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Short communication

Ameliorative effect of rosmarinic acid on scopolamine-induced memory impairment in rats

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HIGHLIGHTS

- RA administration (16 and 32 mg/kg) improved learning and memory in control rats.
- RA (8 mg/kg) did not alter cognitive function in sopolamine treated rats.
- RA 16 and 32 mg/kg treated rats had longer STLr in memory deficit groups.
- Higher doses of RA caused increased TDC in scopolamine treated animals.
- RA may protect against memory deficits in a pharmacological model of AD.

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ABSTRACT

Rosmarinic acid (RA) is a natural phenol that exerts different biological activities, such as antioxidant activity and neuroprotective effects. In this study, we hypothesized that administration of RA (8, 16, and 32 mg/kg, *p.o.*) for 7 days would effect on scopolamine-induced cognitive dysfunction as an extensively used model of cognitive impairment.

The rats were divided into ten groups. The acquisition trial was done 1 h after the last administration of RA. Animals were divided into control, RA (8, 16, and 32 mg/kg) and donepezil (2 mg/kg) treated controls, scopolamine, RA (8, 16, and 32 mg/kg), and donepezil (2 mg/kg) treated scopolamine groups. Memory impairment was induced by scopolamine treatment (1 mg/kg, *i.p.*) 30 min after the administration of RA, donepezil, or saline.

Scopolamine administration caused cognition deficits in the PAL and memory paradigm. While orally RA administration (16 and 32 mg/kg) improved learning and memory in control rats, it reversed learning and memory deficits of scopolamine received groups.

Administration of RA at the dose of 8 mg/kg did not alter cognitive function in control and scopolamine treated groups. The combination of anticholinesterase, neuroprotective, and antioxidant properties of RA may all be responsible for the observed effects. These results indicate the beneficial effects of subchronic RA administration in passive avoidance learning and memory in control rats as well as in a pharmacological model of cholinergic deficit which continue to expand the knowledge base in creating new treatment strategies for cognition deficits and dementia. Of course, further studies are warranted for clinical use of RA in the management of demented subjects.

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1. Introduction

Cholinergic deficit is correlated with cognitive dysfunction and memory loss in animal models of Alzheimer's disease (AD) induced by intracerebroventricular or intrahipocampal administration of β-amyloid peptides (Aβ) as well as in aged subjects [1,2]. Scopolamine, an anti-cholinergic agent, can also inhibit central cholinergic neuronal activity and impairs learning and memory [3,4]. Therefore, scopolamine may therefore be effective for use in animal models of amnesia as well as characterizing potential cognition enhancing drugs [4,5].

Recently, several AChE inhibitors have been approved for cognitive dysfunctions. However, these drugs are not ideal for clinical use due to side effects such as hepatotoxicity [6,7]. Thus, it is necessary

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to continue to seek alternative drugs with cholinomimetic and neuroprotective activities for the treatment of memory impairments and prevention of clinical problems [5].

Rosmarinic acid (RA) is a natural phenol carboxylic acid found in various foods and medicinal herbs [8]. It has been reported that RA exerts different biological activities, such as antioxidant [9], anti-inflammatory [10], analgesic [11], anti-apoptotic, and neuroprotective [12] activity. Previous studies have demonstrated that dietary enrichment with nutritional antioxidants could improve brain damage and cognitive function [13,14]. The principal ethanol-soluble constituent of *Melissa officinalis* and *Salvia officinalis* which are effective in the management of mild to moderate AD in randomized double-blind clinical studies [15,16] is RA [17,18]. Furthermore, previous studies indicated the anti-amnesic activity of RA in Aβ induced neurotoxicity and neurodegeneration in mice. The anti-amnesic activity of RA may occur *via* decreasing levels of the neurotransmitter metabolic enzyme AChE and improving central cholinergic neurotransmission as a main regulatory mechanism in the learning and memory processes [19,20].

Considering the effects of RA on cognition and its interactions with cholinergic system, the aim of the present study was to evaluate the effect of RA sub-chronic administration in different doses on scopolamine-induced memory impairment in rats using the passive avoidance test. We also compared the effects of RA with those of donepezil, which is a reference drug used for treatment of cognitive deficits.

