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Protective effects of resveratrol on aging-induced cognitive impairment in rats

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ABSTRACT

Resveratrol, a polyphenol phytoalexine, has been shown to play a neuroprotective role in the neurodegenerative process in Alzheimer's disease (AD) and improve memory function in dementia. However, the *in vivo* effect of resveratrol in normal aging models of learning and memory has not yet been evaluated. Therefore, the present neurobehavioral study was undertaken to evaluate the effect of resveratrol on cognitive impairment induced by aging in passive avoidance and Morris water maze (MWM) tests. Male Wistar albino rats were divided into four groups: young control (4 month), young resveratrol (4 month + RESV), old control (24 month) and old resveratrol (24 month + RESV). Resveratrol (50 mg/kg/-day) was given to the 4 month + RESV and 24 month + RESV groups orally for 12 weeks. There was no significant difference between the groups for the first day of latency, while in aged rats, the second day of latency was significantly shortened compared to the young group in the passive avoidance test ($p < 0.05$). Additionally, in the MWM test, the results showed a decrease in the time spent in the escape platform's quadrant in the probe test in aged rats ($p < 0.05$). The administration of resveratrol at 50 mg/kg/day increased the retention scores in the passive avoidance test and the time spent in the escape platform's quadrant in the MWM task ($p < 0.05$). Furthermore resveratrol attenuated the protein levels of TNFα and IL1β in the 24-month group. These findings indicate that aging impairs emotional and spatial learning-memory and resveratrol reverses the effect of age-related learning and memory impairment. The results of this study suggest that resveratrol is effective in preventing cognitive deficit in aged rats by inhibiting the production of inflammatory cytokines.

1. Introduction

Normal aging generally induces cognitive impairment, with older people often considered to be less efficient than younger people in using memory, attention, visuospatial capacities or executive function (Tromp, Dufour, Lithfous, Pebayle, & Despres, 2015). There is profound evidence of increased inflammation, oxidative damage and deficient antioxidative defense mechanisms in different regions of the brain in the aging process (Butcher & Lord, 2004; Gemma, Vila, Bachstetter, & Bickford, 2007, chap. 15). Several studies have found that inflammatory markers, such as tumor necrosis factor-α (TNF α) and interleukin-1 β (IL-1 β) are elevated in the elderly and are associated with age-related cognitive impairment and decline (Dimopoulos et al., 2006; Engelhart et al., 2004; Trollor et al., 2011; Zuliani et al., 2008) as well as Alzheimer's Disease (Mucke, 2009; Vetrivel & Thinakaran, 2010). The deterioration of brain function in the physiological process of aging causes a decrease in learning and memory skills. In age-related neuronal disorders, free radicals, oxidative stress and inflammatory cytokines are known to be the candidates responsible for producing cell changes in such diseases (Cantuti-Castelvetri & Shukitt-Hale, 2000; Harman, 1994).

The learning and memory deficits associated with aging may be alleviated using numerous contents within dietary fruits and vegetables exhibit anti-aging activities in various systems, among which one component, resveratrol, is a promising candidate (Baur & Sinclair, 2006). Resveratrol is a polyphenol phytoalexine found in grape skins and red wine (Jang et al., 1997; Vinson, 1998). Accumulating evidence has shown that resveratrol can prevent or slow the progression of a variety of diseases, including

