CERTAIN MECHANISMS OF NICOTINE ACTION ON MEMORY AND LEARNING PROCESSES TESTED BY PERFORMANCE OF RATS IN THE SHUTTLE BOX TASK

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Abstract: consecutive days nicotine administration (0.3 mg/kg b.w., i.p.) improve the conditioned avoidance response and crossing latency tested by means of shuttle box. Scopolamine hydrobromide (0.7 mg/kg b.w., i.p.) decreases conditioned avoidance response and enhance crossing latency tested by means of shuttle box. This result suggests that nicotine improve memory and learning processes in rats with muscarinic acetylcholine receptors blocked by scopolamine.

INTRODUCTION

Extensive evidence supports the view that cholinergic mechanisms modulate learning and memory formation. Recent studies of acetylcholine (Ach) release, obtained with in vivo microdialysis samples during training, together with direct injections of cholinergic drugs into different neural systems, provide evidence that release of ACh is important in engaging these systems during learning, and the extent to which the systems are engaged is associated with individual differences in learning and memory (Gold, 2003). In the present study we examined certain mechanisms of nicotine action on memory and learning processes on rat performance in the shuttle box task.

MATERIAL AND METHODS

Male Wistar rats weighing 250 ± 25g at the beginning of experiments were used. They were fed and allowed to drink water ad libitum. The rats were treated in accordance with the Guidelines for Animal Experiments of the "Al.I.Cuza" University and of the U.S. National Institute of the Health Guide for the Care and Use of Laboratory Animals. The rats were housed four per cage under controlled laboratory condition (a 12-h light/dark cycle with lights on at 8: oo a.m., 22 ± 0.5o C).

Apparatus for evaluation of conditioned avoidance response (CAR).

The shuttle box used in the present study was constructed of grey plexiglas and measured 66 x 33 cm wide x 39 cm high. The floor made of 2 mm diameter stainless steel rods spaced 0.5 cm apart. The box was divided into two equal compartments by a 5 cm high plexiglas barrier. Each compartment could be electrified separately. A ringer was mounted in the centre on the top of the box for delivery of auditory stimuli (unconditioned stimuli).

Rats were placed in the shuttle box and allowed to freely explore the apparatus for 180 s. Then, they received 20 shuttle trials/day, where they were trained to terminate a shock by jumping over a barrier to the adjoining compartment. Each trial began with 5 s ring tone followed by 5 s 0.3 mA foot shocks. After 60 s, the next trial was initiated. If the animal crossed the barrier during the ring tone, the stimulus was terminated and no shock was delivered (avoidance response). If the animal crossed the barrier during shock delivery, an escape response was measured. After 30 s, the next trial was initiated in this experimental situation. The crossing latency (the time elapsed between the delivery of unconditioned stimulation and the start of conditioned avoidance responses) was also recorded (Thiel et al., 2000).

DRUG ADMINISTRATION

All drugs were administrated 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 14 days.

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.

REZULTATS AND DISCUSSIONS

1. Effects of nicotinic treatment on conditioned avoidance responses in the rats with muscarinic acetylcholine receptors blocked by scopolamine.

The experimental data are shown in Fig. 1-2. The nicotinic treatment enhances conditioned avoidance response in rats treated with scopolamine (Fig.1). The same conclusion can be inferred from average conditioned avoidance responses (Fig. 2).

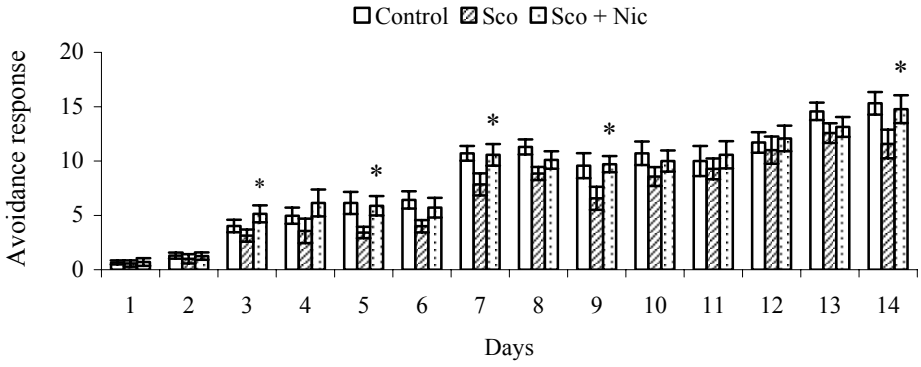

Fig.1 Effect of nicotine (Nic) on conditioned avoidance responses formation in rats during 14 consecutive days training. The values are means ± S.E.M.*$p<0.05$ vs. scopolamine groups (Sco).

