Pharmacology, Biochemistry and Behavior 99 (2011) 316–323

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Beneficial effects of resveratrol on scopolamine but not mecamylamine induced memory impairment in the passive avoidance and Morris water maze tests in rats

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ARTICLE INFO

Article history:
Received 14 December 2010
Received in revised form 8 May 2011
Accepted 14 May 2011
Available online 23 May 2011

Keywords:
Resveratrol
Cognition
Morris water maze
Passive avoidance
Rat

ABSTRACT

Resveratrol (3,5,4-trihydroxy-trans-stilbene), which is found in grapes and red wine has been shown to protect neuronal cells with its antioxidant activity, improve memory function in dementia and reverse acetylcholine esterase (AChE) activity. The aim of this study was to investigate the effect of resveratrol on emotional and spatial memory in naive rats, as well as on scopolamine- and mecamylamine-induced memory impairment in the passive avoidance and Morris water maze (MWM) tests. Resveratrol (12.5, 25 and 50 mg/kg), scopolamine (0.6 mg/kg) and mecamylamine (10 mg/kg) were administered to male Wistar rats. In the passive avoidance test, there was no significant difference in the first day latency between all groups, whereas scopolamine and mecamylamine significantly shortened the second day latency compared to the control group. Resveratrol reversed the effect of scopolamine at all doses used, but it had no effect on mecamylamine-induced memory impairment in the passive avoidance test. Both scopolamine and mecamylamine significantly decreased the time spent in the escape platform quadrant during the probe trial of the MWM test compared to the control group. Resveratrol reversed the effect of scopolamine at all doses, but did not change the effect of mecamylamine in the MWM test. There were no significant differences in the locomotor activities of any of the groups. In conclusion, we suggested that resveratrol had improving effects on learning and memory by acting on muscarinic cholinergic receptors and at least in part, may reverse AChE activity.

1. Introduction

It is well known that resveratrol (3,5,4-trihydroxy-trans-stilbene) is a polyphenol that is mainly found in grapes and red wine and exerts biological activity. It has antioxidant, anti-inflammatory, cardioprotective and anti-carcinogenic effects (Baur and Sinclair, 2006; Saiko et al., 2008). There are also studies that show neuroprotective effects of resveratrol, such as diminishing the toxicity induced by amyloid β peptide (Anekonda, 2006), preventing cerebral ischemic damage (Uguralp et al., 2005) and protecting against kainic acid induced excitotoxicity (Wang et al., 2004). Resveratrol also protects neuronal tissue with its antioxidant activity and has beneficial effects in neurodegenerative disturbances that are due to oxidative stress (Quincozes-Santos et al., 2007).

It is important to discover new mechanisms and new drug molecules for the treatment of Alzheimer's disease (AD) and dementia. It is well known that cholinergic neurons and projections play important roles in the regulation of several survival functions, including learning, memory, movement and the control of cerebral blood flow in the central nervous system (Mesulam et al., 2002). In addition, acetylcholine esterase (AChE) plays an important role in cholinergic functions (Appleyard, 1992). AChE is also related to several central nervous system disturbances, such as stroke (Ozkul et al., 2007), AD (Chauhan and Chauhan, 2006) and dementia associated with diabetes mellitus (Kuhad et al., 2008). In recent studies, moderate red wine consumption has been shown to decrease the risk for Alzheimer's disease and clinical dementia (Dartigues et al., 1993; Truelsen et al., 2002). Additionally, the cholinergic system has been reported to be responsible for some of the

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doi:10.1016/j.pbb.2011.05.017

beneficial effects of resveratrol on cognition (Sharma and Gupta, 2002). Moreover, resveratrol has been shown to improve memory function and reverse the effects of AChE in streptozotocin-induced models of dementia (Sharma and Gupta, 2002).

Scopolamine is a commonly used muscarinic cholinergic receptor antagonist while mecamylamine is a nicotinic cholinergic receptor antagonist. In this study, we evaluated the effect of resveratrol on learning and memory in the passive avoidance and MWM tests in naive animals and on scopolamine and mecamylamine induced memory impairment to understand if the effect of resveratrol is dependent on muscarinic and/or nicotinic cholinergic receptors.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (Kocaeli University Experimental Medical Research and Application Unit, DETAB, Kocaeli-Turkey), 7–8 month aged, weighing 200–250 g, were kept in an animal colony at a density of five to six rats per cage for two weeks before the start of the experiment. All procedures were in compliance with the European Community Council Directive of November 24, 1986. Ethical approval was granted by the Kocaeli University Animal Research Ethics Committee (Number: AEK 9/2, Kocaeli, Turkey). Standard laboratory conditions were maintained (22 ± 2 °C room temperature; 12-hour light/dark cycle with lights on at 7:00). Food pellets and tap water were provided ad libitum. All animals used in the study were naive to the behavioral tests. The experiments were conducted between 9:00 and 12:00 in a semi-soundproof and semi-dark laboratory. Different rats were used in each experiment.

2.2. Passive avoidance test

A one-trial, step-down, light-dark passive avoidance apparatus (Ugo Basile model 7551, Italy) was used for the evaluation of emotional memory based on contextual fear conditioning (Ogren et al., 1985). The animal learns to avoid a specific place associated with an aversive event. The reduction in step-down latency was used as an indicator of learning.

