixed with 10% neutral buffered formalin. Sections were deparaffinized in xylene, rehydrated using serial dilutions of alcohol, and washed with phosphate-buffered saline (PBS). An antigen retrieval procedure was then performed by treating the samples in 10 mM citrate buffer (pH 6.0) in a microwave oven at 600 W for two 5-min periods. The samples were allowed to cool for 20 min at room temperature and incubated in 3% H2O2 for 15 min. Sections were then incubated in blocking serum (Histostain-Plus Kit, Broad Spectrum, Invitrogen, Carlsbad, CA, USA) at the same concentration. After several washes, the slides were incubated with a biotinylated reagent solution, Invitrogen, Carlsbad, CA, USA at the same concentration. After several washes, the slides were incubated with a biotinylated secondary antibody (Histostain-Plus Kit, Broad Spectrum, Invitrogen, Carlsbad, CA, USA) for 20 min at room temperature, and diaminobenzidine (DAB) (DAB Substrate Kit, Invitrogen, Carlsbad, CA, USA) was applied for visualization. Sections were briefly counterstained with Mayer’s hematoxylin (Invitrogen, Carlsbad, CA, USA) and mounted on glass slides with ClearMount (Invitrogen, Carlsbad, CA, USA). The slides were examined under a light microscope (Olympus BX 50, Tokyo, Japan), and photomicrographs were taken with a Leica DM 100 system (Leica DFC 290HD, Wetzlar, Hessen, Germany). All samples were treated following the same protocol. Two independent observers who were blinded to the groups in this study graded the immunohistochemical staining intensity on a semiquantitative scale ranging from no expression (−) to very weak (1+), moderate (2+), strong (3+), and very strong (4+) expression. The concordance between the grading of the two observers was 91%. Scores were assigned based on percentage of positive cells as follows: 0, <5%; 1, 6–15%; 2, 16–50%; 3, 51–80%; and 4, >80%.

2.7. Cytokine analyses
Following behavioral testing, serum samples were collected to measure cytokine concentrations. The serum was immediately separated by centrifugation at 4000 rpm for 15 min, at 40 °C; it was divided into aliquots and stored at −70 °C until assayed. Serum levels of the proinflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) were quantified using enzyme-linked immunosorbent assays (ELISA, Biosource, Invitrogen, Carlsbad, CA) according to the manufacturer’s recommendations. Samples were then analyzed with a VersaMax microplate reader (Molecular Device, Sunnyvale, CA, USA) using SoftMaxPro 5 software.

2.8. Drugs and treatments
Resveratrol was purchased from Sigma Chemical Co. (St. Louis, USA). For intraperitoneal (i.p.) administration, fresh resveratrol was dissolved in saline mixed with 5% DMSO and given in a volume of 0.2 mL per 100 g body weight of the rats. Resveratrol (5 and 20 mg/kg) was administered daily for 35 days. Behavioral testing commenced 60 min after the last drug treatment. In a preliminary experiment, DMSO (i.p., 0.2 mL/100 g) and saline (i.p., 0.2 mL/100 g) were used as control treatments and the behavioral data did not differ between the rats that received the two vehicle solutions.

2.9. Statistical analysis
All results were expressed as mean ± SEM. Acquisition (1–4 day) latency scores in the water maze task were analyzed by two-way ANOVA, followed by post hoc Bonferroni test. Scores for the time spent in the escape platform quadrant and total locomotor activity were analyzed by one-way ANOVA. Further statistical analysis for individual groups was carried out by Bonferroni’s test. Training and retention latency-based scores in the passive avoidance test as well scores for immunoreactivity were analyzed using the Kruskal–Wallis test followed by Dunn’s multiple comparison test. The criterion for statistical significance was p < 0.05.

