THE EFFECTS OF NICOTINIC TREATMENT ON MEMORY AND LEARNING IMPAIRMENT INDUCED BY BLOCKADE OF MUSCARINIC ACETYLCHOLINE RECEPTORS ON PERFORMANCE IN RADIAL ARM-MAZE TASK IN RATS

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Abstract: 10 consecutive days nicotine administration (0.3 mg/kg b.w., i.p.) improve working and reference memory tested by means of radial arm-maze. The effect of nicotine is more pronounced on short-term memory (working memory) than on long-term memory (reference memory). Scopolamine hydrobromide (0.7 mg/kg b.w., i.p.) decreases the performance on both short and long term memory, respectively.

INTRODUCTION

Although studies regarding the implication of cholinergic system in learning and memory began long ago, the statement that in Alzheimer's disease patients, this system suffers an impairment (James and Nordberg, 1995) has led to a intensification of researches concerning the responsible cholinergic structures (receptors, neurotransmitters) and their interaction with other nervous structures (Dutar et al., 1995; Van der Zee and Luiten, 1999). Muscarinic and nicotinic acetylcholine receptors mediate the action of acetylcholine.

Concerning the influence of nicotine, specific acetylcholine stimulus experimental studies in animals and human have shown contradictory results (Levin and Simon, 1998). In the present study we examined the effects of nicotinic treatment on memory and learning impairment induced by blockade of muscarinic acetylcholine receptors on performance in radial arm-maze task in rats.

MATERIAL AND METHODS

Male Wistar rats weighing 250g ± 25g at the beginning of experiments were used. They were fed and allowed to drink water ad libitum. Rats were treated in accordance with institutional guidelines.

Radial arm-maze task

The radial arm-maze used in the present study consisted of 8 arms, numbered from 1 to 8 (48x12 cm), extending radially from a central area (32 cm in diameter). The apparatus was placed 40 cm above the floor, and surrounded by various extra maze cues placed at the same position during the study. At the end of each arm there was a food cup that had a single 50 mg food pellet. Prior to the performance of the maze task, the animals were kept on restricted diet and body weight was maintained at 85% of their free-feeding weight over a week period, with water being available ad libitum.

Before the actual training began, the animals were shaped for 4 days to run to the end of the arms and consume the bait. The bait was initially available throughout the maze, but gradually was restricted to the food cup. Briefly, each animal was placed individually in the center of the maze and subjected to working and reference memory tasks, in which same 5 arms (no. 1, 2, 4, 5, and 7), were baited for each daily training trial. The other 3 arms (no. 3, 6, 8) were never baited. The training trial continued until all 5 baits had been consumed or until 5 minutes had elapsed. An arm entry was counted when all four limbs of the rat where within an arm. Measures was made of the number of working memory errors (entering an arm containing food, but previously entered), and reference memory errors (entering an arm that was not baited). The time taken to consume all five baits was also recorded. Reference memory is regarded as a long-term memory for information that remains constant over repeated trials (memory for the positions of baited arms), whereas working memory is considered a short-time memory in which the information to be remembered changes in every trial (memory for the positions of arms that had already been visited in each trial) (Durkin, 1994; Olton et al., 1979). Each animal was subjected to one trial each day.

DRUG ADMINISTRATION

All drugs were injected intraperitoneally (i.p.), in a single dose, in a volume of 1ml/kg b.w. (-) – Nicotine (free base; 0.3 mg/kg b.w., i.p.) and scopolamine hydrobromide (0.7 mg/kg b.w., i.p.) were administrated individually (scopolamine hydrobromide) or in the combination (nicotine + scopolamine), daily, 30 minutes before training during consecutive 10 days. Before starting the experiments, the rats used in radial arm-maze task were treated previously 4 days with scopolamine or scopolamine + nicotine, 30 minutes before training trials.

Statistical analysis

Results were expressed as means ± S.E.M. The results were analyzed statistically by means of the Student's "t" test. $p<0.05$ was taken as the criterion for significance.

RESULTS AND DISCUSSIONS

1. Effects of nicotinic treatment on memory performance in rats with muscarinic receptors blocked by scopolamine.

The experimental data are shown in Fig. 1-4. The nicotinic treatment improves short-term and long-term memory, as number of working and respectively reference memory errors decreased in treated rats. The same conclusion can be inferred from average working and reference memory errors.