The apparatus consisted of two compartments, each measuring $22 \times 21 \times 22$ cm. The illuminated white chamber was connected to a dark chamber, 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 chambers were separated by a flat-box partition, including an automatically operated sliding door at floor level.

The training trial was carried out as described by Monleón 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 door between the two boxes was opened after 30 s, and each 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, the door between the compartments was opened. 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. When the animal completely entered into the dark compartment, 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 animal was then removed from the dark chamber and put back in its home cage. Both compartments of the chamber 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. Memory of the painful 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 administered during this trial. If the animal did not enter into 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 step-down avoidance response.

2.3. Morris water maze test

The Morris water maze consisted of a circular pool (150 cm diameter) that was filled with water (25 °C). Small black pieces of plastic were placed on the surface of the water to obscure the platform (Pothion et al., 2004). The pool was located in a dimly lit, soundproof test room with a number of extra-maze visual cues, including a white and black poster on the wall, a halogen lamp, a camera and the experimenter.

The maze was divided into four quadrants. Three equally spaced points around the edge of the pool were used as the release positions. The order of the release positions was varied systematically throughout the experiment. An escape platform (6 cm in diameter and 12 cm high) was located in one quadrant, 1 cm above the water surface during the familiarization session and 1 cm below the water surface during the other sessions.

Video tracking was conducted with a video camera focused on the full diameter of the pool. Navigation parameters were analyzed by using the Ethovision 3.1 video analysis system (Noldus, Amsterdam, Netherlands). The rats were trained in the Morris water maze over five daily sessions (familiarization session, S1, S2, S3, S4). The five sessions were performed on consecutive days between 9:00 and 12:00. During the acquisition phase of the experiments, each rat participated in three trials per day (Cachard-Chastel et al., 2008).

For each daily trial, the rat was taken from the home cage and placed into the water maze at one of three randomly determined locations with its head facing the center of the water maze. A trial was started when the rat was released from one of three randomly chosen start positions. After the rat found and climbed onto the platform, the trial was stopped and the escape latency was recorded. The maximum trial length was 60 s. If the rat had not climbed onto the platform in 60 s, the experimenter guided the rat by hand to the platform and an escape latency of 60 s was recorded.

The inter-trial time was 60 s. During this time, the rat was kept on the escape platform before starting the next trial. The rat was then placed in the pool again, but at a different location, and the next trial began upon its release. Normally, the escape latency declines during acquisition as the animal learns the location of the hidden platform. At the end of the third trial, the rat was returned to its cage.

Twenty-four hours after the last acquisition session, a 'probe trial' was used to assess the rats' spatial retention of the location of the hidden platform. During this trial, the platform was removed from the maze, and each rat was allowed to search the pool for 60 s before being removed. During this trial, animals should spend more time swimming in the quadrant that previously contained the hidden platform than in the other three quadrants.

2.4. Locomotor activity test

Locomotor activity was assessed in a locomotor activity cage (May 9803 Activity Monitor, Commat İletişim Ltd. May Pentium Computer) after the injection of different doses of resveratrol, scopolamine, mecamylamine, resveratrol + scopolamine, resveratrol + mecamylamine, DMSO or saline ($n = 6$ for each group). The total number of movements was evaluated over a 5-min period.

2.5. Drugs and treatments

Resveratrol was from Sigma (St. Louis, USA). It was dissolved in saline mixed with 5% DMSO. All drugs were freshly prepared and

given intraperitoneally (i.p.) in a volume of 0.2 ml per 100 g of body weight. In the passive avoidance test, resveratrol (12.5, 25 and 50 mg/kg), scopolamine (0.6 mg/kg) and mecamylamine (10 mg/kg) were injected 60, 30 and 30 min, respectively, before the acquisition session, which was performed 24 h before the retention test. The combination of three different doses of resveratrol with scopolamine ($n=8$–11) and mecamylamine ($n=8$–9) were also evaluated. In the Morris water maze test, rats were trained over five consecutive sessions. Resveratrol (12.5, 25 and 50 mg/kg), scopolamine (0.6 mg/kg), mecamylamine (10 mg/kg) and a combination of three different doses of resveratrol with scopolamine ($n=7$–9) and mecamylamine ($n=7$–10) were given before the probe trial, which was performed on the sixth day of testing. The drug doses and the administration times were selected according to previous studies (Chander and Chopra, 2005; Hıramatsu et al., 1998; Sharma and Gupta, 2002; Moran, 1993).

2.6. Statistical analysis

After performing the normality of samples and homogeneity of variance tests, statistical analyses were carried out using two-way analysis of variance (ANOVA). The Holm–Sidak method was used for multiple pair-wise comparisons. Data were expressed as mean values ± SEM. Differences were considered to be statistically significant when p was less than 0.05.

