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EFFECTS OF GALANTAMINE ON PASSIVE AVOIDANCE TESTS IN RATS

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ABSTRACT

PURPPOSE: Galantamine is a phenanthrane alkaloid, a competitive and reversible cholinesterase inhibitor. It has unique mechanism of action includes allosteric modulation of nicotinic receptors. The aim of our study was to compare the effects of different doses galantamine on learning and memory in rats using passive avoidance tests. METHODS: The male Wistar rats (9 per group, with body weight 220-240g) treated per os with: 1st Saline 0.1ml/100g (controls); 2nd Galantamine 0.1 mg/kg; 3rd Galantamine 0.5 mg/kg; 4th Galantamine 1.0 mg/kg. Animals were trained in step-through and step-down tests, using original made apparatus (Ugo Basile, Italy). In passive avoidance tests was calculated the latency of reactions in seconds. The comparison between groups was made by Instat program. RESULTS: In step-through test rats with highest dose galantamine significantly increased latency of reactions on 1st day learning and on long memory test. In step-down test all groups with galantamine increased latency of reactions on learning session. The rats with 1.0 mg/kg galantamine increased the latency on short memory test and rats with 0.1 mg/kg galantamine increased latency on long memory retention. CONCLUSION: Our results allow us to conclude that galantamine has improving effect on learning and memory in rats which is dose independent.

Key words: Alzheimer's disease, cholinesterase inhibitor, learning, memory

INTRODUCTION

The main strategy for treating of cognitive impairment in Alzheimer's disease (AD) remains cholinesterase inhibitors and glutamate blockers (1).

Galantamine is a phenanthreane alkaloid obtained from bulbs and flowers of the plant (Galanthus woronowii) and related species (2). In the last galantamine was made by original technology from leaves and flowers of the Galanthus nivalis, nowerdays is made from Leucojum aestivum L. (Amaryllidaceae).

It is a competitive and reversible cholinesterase inhibitor used for treatment of mild to moderate AD (2). Galantamine has unique mechanism of action includes allosteric modulation of alpha-4/beta-2 and alpha-7 nicotinic receptors in central nervous system. Interaction between galantamine and receptors protects neurons from glutamate neurotoxic action and inhibits apoptosis (3). Takada-Takatory et al. (4) suggested that neuroprotective effect of galantamine and donepezile is independent from level of cholinesterase inhibition. Neuroprotective effect of galantamine depends on increasing number of alpha-4 and alpha-7 nicotinic receptors.

The aim of our study was to compare the effects of three doses galantamine on learning and memory processes in rats using passive avoidance tests (step-through and step-down).

MATERIAL AND METHODS

All experiments were carried out according to the guidelines for the use of laboratory animals in EU and Bulgaria. Official permission for the study was obtained by Bulgarian Food Safety Agency №49/30.06.2011 and Ethics Committee of the Medical University Plovdiv №3/05.07.2012.

Drug

Galantamine - 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-

benzofuro[3a,3,2ef][2]benzazepin-6-ol,hydrobromide (Nivalin Sopharma).

Experimental animals

This study used male Wistar rats with body weight of 220-240 g divided into 4 groups (n=9). The animals were kept under standard laboratory conditions in 08:00 – 20.00h light/dark cycle and were provided with food and water ad libitum. The rats were treated per orally once daily with: 1st group - Saline (0.1 ml/100g body weight), 2nd group - Galantamine 0.1 mg/kg, 3rd group - Galantamine 0.5 mg/kg and 4th group Galantamine 1.0 mg/kg. The tests were performed 60 min after drug application.

Behavioral tests

Two tests for passive avoidance were used – step-through and step-down. An automatic set-up for a passive avoidance "step-through" test (Ugo Basile, Italy) was made in a wire cage with two separate light and dark compartments. The parameters were as follows: door delay for 7s, open door for 12s, followed within 9s 0.4mA foot shock. Sessions were consisted the three consecutive trials with 60 minutes pause between them. Learning sessions were performed in two consecutive days, a short term memory was performed 24 hours later, and long term memory retention was perform 7 days later (on the 10th day). The learning criterion used was a latency of reactions 3 minutes (180 ± 2 seconds) resting in the light chamber.