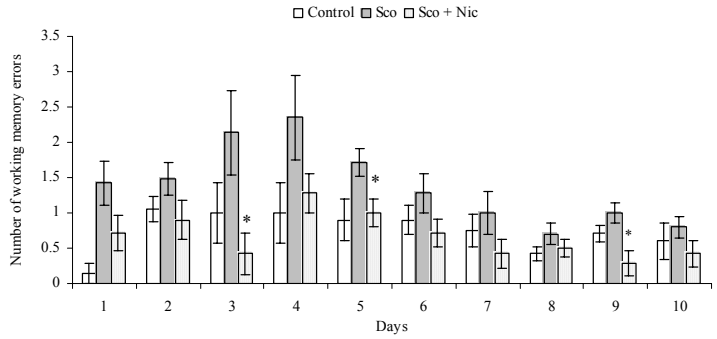

Fig.1 Effects of nicotinic treatment on spatial working memory formation in rats during 10 days training. The values are means ± S.E.M.*$p<0.05$ vs. vehicle (Sco) groups.

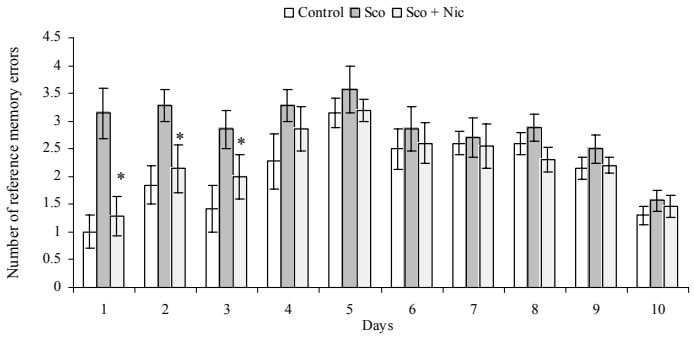

Fig. 2 Effects of nicotinic treatment on spatial reference memory formation in rats during 10 days training. The values are means ± S.E.M.*$p<0.05$ vs. scopolamine (Sco) group.

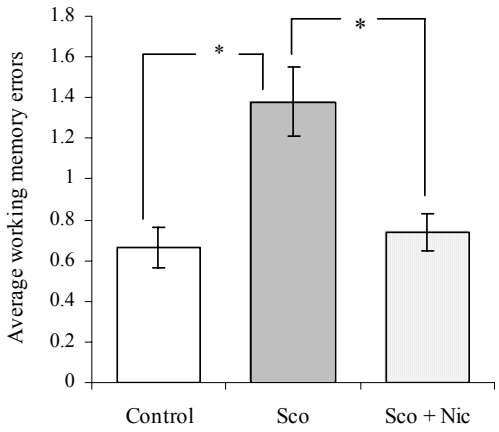

Fig. 3 Average working memory errors during 10 days training of rats treated with nicotine. The values are means ± S.E.M. *p<0.05.

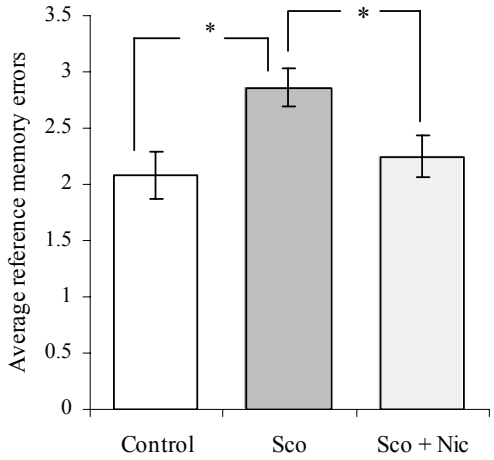

Fig. 4 Average reference memory errors during 10 days training of rats treated with nicotine. The values are means ± S.E.M. *p<0.05.

2. Effects of nicotine treatment on time taken to consume all five baits in rats with muscarinic receptors blocked by scopolamine.

The experimental data are shown in Fig. 5-6. The nicotinic treatment decrease the time taken to consume all five baits and average time taken to consume all five baits, respectively.