3. Results

3.1. Effects of the systemic administration of resveratrol on scopolamine- and mecamylamine-induced memory impairment in the passive-avoidance test in rats

During the training session (on day 1) of the step-through type passive avoidance task, there were no significant differences between any groups [$F(8,76)=1,80$, $p=0.09$, two way-ANOVA, Fig. 1a; $F(8,65)=1,93$, $p=0.13$, two way-ANOVA, Fig. 2a]. However, there was a significant difference between groups in the retention test [$F(8,76)=8,54$, $p<0.001$, two way-ANOVA; Fig. 1b; $F(8,65)=3,45$, $p=0.002$, two way-ANOVA; Fig. 2b]. Scopolamine- (0.6 mg/kg) and mecamylamine-treated (10 mg/kg) rats showed a significantly lower latency compared to control rats during the retention test, which was performed 24 h after the training test ($p<0.001$; Fig. 1b, 2b). The reduced retention latency indicates impaired retention of the passive avoidance task. The effect of scopolamine was reversed by 12.5, 25 and 50 mg/kg of resveratrol ($p<0.01$; $p<0.01$; $p<0.001$, respectively; Fig. 1b), though resveratrol had no effect on mecamylamine-induced memory impairment at all doses used (Fig. 2b). Additionally, 50 mg/kg

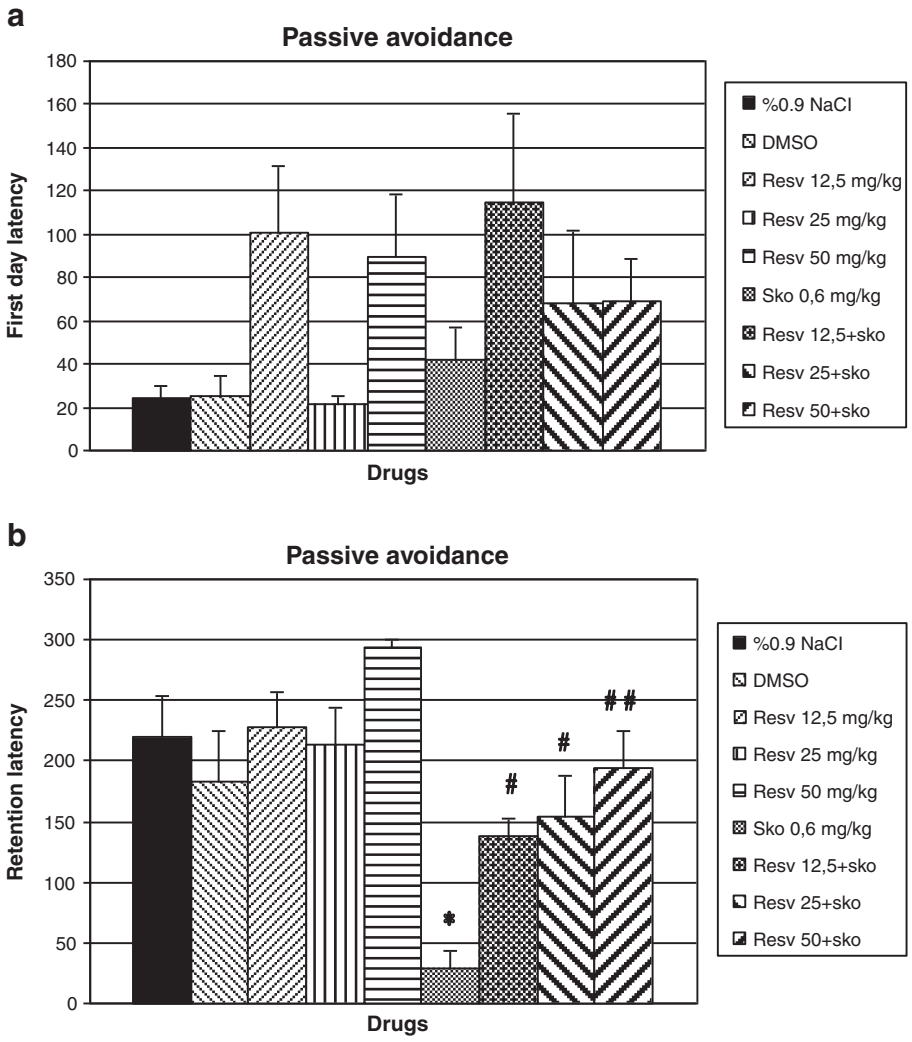

Fig. 1. a: Effects of resveratrol (12,5; 25; 50 mg/kg), scopolamine (0,6 mg/kg) and the combination of drugs on first day latency in the passive avoidance test ($n=8$–11). The data are expressed as mean ± SEM values. b: Effects of resveratrol (12,5; 25; 50 mg/kg), scopolamine (0,6 mg/kg) and the combination of drugs on retention latency in the passive avoidance test ($n=8$–11). *$p<0.001$ vs control group; #$p<0.01$, ##$p<0.001$ vs. scopolamine group. The data are expressed as mean ± SEM values.