3. Results

3.1. Effects of CUMS and resveratrol on body weight
Average body weights (g) recorded for different groups were as follows: saline control group, 314.0 ± 6.05; CUMS group, 226.0 ± 6.09; DMSO group, 299.0 ± 14.42; 5 mg/kg resveratrol group, 260.0 ± 7.0; and 20 mg/kg resveratrol group, 306.0 ± 3.23. The average body weight of CUMS group after 35 days was significantly lower than that of the control group [F(4,40) = 19.23, one-way ANOVA, Bonferroni’s test, p < 0.0001]. Treatment with 20 mg/kg resveratrol in rats receiving CUMS significantly increased the rats’ body weights; further, the overall body weight change in these rats over the 35-day period was significantly different from that of rats receiving CUMS alone (p < 0.0001), but comparable to that of control rats (p > 0.05). DMSO and 5 mg/kg resveratrol treatment did not affect body weight (p > 0.05).

3.2. Effects of CUMS and resveratrol on locomotor activity
CUMS rats exhibited a significant decrease in locomotor activity [F(4,45) = 5.848, p < 0.01; one-way ANOVA, Bonferroni’s test; Fig. 1] compared to non-stressed control rats. Treatment with 5 or 20 mg/kg resveratrol did not reverse the suppressive effects of CUMS on locomotor activity. DMSO did not affect locomotor activity (p > 0.05).

3.3. Effects of CUMS and resveratrol on BDNF and c-Fos protein expression and on plasma levels of proinflammatory cytokines
In the CA1 region of the hippocampus, BDNF and c-Fos protein expression were significantly decreased in CUMS group compared to non-stressed controls (p < 0.05, Kruskal–Wallis test; Fig. 2A and B, respectively). Treatment with 20 mg/kg resveratrol significantly attenuated these effects of CUMS (p < 0.05, Kruskal–Wallis test; Fig. 2A and B, respectively). CUMS rats receiving treatment with 20 mg/kg resveratrol had levels of BDNF and c-Fos protein similar to those in the non-stressed control group (p > 0.05, Kruskal–Wallis test; Fig. 2A and B, respectively). In the CA3 region of the hippocampus, BDNF and c-Fos protein levels were likewise significantly lower in the CUMS group than in the nonstressed control group (p < 0.05, Kruskal–Wallis test;
In the 20 mg/kg resveratrol + CUMS treatment group, BDNF and c-Fos protein expression were significantly increased compared to the CUMS group (p < 0.05, Kruskal–Wallis test; Fig. 2A and B, respectively). However, the dose of 5 mg/kg resveratrol did not affect BDNF and c-Fos protein levels in either the CA1 or CA3 regions of the hippocampus.

Fig. 2A and B, respectively). In the 20 mg/kg resveratrol + CUMS treatment group, BDNF and c-Fos protein expression were significantly increased compared to the CUMS group (p < 0.05, Kruskal–Wallis test; Fig. 2A and B, respectively).
Plasma TNF-α levels (pg/ml) were 21.23 ± 1.31 for nonstressed control group, 30.52 ± 3.76 for CUMS group, and 23.39 ± 0.69 for 20 mg/kg resveratrol + CUMS group. Plasma IL-1β (pg/ml) levels for the nonstressed control group were 43.91 ± 3.27, whereas for the CUMS group, IL-1β levels were 58 ± 6.22, and for the 20 mg/kg resveratrol group, they were 36.31 ± 4.9. Plasma levels of TNF-α and IL-1β (pg/mL) were significantly increased in the CUMS group compared to the resveratrol (20 mg/kg) + CUMS and nonstressed control groups (p < 0.05; one-way ANOVA, Bonferroni’s test).

3.4. Effects of the systemic administration of resveratrol on CUMS-induced memory impairment in the passive-avoidance test in rats

During the training session (on day 1) of the light–dark passive avoidance task, there were no significant differences between any groups (KW = 5.112, Kruskal–Wallis, Dunn’s test; Fig. 3A).