An automatic set-up for passive avoidance "step-down" test (Ugo Basile, Italy) was used in a wire-floor cage with a round central plastic platform. Learning sessions were consisted of 2 trials separated by a 60 minute interval. Learning sessions were performed in two consecutive days, short term memory – 24 hours later (3rd day), and long memory retention test was performed on the 7th day. During each trial electrical stimulation (0.4mA) was delivered to the wire floor for a duration of 10s. The learning criterion used was latency of reactions 60 seconds staying on the platform. Memory retention tests were performed using the same parameters but with an absence of a foot shock.

Statistical analysis

It was used Instat computer program for analysis of variance. The mean and standard error of mean (± SEM) for each group was calculated. A two-way ANOVA for repeated measurements was used to compare different groups with the respective controls. A p-value of $P<0.05$ was considered representative of a significant difference.

RESULTS

In step-through passive avoidance test control group increased the latency of reactions on 2nd day of learning session ($p<0.05$) and on short memory tests ($p<0.05$), compared to the first day. The groups with galantamine 0.1 mg/kg and 0.5 mg/kg did not changed the latency of reactions on learning and memory tests, compared to the same days saline group. The rats treated with galantamine 1.0 mg/kg significantly increased the latency of reactions on 1st day learning ($p<0.05$) and on long memory test ($p<0.05$), compared to the same days control group **(Figure 1).**

In step-down passive avoidance test control rats did not change the latency of reactions (time spend on the plastic platform) on two days learning, but significantly increased it on short ($p<0.05$) and long ($p<0.01$) memory tests compared to the first day. The group with galantamine 0.1 mg/kg increased the latency of reactions on 1st and 2nd days of learning session ($p<0.05$) and on long memory test ($p<0.05$), compared to the same days saline group. The rats with galantamine 0.5 mg/kg significantly increased the latency of reactions on two days learning ($p<0.01$), but not kept it on memory retention tests, compared to the same days saline group. The experimental animals treated with galantamine 1.0 mg/kg statistically significant increased the time spend on the platform on 1st ($p<0.01$) and 2nd ($p<0.05$) days of learning session and on short memory retention test ($p<0.01$), compared to the same days control rats **(Figure 2).**

DISCUSSION

In step-through passive avoidance test only highest dose galantamine improved learning capacity of rats and formed long memory traces.

In step-down passive avoidance test galantamine in three studied of us doses showed improving effect of learning, most expressed at dose 0.5 mg/kg. In this passive avoidance short memory traces formed rats with doses of 1.0 mg/kg galantamine, but long memory traces – animals with 0.1 mg/kg.

Our results allow us to conclude that galantamine has improving dose independent effect on learning and memory processes in rats.