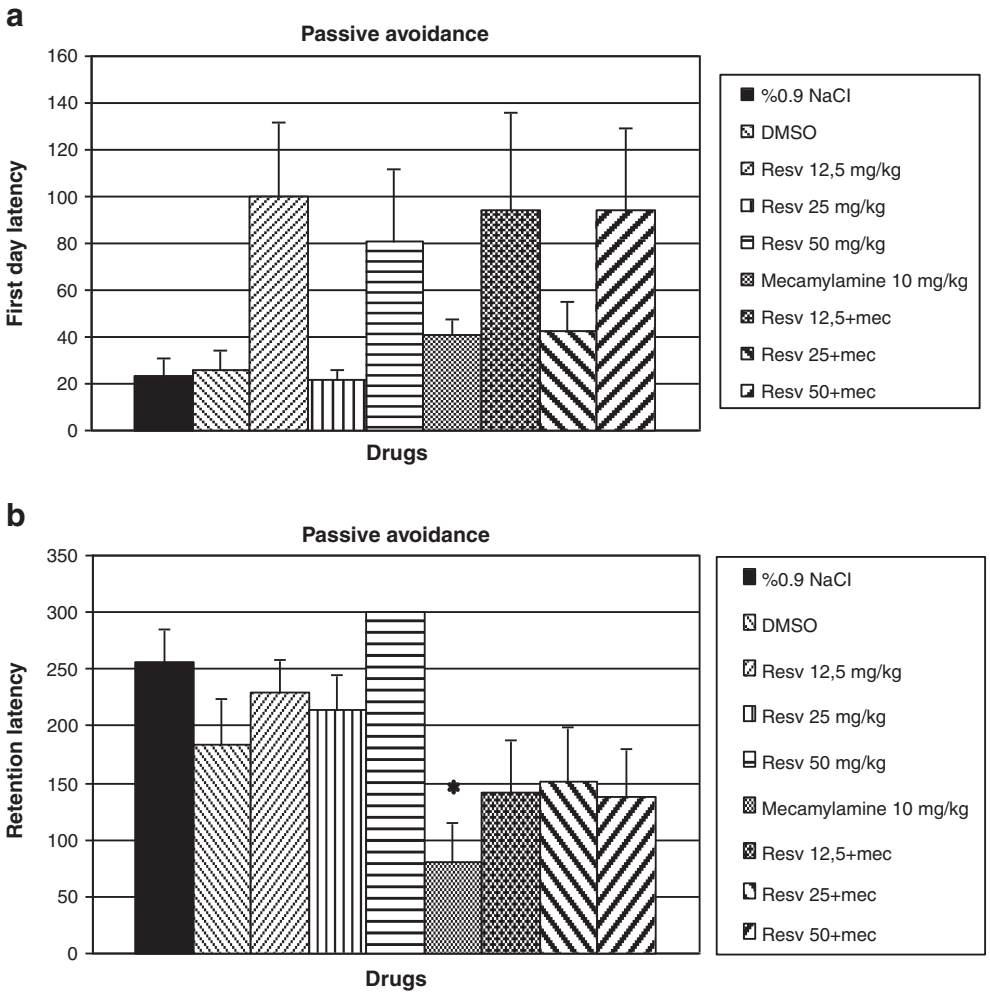

Fig. 2. a: Effects of resveratrol (12,5; 25; 50 mg/kg), mecamylamine (10 mg/kg) and the combination of drugs on first day latency in the passive avoidance test ($n=8$–9). The data are expressed as mean ± SEM values. b: Effects of resveratrol (12,5; 25; 50 mg/kg), mecamylamine (10 mg/kg) and the combination of drugs on retention latency in the passive avoidance test ($n=8$–9). *$p<0.05$ vs control group. The data are expressed as mean ± SEM values.

resveratrol-injected rats performed better in the retention trial of the passive avoidance test compared to the control group, although this result was not significant ($p=0.05$).

3.2. Effects of systemic administration of resveratrol on scopolamine- and mecamylamine-induced memory impairment in the Morris water maze test in rats

The effects of resveratrol or scopolamine in the Morris water maze were examined after acute injection. We only present data from the probe trial because the acute injections were administered before this trial. After the acute injection of resveratrol or scopolamine before the probe trial, there was a significant difference between all groups for the time spent in the target quadrant (the quadrant in which the platform was previously located) [$F(8,63)=8,16$; $p<0.001$; two way-ANOVA; Fig. 3a]. Acute administration of 50 mg/kg resveratrol produced a significant increase in the time spent in the target quadrant ($p<0.05$), whereas scopolamine (0.6 mg/kg) significantly decreased the time spent in the target quadrant ($p<0.001$) compared to the control group. The impairing effect of scopolamine was reversed by 12.5, 25 and 50 mg/kg resveratrol ($p<0.05$, $p<0.01$ and $p<0.001$, respectively). When the speed of the animals during the probe trial was compared, there was no significant difference between the groups [$F(8,63)=1,21$, $p=0.3$; two way-ANOVA; Fig. 3b]. The effects of acute injections of resveratrol and mecamylamine were also evaluated in the Morris water maze. There was a significant difference between all groups for the time spent in the target quadrant [$F(8,65)=7,11$; $p<0.001$; two way-ANOVA; Fig. 4a]. Mecamylamine (10 mg/kg) significantly decreased the time spent in the target quadrant ($p<0.01$) compared to the control group. This effect of mecamylamine was not reversed by resveratrol ($p>0.05$). When the speed of the animals during the probe trial was compared, there was no significant difference between the groups [$F(8,65]=0,75$; $p=0,65$ two way-ANOVA; Fig. 4b].