However, there was a significant difference between groups in the retention test (KW = 28.91, Kruskal–Wallis, Dunn’s test; Fig. 3B). CUMS rats showed significantly lower latencies to enter the dark side compared to nonstressed control rats during the retention test, which was performed 24 h after the training test (p < 0.001; Kruskal–Wallis, Dunn’s test; Fig. 3B). The reduced retention latencies indicate impaired retention of the passive avoidance task. The effect of CUMS on this measure was reversed by 20 mg/kg of resveratrol (p < 0.05 vs. control; Kruskal–Wallis and Dunn’s tests; Fig. 3B). The dose of 5 mg/kg resveratrol had no effect on CUMS-induced memory impairment (p < 0.05 vs. control; Kruskal–Wallis–Dunn’s test; Fig. 3B).

3.5. Effects of systemic administration of resveratrol on CUMS-induced memory impairment in the Morris water maze test in rats

We found that subjecting animals to the chronic stress protocol for 35 days similarly resulted in performance deficits in the water maze task. As displayed in Fig. 4A, statistical analysis showed no significant effect of day in the data set [two-way ANOVA, Bonferroni’s test, effect of day, F(12,180) = 0.97, p = 0.4078]. However, an extremely significant effect of treatment was demonstrated (two-way ANOVA, Bonferroni’s test, effect of treatment, F(4,180) = 70.33, p < 0.0001). Further analysis revealed that day × treatment interaction was not significant [two-way ANOVA, F(12,180) = 0.041, p = 0.9567]. Post hoc comparisons showed that stress caused a significant disruption of learning and memory, as indicated by increased escape latencies in the CUMS group during the first 1–4 days, compared to the nonstressed control animals (two-way ANOVA, Bonferroni’s test, effect of treatment, p < 0.001, p = 0.0001, p = 0.0001, p = 0.0001, respectively, Fig. 4A). Resveratrol at a dose of 5 mg/kg had no effect on escape latencies in stressed rats (two-way ANOVA, effect of treatment, p > 0.05). However, Bonferroni’s test suggested that administration of resveratrol at a dose of 20 mg/kg/day prevented CUMS-induced impairment of the escape latency in the water maze task during the first 1–4 days (two-way ANOVA, effect of treatment, p < 0.05, p < 0.05, p < 0.05, p < 0.01, respectively). Additionally, we used DMSO as a carrier for resveratrol. DMSO did not have a significant effect on acquisition latency in the water maze test during the first 1–4 days, compared to saline-treated control rats (p > 0.05).

There was a significant difference between stressed and control groups with regard to the time spent in the escape platform quadrant during the probe trial (one-way ANOVA, Bonferroni’s test, F(4,45) = 17.55, p < 0.001; Fig. 4B). Post hoc comparisons showed that 5 mg/kg resveratrol had no effect on the time spent in the escape platform quadrant in stressed rats (p > 0.05, Bonferroni’s test). However, 20 mg/kg resveratrol prolonged the time spent in the escape platform quadrant. These results suggest that resveratrol administration reversed the effects of chronic stress on probe trial performance in a dose-dependent manner. In addition, DMSO had no effect on time spent in the escape platform quadrant compared to controls (p > 0.05, Bonferroni’s test, Fig. 4B).

4. Discussion

Our study demonstrates that treatment with resveratrol can reverse impaired cognition induced by CUMS in rats. In addition to the maintenance of cognitive function, a reversal of BDNF and c-Fos expression in the hippocampus was also seen in animals treated with resveratrol. Moreover, resveratrol treatment prevented CUMS-induced elevations in plasma TNF-α and IL-1β levels. It is well known that stress is an unavoidable life experience that can disturb both cognitive processing and neuroplasticity. In the present study, rats were subjected
to chronic unpredictable stress for 35 consecutive days during which time they were treated with either vehicle or resveratrol. Escape latencies of untreated CUMS rats in the Morris water maze test were significantly longer than normal, indicating a deficit in spatial learning. In the resveratrol-treated CUMS group, the animals had shorter escape latencies than the untreated stressed group. Moreover, the untreated stressed rats performed poorly in subsequent testing compared to control rats on probe trials 24 h later, indicating impaired memory retrieval; however, resveratrol prevented these impairments and restored spatial memory and learning in CUMS rats. A similar effect was seen in the passive avoidance test. Resveratrol prevented stress-induced cognitive abnormalities in retention trials 24 h later, indicating improvement of emotional learning and memory. Therefore, the present results confirm our hypothesis that resveratrol could ameliorate both spatial and emotional learning and memory dysfunction induced by CUMS.