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cancer, cardiovascular diseases, ischemic injuries and Alzheimer's disease (Baur & Sinclair, 2006; Bradamante, Barenghi, & Villa, 2004). Resveratrol has various biological properties, including antioxidant, anti-inflammation and neuroprotective effects (Baur & Sinclair, 2006; Saiko, Szakmary, Jaeger, & Szekeres, 2008). Recently, a number of studies have focused on the neuroprotective effects of resveratrol, such as diminishing the toxicity induced by the amyloid beta peptide (Anekonda, 2006; Han, Zheng, Bastianetto, Chabot, & Quiron, 2004) and kainic acid (Wang, Yu, Simonyi, & Rottinhaus, 2005), preventing cerebral ischemic damage (Wang, Xu, & Rottinhaus, 2002). The neuroprotective effects of resveratrol are attributable to its antioxidant activity (Poulose, Thangthaeng, Miller, & Shukitt-Hale, 2015). Furthermore, resveratrol has been shown to improve cognitive function in an age-accelerated mouse (SAMP8) model of Alzheimer's disease (Porquet et al., 2012). Other studies show that resveratrol could be a useful therapeutic agent for Alzheimer's disease (Ono et al., 2008; Turner et al., 2015). Similarly, previous studies in our laboratory have shown that resveratrol has a beneficial effect on cognitive deficit induced by scopolamine (Gacar et al., 2011). In addition, resveratrol has been shown to improve memory function and reverse the effects of acetylcholinesterase in streptozotocin-induced models of dementia (Sharma & Gupta, 2002).

Therefore, in this study we aimed to evaluate whether resveratrol improves the age-related spatial and emotional cognitive impairment using a water maze and a passive avoidance task and decreases inflammatory cytokines, respectively.

2. Materials and methods

2.1. Animals

Young (4 months old, 200–250 g, $n = 30$) and aged (24 months old, 550–600 g, $n = 20$) male Wistar-albino rats (Kocaeli University, Experimental Medical Research and Application Center, Kocaeli, Turkey) were kept in an animal colony with approximately 5–6 per cage for 2 weeks prior to the experiments. All experiments were conducted between 9:00 A.M. and 12:00 P.M. under standard laboratory conditions (22 ± 2 °C room temperature; 12-h light/dark cycle with lights on at 7:00 A.M.). Tap water and food pellets were provided ad libitum. All animals used in this study were naive to the experimental tests, and different rat groups were used in each experiment.

The experiments reported in this study were conducted in accordance with the Regulation of Animal Research Ethics Committee in Turkey (July 6, 2006, Number 26220). Ethical approval was granted by the Kocaeli University Animal Research Ethics Committee (Project number: HADYEK 28, Kocaeli, Turkey).

Animals were divided into five groups ($n = 10$ per group): young control (4 month), old control (24 month), young resveratrol (4 month + RESV) and old resveratrol (24 month + RESV). Control groups received physiological saline and the second control group received DMSO for 12 weeks. There were no significant differences between data obtained from the rats that received two vehicle solutions. Therefore, the group that received DMSO was accepted as the control for comparison. Resveratrol (50 mg/kg/day) was given to the 4 month + RESV and 24 month + RESV groups orally by lavage for 12 weeks.

2.2. Locomotor activity test

Locomotor activity was measured with a computerized system (40 × 40 × 35 cm box; May Commat, Ankara, Turkey). Total locomotor activity was measured before the behavioral tests over a 5-min period and expressed as the stereotypic, ambulatory, and vertical activities and the total number of movements of animals.

2.3. 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 learning. The animal learns to avoid a specific place associated with an aversive event. The reduction of latency was used as a learning index. The apparatus consisted of two compartments, each measuring 22 × 21 × 22 cm. The illuminated white box was connected to the dark box, which was equipped with an electrifiable grid floor. An inescapable electrical shock was 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 et al. (2002). 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 a 3-s electric foot-shock (0.5 mA) was delivered through the grid floor. The time taken to enter the dark compartment was recorded as the training latency. 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 this inhibitory 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.

2.4. Morris water maze test

The Morris task was assessed in a water tank (150 cm in diameter) as has been previously described (Pothion et al., 2004). 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's surface. The plastic was invisible to the rats due to its placement, and it was used to monitor spatial learning. The platform position remained stable over 4 days, and the acquisition of finding 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 four randomly ordered trials. Each trial was terminated as soon as the rat had climbed onto the escape platform or when 60 s had elapsed. A rat was allowed to stay on the platform for 20 s. Then, it was taken from the platform and the next trial was started. Rats that did not find the platform within 60 s were placed on the platform by the experimenter and were allowed to stay there for 20 s.