3.3. Effects of systemically administered resveratrol, scopolamine and mecamylamine on the number of total movements during the locomotor activity test in rats

Increased locomotor activity may produce behavioral disinhibition and can affect learning and memory processes. To exclude this possibility, the locomotor activity of the animals was assessed by measuring the number of movements over a 5 min period. Statistical analysis of the data showed that resveratrol (12.5, 25, and 50 mg/kg) and scopolamine (0.6 mg/kg), alone or in combination, did not significantly modify the number of movements [$F(8,45)=1,20$; $p>0.05$, Fig. 5a] during the locomotor activity test. When the effects of resveratrol (12.5, 25, and 50 mg/kg) and mecamylamine (10 mg/kg), alone or in combination, on the number of movements in the locomotor activity test were compared, there was a significant

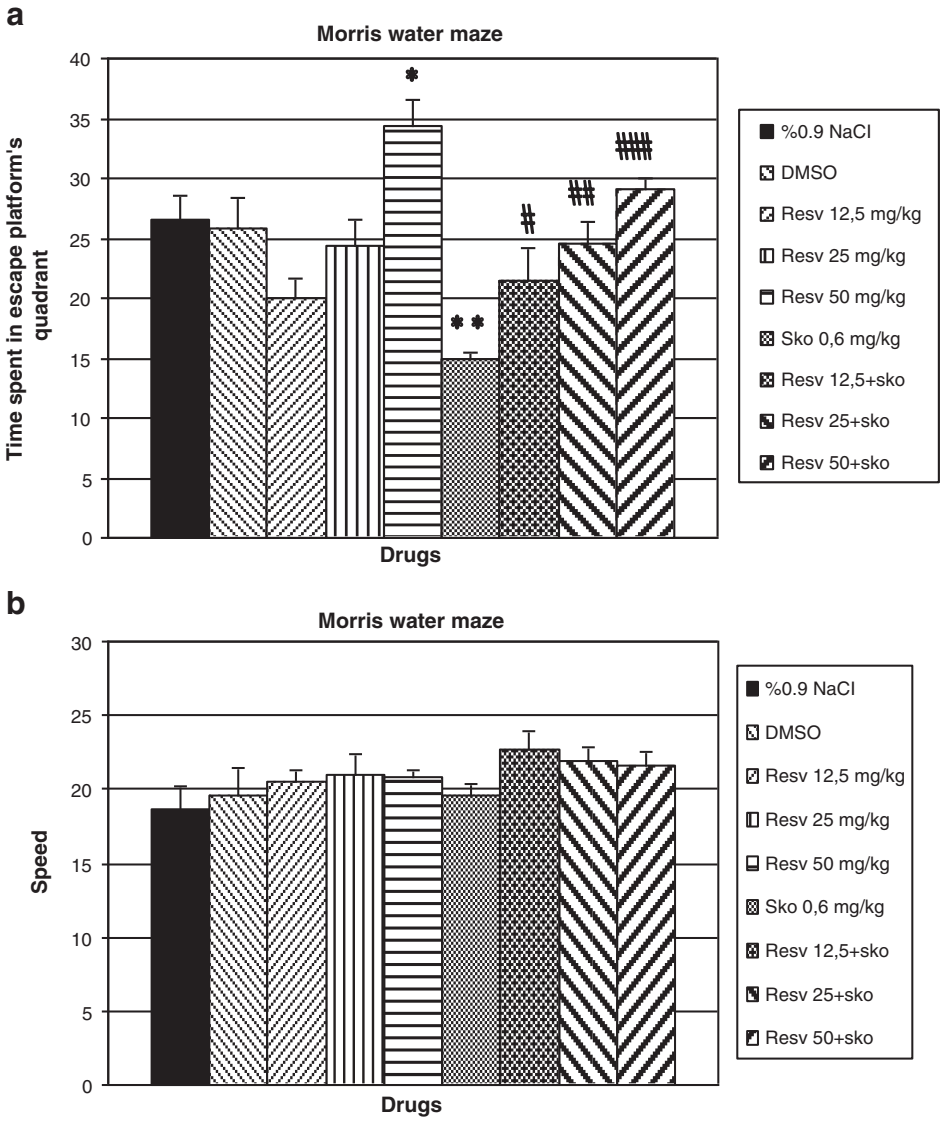

Fig. 3. a: Effects of resveratrol (12,5; 25; 50 mg/kg), scopolamine (0,6 mg/kg) and the combination of drugs on time spent in escape platform's quadrant in the probe trial of MWM test ($n=7$–9). *$p<0.05$, **$p<0.01$ vs control group; #$p<0.05$, ##$p<0.01$, ###$p<0.001$ vs scopolamine group. The data are expressed as mean ± SEM values. b: Effects of resveratrol (12,5; 25; 50 mg/kg), mecamylamine (10 mg/kg) and the combination of drugs on time spent in escape platform's quadrant in the probe trial of MWM test ($n=7$–10). *$p<0.05$ vs control group. The data are expressed as mean ± SEM values.

difference between the groups [$F(8,54)=2,41$; $p<0.05$, Fig. 5b]. There was a significant difference between the 25 mg/kg resveratrol combined with mecamylamine group compared to control, although there were no significant differences between any other groups.