As discussed previously by Phelps [24] and Roozen et al. [25], the hippocampus is the primary structure necessary for declarative memory (remembering facts) whereas the amygdala is required to control emotional processing, particularly involving fear and aggression. Moreover, the hippocampus and amygdala are thought to regulate memory by modulating attention and consolidation processes, due to their many reciprocal connections. It is well known that BDNF is a key molecule in regulating hippocampal plasticity [26]. Improvement of cognitive and affective disabilities in major depression after antidepressant treatment has been attributed to elevations in BDNF [27]. It has been proposed that enhancing BDNF levels by administering antidepressants could also potentially prevent cognitive impairment associated with Alzheimer’s [27]. Furthermore, hippocampus-dependent learning and memory deficits, which could be correlated to a reduction in neurogenesis, were observed in mouse models of Alzheimer’s disease [28]. Finally, chronic stress leads to reductions in hippocampal BDNF mRNA levels [20,29]. If the effects of stress on the mechanisms of neuroplasticity contribute to the pathophysiology of cognitive functions, then BDNF treatments would be predicted to have the opposite effect and enhance them. Correspondingly, hippocampal BDNF administration has been demonstrated to prevent cognitive impairment induced by stress [30]. Moreover, we found similar effects after CUMS, which produced a significant reduction in hippocampal BDNF expression; treatment with resveratrol attenuated these stress-induced effects.

Like BDNF, the transcription factor c-Fos is known to have a role in memory formation and it has been reported that it can be used as a memory marker [31]. Experience and spatial learning stimulate c-Fos expression [32] and c-Fos knockout mice exhibit deficits in long-term memory and synaptic plasticity [33]. Moreover, c-Fos has been implicated in the actions of stress and cognitive impairments. Lizalde and coworkers reported that CUMS affects hippocampal cell proliferation and neurogenesis, as well as the regulation of c-Fos immunoreactivity in mice [34]. Consistent with these observations, we found that c-Fos expression was decreased by CUMS in the hippocampus and this decrease was blocked by resveratrol treatment. From these findings, it is clear that the neuroprotective properties of resveratrol could help protect against cognitive decline due to chronic stress.

