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Resveratrol prevents impaired cognition induced by chronic unpredictable mild stress in rats

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ABSTRACT

Depression is one of the most common neuropsychiatric disorders and has been associated with impaired cognition, as well as causing neuroendocrine systems and brain proteins alterations. Resveratrol is a natural polyphenol enriched in *polygonum cuspidatum* and has diverse biological activities, including potent antidepressant-like effects. The aim of this study was to determine whether resveratrol administration influences chronic unpredictable mild stress (CUMS)-induced cognitive deficits and explores underlying mechanisms. The results showed that CUMS (5 weeks) was effective in producing cognitive deficits in rats as indicated by Morris water maze and novel object recognition task. Additionally, CUMS exposure significantly elevated serum corticosterone levels and decreased BDNF levels in the prefrontal cortex (PFC) and hippocampus, accompanied by decreased phosphorylation of extracellular signal-regulated kinase (pERK) and cAMP response element-binding protein (pCREB). Chronic administration of resveratrol (80 mg/kg, i.p., 5 weeks) significantly prevented all these CUMS-induced behavioral and biochemical alterations. In conclusion, our study shows that resveratrol may be an effective therapeutic agent for cognitive disturbances as was seen within the stress model and its neuroprotective effect was mediated in part by normalizing serum corticosterone levels, up-regulating of the BDNF, pCREB and pERK levels.

1. Introduction

Stress is known to be one of the causal factors for development of major depression. Based on this observation, the chronic unpredictable mild stress (CUMS) animal model has been developed to mimic the development and progress of clinical depression (Willner, 1997). There is strong evidence that impaired cognition is a core element of major depression, and antidepressant treatment may ameliorate cognitive impairments in parallel to mood improvement of depressive patients (Airaksinen et al., 2004). With an increasing consensus, CUMS animals were also found to cause cognition impairment (McEwen, 2005).

Chronic exposure to stress and stress hormones has an impact on brain structures and function involved in cognition and mental health. For example, glucocorticoids, produced by the stress-responsive hypothalamic–pituitary–adrenal (HPA) axis, are known to regulate various brain functions, with well-described effects on human cognition (Lupien et al., 2007). In the same way, in animal, high circulating levels of glucocorticoids or following infusions of glucocorticoid receptor agonists into the hippocampus led to impaired memory retrieval processes (Roozendaal, 2002). In addition, stress-associated cognitive deficits were observed together with reduced synaptic proteins and neurotrophic factor expression. For example, brain derived neurotrophic factor (BDNF), as a member of the neurotrophin family, plays an important role in memory and synaptic plasticity. It has been shown that BDNF infusion ameliorates impairment of spatial learning and memory and long-term potentiation (LTP) caused by chronic stress (Radecki et al., 2005). Neurons in the prefrontal cortex (PFC) and hippocampus respond to repeated stress by showing atrophy and a down-regulation BDNF expression that is associated with memory impairment (McEwen, 2005). These data suggest that HPA axis and BDNF may be the potential target of antidepressants and participate in the molecular mechanism of stress-associated cognitive deficits.

Resveratrol (*trans*-3,4′,5-trihydroxystilbene), is a phenolic compound enriched in *polygonum cuspidatum* and also found abundantly in the skin of red grapes and red wine. Several recent studies have demonstrated that resveratrol exerts a variety of pharmacological effects, including anti-inflammatory, antioxidant and antiapoptotic (Orsu et al., 2013;

Abbreviations: BDNF, brain derived neurotrophic factor; CUMS, chronic unpredictable mild stress; CREB, cAMP response element-binding protein; ERK, extracellular signal-regulated kinase; HPA, hypothalamic–pituitary–adrenal; RT-PCR, reverse transcription-polymerase chain reaction; PFC, prefrontal cortex; MWM, Morris water maze; NORT, novel object recognition task.

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Zhang et al., 2010). Interestingly, accumulating evidence suggested that resveratrol acted as a powerful neuroprotective agent. It was demonstrated that resveratrol protected primary rat cortical neurons from oxidative stress-induced injury (Zhuang et al., 2003). It was also reported that resveratrol reversed the ethanol or Aβ-induced toxicity in the PC12 cells (Jang and Surh, 2003; Sun et al., 1997). Resveratrol abrogated alcohol-induced cognitive deficits and neuronal apoptosis (Tiwari and Chopra, 2013). Furthermore, the powerful neuroprotective effect of resveratrol has also been confirmed in neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease (Albani et al., 2009; Wang et al., 2006). Although there is only limited information about the antidepressant-like effect of resveratrol, the potential therapeutic value of resveratrol for depression has been increasingly recognized (Xu et al., 2010; Yu et al., 2013). In addition, resveratrol has low bioavailability, and this has been associated with its poor water solubility, its low stability against environmental stress, and its inability to reach a target site in the body to exert the desired health effect (Augustin et al., 2013). Further research is required in enhancing the delivery and bioavailability of resveratrol to obtain the desired biological effects.

However, the potential neuroprotective effects of resveratrol against CUMS-induced cognitive deficits and the mechanisms remain to be clarified. In the present study, chronic administration of resveratrol significantly prevented the CUMS-cognitive disturbances, at least in part, by normalizing serum corticosterone levels, up-regulating of the BDNF, phosphorylation of extracellular signal-regulated kinase (pERK) and cAMP response element-binding protein (pCREB) levels in prefrontal cortex (PFC) and hippocampus.