4. Discussion

In our study, resveratrol alone had no effect on emotional memory, although 50 mg/kg resveratrol significantly improved spatial memory in the Morris water maze test compared to the control group. Both scopolamine (0.6 mg/kg) and mecamylamine (10 mg/kg) disturbed emotional and spatial memory in the passive avoidance and Morris water maze tests. Resveratrol reversed the effect of scopolamine at all doses used (12.5, 25 and 50 mg/kg), but it had no effect on mecamylamine-induced memory impairment in the passive avoidance and MWM tests. None of the drugs had an effect on swimming speed in the MWM test or the number of movements in the locomotor activity test.

The passive avoidance test used in this study is amygdala-dependent and it evaluates emotional memory. It had been reported to be related to 'long-term' or reference memory. NMDA receptors are involved in the formation of post-training memory in the amygdala and hippocampus (Izquierdo et al., 1992). The passive avoidance paradigm has been used to study learning and memory for a stressful stimulus. The procedure is based on the innate preference of rodents for the dark compartment of the apparatus and the suppression of this innate preference following exposure to an inescapable shock; that is, passive avoidance performance is an adaptive response to a stressful experience that serves as a measure of learning and memory (Tsuji et al., 2003). Because we administered the drugs just before the acquisition trial, potential drug effects on cognition may be confounded by effects of the compound on nonspecific processes, such as arousal, attention, or sensory motor functions (Hunter et al., 1988). To rule out this possibility, we assessed locomotor behavior immediately after the inhibitory avoidance test session to identify any motor disability that might influence inhibitory avoidance performance. Our results demonstrated that locomotor activity in the control, resveratrol and other groups was the same. These data exclude the possibility that locomotor activity or shock sensitivity may have contributed to the change in step-down latencies during testing.

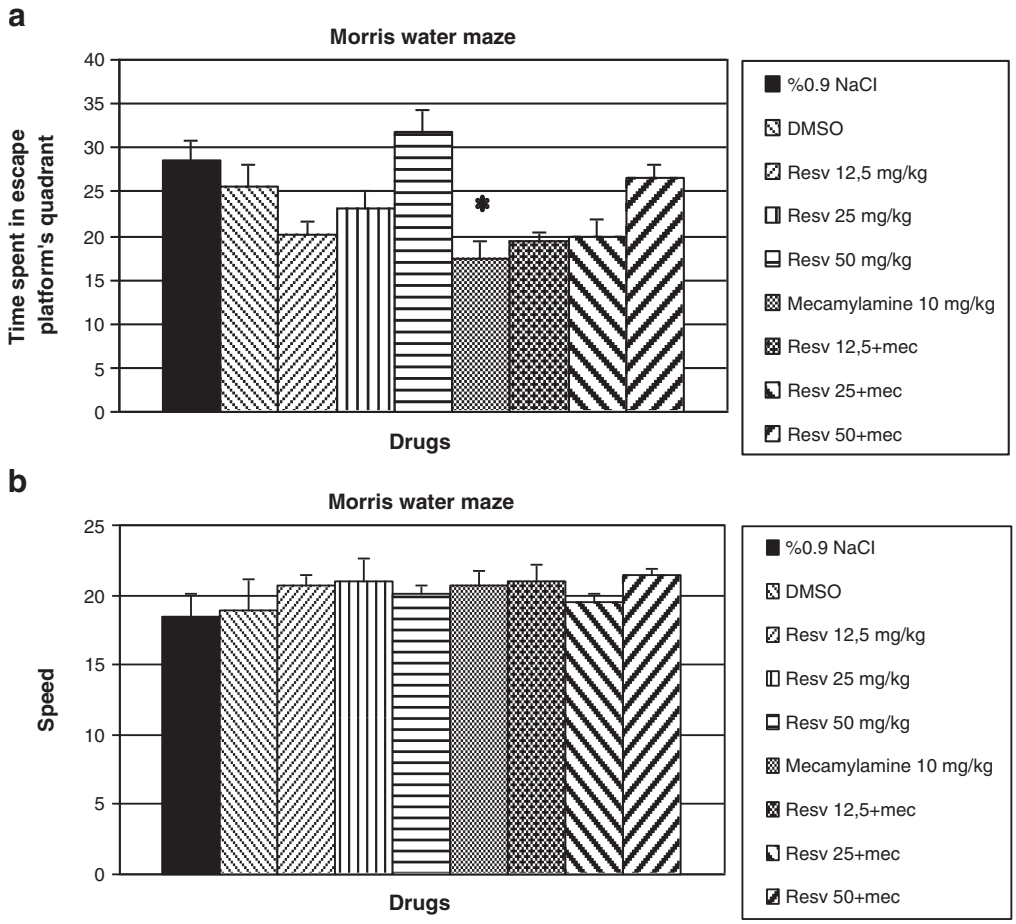

Fig. 4. a: Effects of resveratrol (12,5; 25; 50 mg/kg), scopolamine (0,6 mg/kg) and the combination of drugs on speed of the animals in the probe trial of MWM test ($n = 7–9$). The data are expressed as mean ± SEM values. b: Effects of resveratrol (12,5; 25; 50 mg/kg), mecamylamine (10 mg/kg) and the combination of drugs on speed of the animals in the probe trial of MWM test ($n = 7–10$). The data are expressed as mean ± SEM values.