2. Material and methods

2.1. Animals

Sixty-four locally produced male Wistar rats (250–280 g) were used. All animals were maintained at a constant temperature (22 ± 0.5 °C) with a 12 h light/dark cycle and free access to laboratory chow and tap water. Each experimental group consisted of eight animals that were chosen randomly from different cages and each was used only once. Animals were handled in accordance with the criteria outlined in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health (NIH) publication 86-23; revised 1985;http://www.oacu.od.nih.gov/regs/guide/guidex.htm). The protocols were also approved by the institutional ethics committee of Bu-Ali Sina University. All procedures and experiments were performed between 10:00 and 14:00.

2.2. Drugs

Scopolamine hydrobromide, donepezil hydrochloride, and rosmarinic acid were purchased from Sigma–Aldrich (Chemie Gmbh, Munich, Germany). Scopolamine was dissolved in a 0.9% saline solution and injected in a volume of 1 ml/kg (*i.p.*). Donepezil and RA were made up in physiological saline for oral administration.

2.3. Experimental design

To examine the memory-protecting properties of treatment with RA, rats were administered RA (8, 16, and 32 mg/kg, *p.o.*), donepezil (2 mg/kg, *p.o.*), or saline once a day for 7 days. The acquisition trial was done 1 h after the last administration of RA, donepezil, or saline. Memory impairment was induced by scopolamine treatment (1 mg/kg, *i.p.*) 30 min after the administrations. The operator was unaware of the specific treatment groups to which an animal belonged.

2.4. Passive avoidance learning (PAL) test (step through test)

The apparatus and procedure were as previously described [21,22]. Briefly, the step-through passive avoidance apparatus consisted of a lighted chamber (20 cm × 20 cm × 30 cm) made of transparent plastic and a dark chamber whose walls were made of dark opaque plastic (20 cm × 20 cm × 30 cm). The floor of both chambers was made of stainless steel rods (3 mm diameter) spaced 1 cm apart. The floor of the dark chamber could be electrified using a shock generator. A rectangular opening (6 cm × 8 cm) was located between the two chambers and could be closed by an opaque guillotine door.

2.5. Training

All experimental groups were given two trials to habituate animals to the apparatus. For these trials, rats were placed in a lighted compartment of the apparatus facing away from the door and 5 s later the guillotine door was raised. The rat has native preference to the dark environment. Upon the rat entering the dark compartment, the door was closed and after 30 s the rat was taken from the dark compartment to its home cage. The habituation trial was repeated after 30 min and followed after the same interval by the first acquisition trial. The entrance latency to the dark compartment (step-through latency, STLa) was recorded when the animal had placed all 4 paws in the dark compartment. After the animal had spontaneously entered the dark compartment, the guillotine door was lowered and a mild electrical shock (0.5 mA) was applied for 3 s. After 30 s, the rat was taken from the dark compartment into their home cage. Then after 2 min, the procedure was repeated. The rat received a foot-shock each time it reentered the dark and had placed all 4 paws in the dark compartment. Training was terminated when the rat remained in the light compartment for 120 consecutive seconds. The number of trials (entries into the dark chamber) was recorded.

2.6. Retention test

The retention test was performed 24 h after the PAL acquisition trial. The rat was placed in the lighted chamber as in PAL training and 5 s later, the guillotine door was raised, and the step-through latency (STLr), and the time spent in the dark compartment (TDC) were recorded up to 300 s. If the rat did not enter the dark compartment within 300 s, the retention test was terminated and a ceiling score of 300 s was assigned.

2.7. Statistical analysis

All data are expressed as mean ± S.E.M. The analysis was performed using the SPSS statistical software package (version 21.5; SPSS, Chicago, IL, USA). Analysis of data was performed using one-way analysis of variance (ANOVA). *Post hoc* analysis (Tukey's test) was performed for multiple comparisons between different groups of these experiments. Probability values less than 0.05 were considered significant.

3. Results

3.1. Effects of RA on the PAL and memory

There was no significant difference in the STLa among different groups in the first acquisition trial (before receiving the electrical shock) ($P > 0.05$, Fig. 1A). There was a significant difference ($P < 0.05$, $P < 0.01$) in the number of trials to acquisition between 16 and 32 mg/g treated control groups (1.75 ± 0.25, 1.62 ± 0.26, respectively), and untreated ones (3.12 ± 0.35). Donepezil caused

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