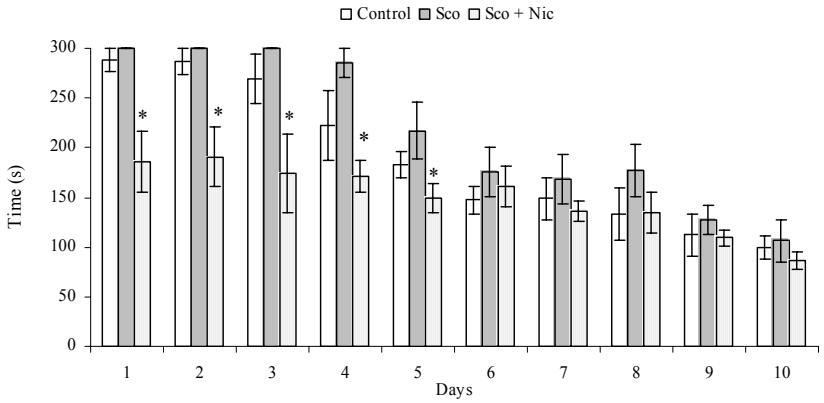

Fig. 5 Effect of nicotinic treatment on time taken to consume all five baits during 10 days training. The values are means ± S.E.M.*p<0.05 vs. scopolamine (vehicle) groups.

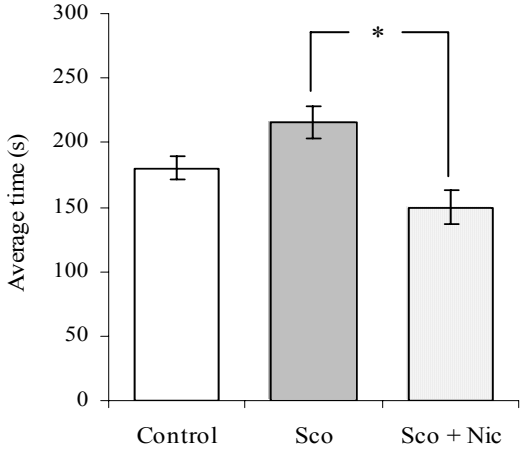

Fig. 6 Average time taken to consume all five baits during 10 days training of rats treated with nicotine. The values are means ± S.E.M. *p<0.05 vs. scopolamine.

Our results showed that muscarinic acetylcholine receptor blockade with scopolamine (a specific antagonist of muscarinic acetylcholine receptor) induced a decrease in both long-term memory (evidenced by reference memory errors) and short-term memory (evidenced by working memory errors) and increase the time taken to consume all five baits during 10 days training in the radial arm-maze task. These data confirmed those from the literature concerning the facilitating role of muscarinic acetylcholine receptors in memory processes (Dutar et al., 1995; Hefco et al., 2003b).

About the role of nicotinic acetylcholine receptors explored by means of nicotine, a specific agonist of nicotinic acetylcholine receptors, some research have observed an ameliorating effect of nicotine on memory impairment (Decker et al., 1995; Nitta et al., 1994; Levin and Simon, 1998; Levin and Rezvani, 2000, Hefco et al., 2000;

Hefco et al., 2003a) while other did not observe any effect or the contrary have reported negative effect (Dunnet and Martel, 1990; Heisham et al., 1994; Spilich et al., 1992).

Our present data show that nicotine administrated during 10 days (0.3 mg/kg b.w., i.p./day) has a facilitatory effect on working and reference memory performance in the rats with muscarinic acetylcholine receptors blocked by scopolamine. This data confirmed our previous data concerning the facilitating role of nicotinic acetylcholine receptors in learning and memory processes explored by means of Y-maze and multi-trial passive avoidance task (Hefco et al., 2000; Hefco et al., 2003b).

Several effects of nicotine in the brain may be mediated through neuromodulatory potentiation of the release of a variety of neurotransmitters including acetylcholine, dopamine, GABA, norepinephrine, serotonin and glutamate (Levin and Simon, 1998; Yin and French, 2000). Because nicotine has a stimulatory effect on memory in rat with muscarinic acetylcholine receptor blocked by scopolamine, these data confirmed our previous data concerning the facilitating role of nicotinic acetylcholine receptors in learning and memory processes explored by means of Y-maze and multi-trial passive avoidance task (Hefco et al., 2000), without to clear up the mechanism of nicotine action. The mesotelencephalic dopamine system could be involved in appearance of the stimulatory nicotinic effects on learning and memory as we observed in our previous experiments (Hefco et al., 2000; Hefco et al., 2003c).

CONCLUSIONS

On the basis of our results concerning the effect of nicotine in rats with muscarinic acetylcholine receptors blocked by means of scopolamine, we can conclude that nicotine, by activating the nicotinic acetylcholine receptors, attenuated the impairment of short-term and long-term memory induced by muscarinic receptors blockade by scopolamine.

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