2. Material and methods

2.1. Animals

Male Wistar rats (180–200 g) were purchased from Laboratory Animal Center, Shandong University. Upon arrival, the animals were housed under standard laboratory conditions (temperature 20 ± 2 °C, 12 h:12 h light/dark cycle, lights on 0800 h), had free access to food and water and were allowed to habituate to the novel environment for 1 week.

In the handling and care of all animals, the International Guiding Principles for Animal Research, as stipulated by the World Health Organization (1985) and as adopted by the Laboratory Animal Center at Shandong University were followed. All efforts were made to reduce the number of animal used and their suffering.

2.2. Drug administration and experimental groups

All drugs used in the study were injected intraperitoneally (i.p.) in a total volume of 10 ml/kg. Resveratrol (Sigma, St. Louis, MO, USA) was dissolved in ethanol and diluted to the desired concentration on the day of experiment, and the final concentration of ethanol did not exceed 1% of the total volume.

Rats received resveratrol (80 mg/kg) once daily for 5 weeks. Rats were randomly assigned to 4 groups, group I received vehicle (1% ethanol) and served as control; group II received resveratrol; group III was exposed to CUMS and received vehicle (1% ethanol); group IV were subjected to CUMS and received resveratrol. Drugs were administered between 9:00 a.m. and 10:00 a.m. once a day for 5 consecutive weeks. To habituate to i.p., all rats were administered saline (10 ml/kg) daily for three days prior to the experiment. Dose and route administration schedules of resveratrol used in the present experiment were chosen as based on previous results (Yu et al., 2013).

2.3. CUMS procedure

Rats were subjected to CUMS for 5 weeks. The procedure of CUMS was performed as previously described (Jiang et al., 2013). In brief, the CUMS protocol consisted of a variety of mild stressors: (1) food deprivation for 24 h, (2) water deprivation for 24 h, (3) exposure to noise for 3 h, (4) cage tilt (45°) for 7 h, (5) overnight illumination, (6) soiled cage for 24 h, and (7) forced swimming at 4 °C for 6 min. Stressors were administered in a semi-random manner, at any time of day. In this respect, the stress sequence was changed every week in order to make the stress procedure unpredictable. These stressors were randomly scheduled over a one-week period and repeated throughout the 5-week experiment. Control animals were housed in a separate room and had no contact with the stressed animals.

After 5 weeks of CUMS, animals were submitted to the Morris water maze and Novel object recognition task 60 min after the last drug treatment. Rats were sacrificed following the behavioral test. Immediately after decapitation, serum samples were collected to measure corticosterone concentrations. Then brains were removed, and then the PFC and hippocampus were dissected according to the rat atlas and frozen at −70 °C for further biochemical analysis.

2.4. Morris water maze (MWM) test

40 rats were used in the MWM. The spatial reference memory was assessed using MWM test as previously described with minor modifications (Morris, 1984). A black cylindrical tank (120 cm in diameter) was filled with water (21–24 °C), made opaque with the addition of atoxic acrylic black color. The tank was divided into 4 quadrants and a circular escape platform 10 cm in diameter was placed at a fixed position in the center of one of the four quadrants, the target quadrant. The platform was set 2 cm below the water level where rats could not see it directly. A digital camera was positioned above the centre of the tank and linked to a tracking system in order to record the performance of rat (SMART polyvalent video-tracking system, Panlab, Spain). Rats were allowed to swim freely for 60 s to become acclimatized to the apparatus before the test. From the next day, each rat performed four trials per day for 5 consecutive days to find the hidden platform. Each trial began by placing a rat into one of the four quadrants of the pool, facing the wall of the tank. The daily order of the entries into individual quadrants was fixed and all four quadrants were used once in a series of four trials every day. The time taken to escape onto the hidden platform (escape latency) was measured. Rats were given 60 s to find the hidden platform during each acquisition trial. If it failed to locate the platform within 60 s, it was guided onto the platform. The rat was allowed to stay on the platform for 20 s.

Twenty-four hours after the last place navigation test, the probe test was performed to measure reference memory during which the platform was withdrawn. Each rat was released from the quadrant opposite to where the platform had been located and its behavior was monitored for 60 s. Time taken to reach the target quadrant and time spent in the target quadrant were recorded.

2.5. Novel object recognition task (NORT)

This behavioral paradigm exploits the ability of the rats/mice to explore novel objects over familiar ones during simultaneous presentation and has been employed to evaluate recognition memory as described previously with minor modifications [20]. The object recognition task was conducted in a Plexiglas cage (60 × 40 × 40 cm) with an exchangeable floor. Two days before the experiment, the animals (40 rats, different from those used for MWM) were habituated to the empty experimental arena by allowing them to freely explore for 15 min/day. The objects to be discriminated were water-filled plastic bottles, 8 cm high × 5 cm in diameter, covered with white masking tape, and they were cleaned thoroughly between trials to ensure the absence of olfactory cues. The objects were tested with one independent group of rats and was verified that the rats employed the same time exploring each object.