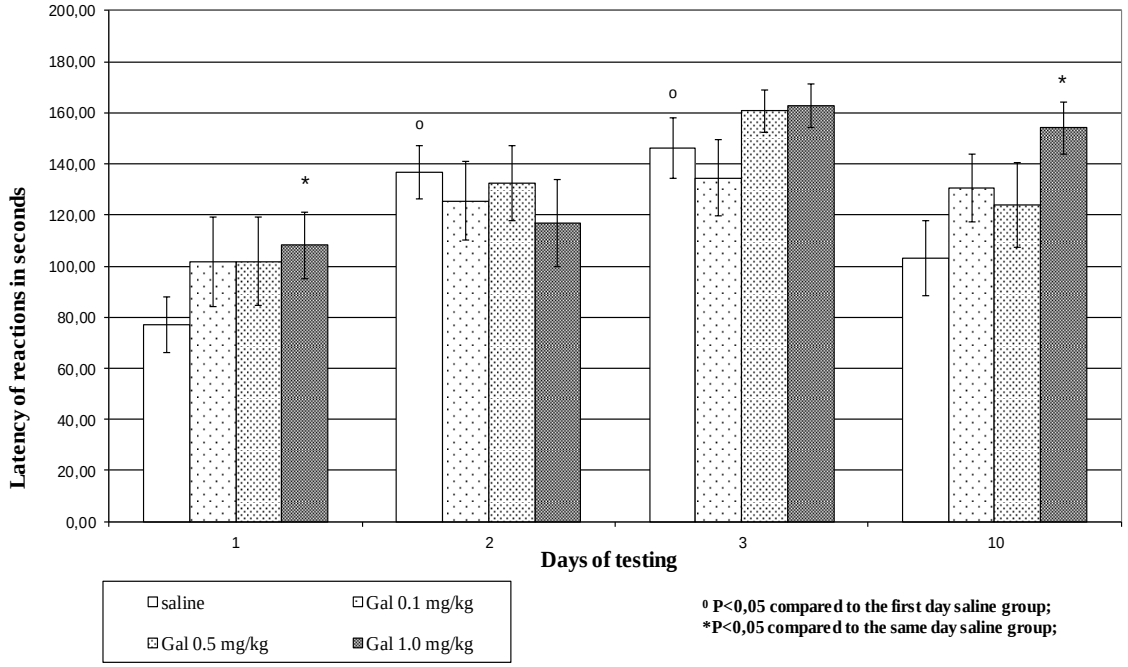

Figure 1. Effects of galantamine on learning and memory processes in rats. Step-through passive avoidance test.

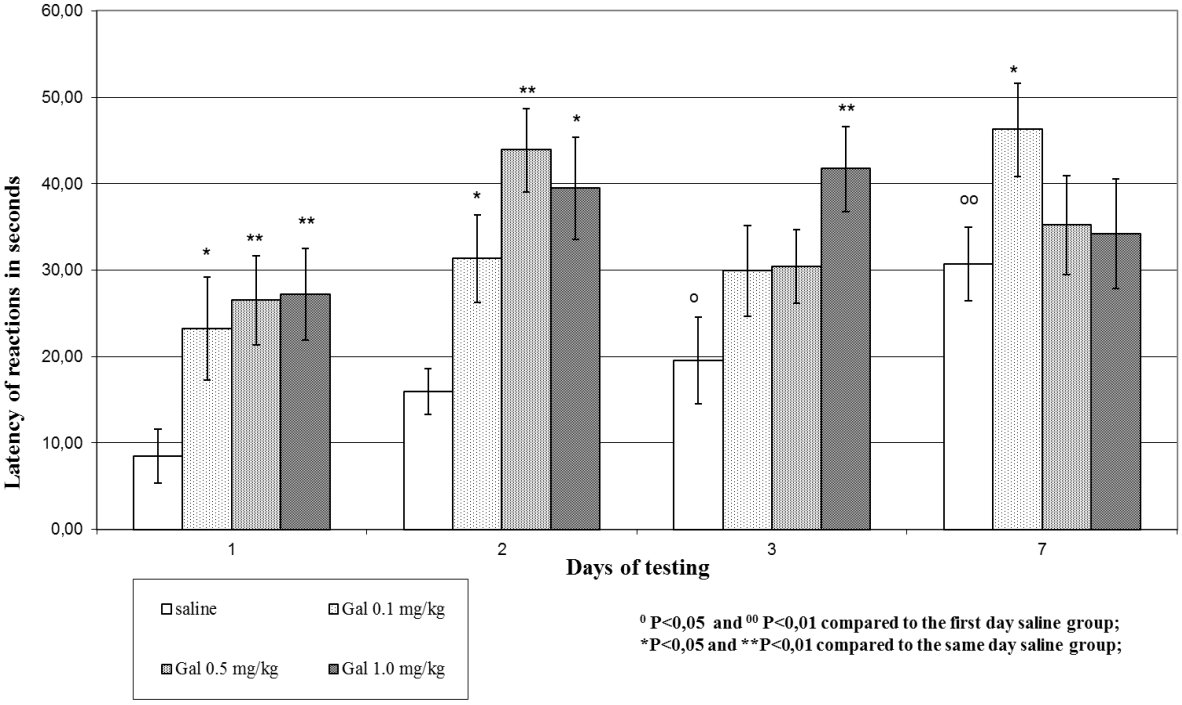

Figure 2. Effects of galantamine on learning and memory processes in rats. Step-down passive avoidance test.

Improving effects of galantamine and tacrine on memory functions of old rats in passive avoidance test was found also by Rispoli V et al. (5). It is result of increasing levels of acethylcholine and stimulation and allosteric modulation of nicotinic receptors in some brain regions having key role in cognitive processes (6). Galantamine also protects against oxidative stress induced by amyloid-beta peptide in cortical neurons (7).

All of this data taken together with its good clinical effectiveness, well tolerated and low price, in comparison with donepezile and

rivasigmine, probably lead to increasing use of galantamine for treatment of Alzheimer's disease nowadays.

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