It is well known that modulation of the glutamergic system seems to play a key role in the regulation of synaptic plasticity in the hippocampus. Previously, it was reported that the hippocampal glutamergic system is activated by stress leading to a local increase in glutamate release [35, 36]. These increased glutamate levels have been proposed to mediate stress-induced morphological damage to the hippocampus. These processes would then contribute to the development of stress-induced behavioral changes. The observation that glutamate, by acting on N-methyl-d-aspartate (NMDA) receptors, can evoke the release of nitric oxide (NO) suggests that NO mediates glutamate-induced neurotoxicity [37,38]. In addition, NO can decrease BDNF release in cultured...
hippocampal neurons, and inhibition of neuronal nitric oxide synthase (nNOS) enhances hippocampal BDNF expression [39]. Moreover, these data suggest that stress-induced release of NO could mediate pathological processes within the hippocampus that account for the plastic changes and behavioral alterations seen in stressed animals. Therefore, inhibition of NO synthesis could protect the hippocampus from stress-induced effects, thus allowing behavioral adaptation to occur in situations of chronic exposure to stress [40]. The activation of nNOS accounts for many of the deleterious effects associated with excessive NMDA receptor activation. Furthermore, recent studies have provided evidence that chronic restraint stress activates pro-inflammatory pathways in the brain, particularly those involving inducible NOS (iNOS) and cyclooxygenase [41]. These preclinical data may have important implications for the treatment and outcome of cognitive dysfunction. It is well known that resveratrol has anti-inflammatory effects and inhibits iNOS [42,43]. We have shown that resveratrol consistently reduced levels of proinflammatory cytokines and improved ileal smooth muscle reactivity in a polymicrobial sepsis model in rats [44]. In agreement with these findings, it has been reported by Abraham and Johnson [45] that resveratrol may be useful for attenuating lipopolysaccharide-induced acute cognitive disorders in aged mice. In addition, recent evidence suggests that proinflammatory cytokines (TNF-α and IL-1β) were elevated both in the peripheral blood and in the central nervous system of CUMS rats [46,47] and that neuroinflammation occurred in CUMS-induced depression [47,48]. There is now evidence that proinflammatory cytokines, and in particular, IL-1β and TNF-α generated in the periphery, are able to initiate cytokine synthesis in the central nervous system. Several mechanisms have been proposed to explain why peripherally born cytokines, through their effects on brain neuroinflammation, might be able to induce physiological and behavioral responses in the central nervous system typical of depression [47]. Furthermore, elevated levels of TNF-α have been documented in Alzheimer’s disease [49,50]. Rats with chronic neuroinflammation displayed impaired performance in both novel place recognition and spatial learning and memory retention tests but inhibition of TNF-α synthesis reversed these cognitive deficits. These data, therefore, support the argument that TNF-α is a critical mediator of neuroinflammation-induced cognitive impairments [51]. Consistently, our recent study showed that infliximab, a TNF-α inhibitor, treatment improved CUMS-induced cognitive deficits in rats [52]. Hence, the regulation of TNF-α signaling may prove beneficial in the context of cognitive disorders associated with neuroinflammation [51,53]. Consistent with these previous findings, in the present study we found that the plasma levels of TNF-α and IL-1β in the stressed group were increased significantly compared to the control group, effects which were significantly prevented by treatment with resveratrol. Therefore, a possible mechanism for the protective effects of resveratrol on cognitive deficits produced by stress relates to its anti-inflammatory activity.

Stress is also known to alter the functioning of the cholinergic system [54]. As reviewed in Dagyte et al. [55], while acute stressors increase acetylcholine release in the hippocampus, the effects of chronic stress are less clear, but may involve a gradual decline of cholinergic function. Chronic stress has been reported to decrease acetylcholinesterase activity in the hippocampus of laboratory animals [36,56]. Such stress-induced malfunction of the cholinergic system may in turn impair learning and memory processes [57]. Besides affecting the cholinergic system, stress also decreases hippocampal neurogenesis, and impairs hippocampal-dependent learning and memory. Pharmacologic augmentation of septohippocampal cholinergic activity enhances learning and memory performance in cognitively impaired animals [58]; in fact, acetylcholinesterase inhibitors are an important therapeutic target for the treatment of many neurologic diseases. Previously, Schamatz et al. [19] showed that resveratrol prevents the increased acetylcholinesterase activity and consequent memory impairment typical of diabetic rats, suggesting that it can modulate cholinergic neurotransmission and consequently improve cognition. This is consistent with our previous study demonstrating that resveratrol prevents scopolamine-induced memory deficits [44]. Based on these findings, we can suggest that a reduction of acetylcholinesterase activity by resveratrol can contribute to increasing levels of acetylcholine and consequently to improvements in learning and memory under conditions of chronic stress.

5. Conclusion

In summary, the current findings suggest that treatment with resveratrol may play an important role in reversing the deleterious effects of stress on cognition. We can speculate that the improved cognitive performance of stressed rats receiving resveratrol may be due to the effects of resveratrol on both BDNF and c-Fos expression and plasma levels of TNF-α and IL-1β. These findings more generally support the role of natural compounds in preventative therapy for several neurodegenerative diseases worsened by stress.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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References