Our protocol for the MWM test evaluates spatial reference memory (Morris, 1989; Morris et al., 1986), which is dependent on stress stimulation and long-term potentiation (LTP) in hippocampus. In the MWM task, two main components are required for successful performance. First it is required that the rodent develop the necessary behavioral strategies which needed to cope with this stressful, aversive situation, e.g., learning to swim and recognizing that the platform is the only means of escape. These behavioral strategies require the animal to have spatial information about the surrounding cues and the location of the escape platform. The second component is the spatial learning component, meaning that the animal must learn the position of the platform and create swimming strategies to move from one of the randomly chosen starting points toward the platform. The swimming efficiency during the probe trial is the best parameter with which to measure real spatial acuity. The MWM test is dependent on the hippocampus (Duva et al., 1997; Broadbent et al., 2004), and long-term potentiation (LTP) is the neuronal basis for learning (Bliss and Collingridge, 1993).

Resveratrol is a polyphenol that belongs to the phytoalexin family and is synthesized from coumaroyl CoA and malonyl CoA by the enzyme resveratrol synthase in response to stress, injury, infection, or UV irradiation (Sonmez et al., 2007). It has been found in the seeds of various plant species, including grapes and peanuts, and is also found in red wine (Chen et al., 2002; Soleas et al., 1997). Recent epidemiological studies indicate that moderate consumption of red wine may lower the relative risk for Alzheimer's disease and clinical dementia (Dartigues et al., 1993; Truelsen et al., 2002). Several epidemiological studies have indicated an inverse relationship between wine consumption and the incidence of AD (Orgogozo et al., 2003; Lindsay et al., 2002), leading to speculation that resveratrol might contribute to the beneficial effect of wine in AD patients. Resveratrol readily crosses the intact blood-brain barrier and penetrates brain tissue (Wang et al., 2002; Mokni et al., 2007), and has been reported to possess potent neuroprotective properties in several models, both in vitro and in vivo (Zamin et al., 2006; Ates et al., 2007; Della-Morte et al., 2009). The effects of resveratrol on memory function have been tested in several animal models. It has been reported that transresveratrol prevents cognitive impairment and spatial memory deficits (Sharma and Gupta, 2002; Sharma et al., 2005; Kumar et al., 2007). For example, central administration of colchicine causes cognitive dysfunction in rats that is associated with excessive free radical generation and a loss of cholinergic neurons. Chronic treatment with resveratrol significantly restored AChE activity in the brains of colchicine-injected rats and improved the colchicine-induced cognitive impairment (Kumar et al., 2007).

It has been demonstrated that AChE performs one of the most important mechanisms responsible for correct cholinergic function (Appleyard, 1992). This enzyme hydrolyzes the neurotransmitter acetylcholine in the synaptic cleft of cholinergic synapses and neuromuscular junctions (Soreq and Seidman, 2001). AChE inhibitors are an important therapeutic target for the treatment of many neurological diseases such as stroke (Ozkul et al., 2007), Alzheimer's disease (Chauhan and Chauhan, 2006) and diabetes mellitus (Kuhad et al., 2008). Previously, it has been reported that drugs that affect cognitive function alter the effects of AChE activity (Hiramatsu et al., 1998). In the literature, scopolamine has been shown to increase acetylcholine

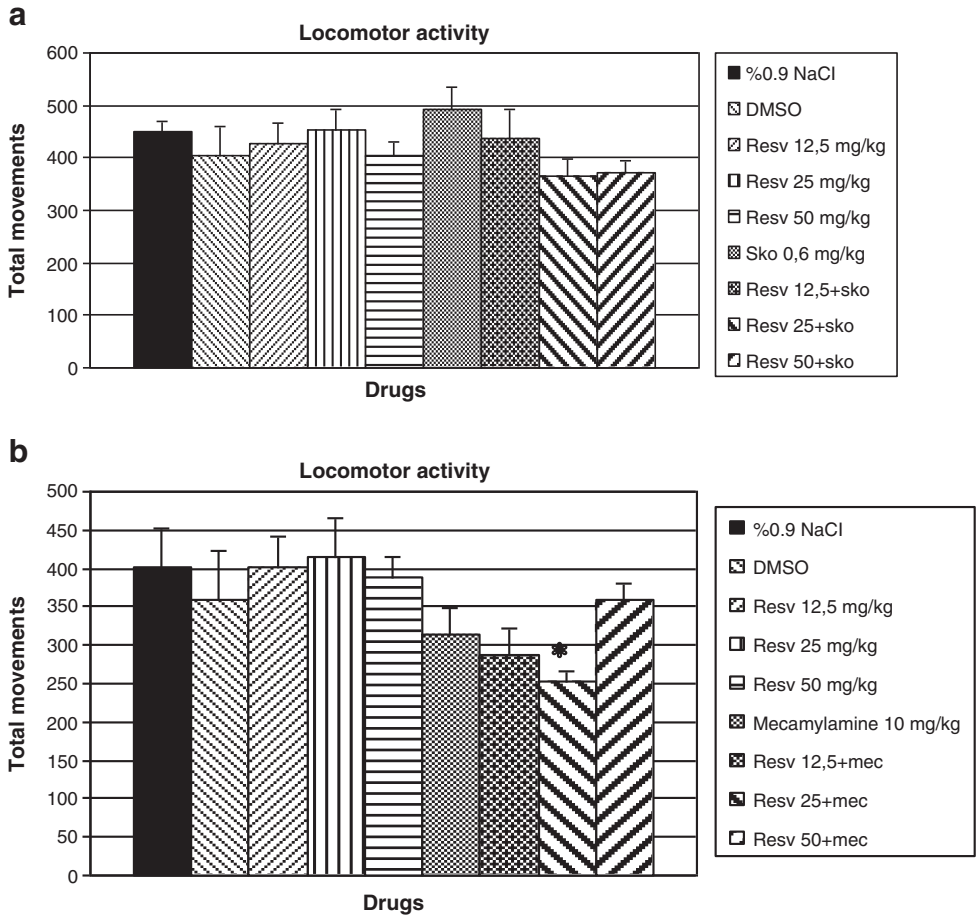

Fig. 5. a: Effects of resveratrol (12,5; 25; 50 mg/kg), scopolamine (0,6 mg/kg) and the combination of drugs on number of total movements in the locomotor activity test ($n=6$). The data are expressed as mean ± SEM values. b: Effects of resveratrol (12,5; 25; 50 mg/kg), mecamylamine (10 mg/kg) and the combination of drugs on number of total movements in the locomotor activity test ($n=6$).*$p<0.05$ vs control group. The data are expressed as mean ± SEM values.

release, whereas mecamylamine decreases acetylcholine release in the hippocampus (Hıramatsu et al., 1998). Additionally, the cholinergic system has been seen to be responsible for the beneficial effects of resveratrol on cognition. Schmatz et al. (2009a, 2009b) also showed that resveratrol prevented the increase of AChE activity in diabetic rats. In our study, resveratrol seemed to have memory enhancing effects at 50 mg/kg doses by reversing AChE activity. It also prevented the memory disturbing effect of scopolamine, probably by acting on AChE. Mecamylamine may not affect AChE activity, which can explain why resveratrol did not reverse the memory disturbing effects of mecamylamine. Our study also proved that resveratrol affected cognition by acting on muscarinic cholinergic receptors, but had no effect on nicotinic cholinergic receptors. The doses of resveratrol, scopolamine and mecamylamine were chosen based on previous studies in which they had the intended effects (Chander and Chopra, 2005; Hıramatsu et al., 1998; Sharma and Gupta, 2002; Moran, 1993). The dose of mecamylamine was higher compared to scopolamine because in some previous studies lower doses of mecamylamine did not disturb memory (Moran, 1993). As a result of our study, we suggest that a decrease of AChE activity by resveratrol can contribute to increased levels of ACh and consequently improve cognitive functions, such as learning and memory, confirming the results from previous studies (Mesulam et al., 2002; Schmatz et al., 2009b).

Scopolamine, an unspecific muscarinic receptor antagonist, has been used as the “gold standard” for memory impairment in both animal and human studies of working memory (Blokland, 1995). In this context, the amnesic effect induced by scopolamine could be related to its influence on sensory/attentional processes (Blokland, 1995). In our study, scopolamine-induced memory impairment was not related to a sedative effect because animals did not show any sign of sedation. In experimental animals, nicotine has been found to improve learning and memory in a variety of tasks, whereas the nicotinic antagonist mecamylamine has been shown to impair memory performance (Levin et al., 1997;,Decker et al., 1995; Brioni et al., 1997). In a previous study, intrahippocampal injection of the nicotinic receptor antagonist mecamylamine significantly increased the number of errors in a test of working memory in the three-panel runway test, although it did not affect the number of errors in a test of reference memory (Ohno et al., 1993). Also in previous studies, nicotine induced improvements in working but not reference memory (Levin et al., 1996, 1997). These results suggest that mechanisms mediated by hippocampal nicotinic receptors play a role in working memory but not in reference memory, which is in accordance with our study.

In conclusion, resveratrol improved learning and memory in naive animals and in drug-induced models of dementia. This could indicate new approaches for the treatment of dementia, and in the future, resveratrol could be used safely in healthy people and in patients with dementia. This is a preliminary study; future studies revealing the mechanism by which resveratrol exerts its effects (e.g., receptor binding profile) in different learning and memory tasks should be carried out to support our results. According to our literature search, this is the first study investigating the effects of resveratrol on memory impairment by both the muscarinic receptor antagonist

scopolamine and the nicotinic receptor antagonist mecamylamine. Our study suggests that centrally acting muscarinic and nicotinic antagonists have dissociable effects on memory processes in rats. Treatment with resveratrol might modulate cholinergic neurotransmission and may, consequently, improve cognition.

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