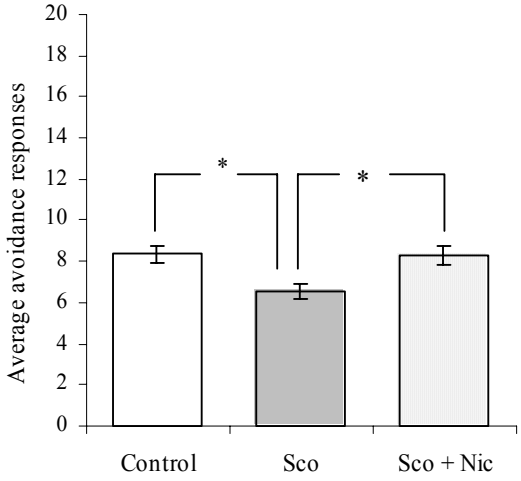

Fig. 2. Effect of nicotine on average conditioned avoidance responses formation in rats during 14 consecutive days training. The values are means ± S.E.M. *$p<0.05$.

2. Effects of nicotinic treatment on crossing latency in the rats with muscarinic acetylcholine receptors blocked by scopolamine.

The experimental data are shown in Fig. 3-4. The nicotinic treatment decrease crossing latency in scopolamine-treated rats (Fig.3). The same conclusion can be inferred from average crossing latency (Fig.4).

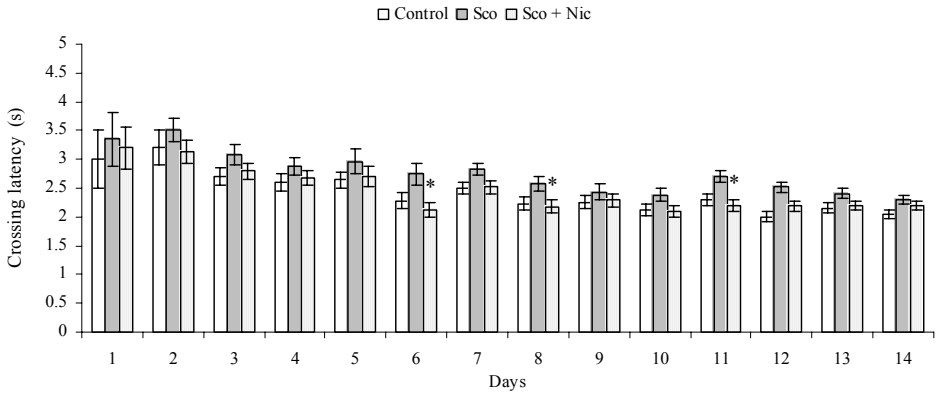

Fig. 3 Effect of nicotine on crossing latency in rats during 14 consecutive days training. The values are means ± S.E.M.*$p<0.05$ vs. scopolamine.

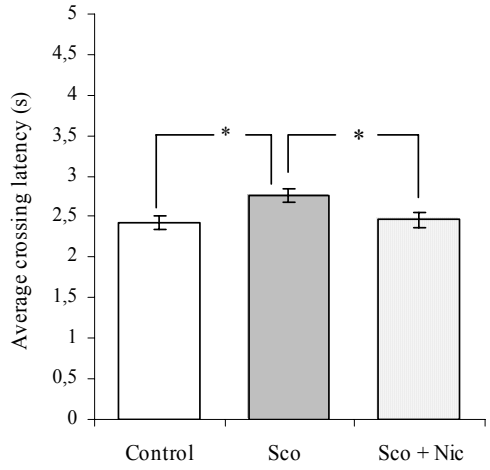

Fig. 4 Effect of nicotine on average crossing latency in rats during 14 consecutive days training. The values are means ± S.E.M. *$p<0.05$.

Our experimental results showed that nicotine administrated 14 consecutive days has facilitating effects on conditioned avoidance response and crossing latency response, respectively. 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).

About the role of nicotinic 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). The equivocal results cited above may be due to differences in dosage, animal strains or different tests used for memory evaluation.

Our present data show that nicotine administered daily during a 14 consecutive days ameliorated the impairment induced by blockade of muscarinic acetylcholine receptors.

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, this suggests that nicotinic acetylcholine receptors play also a facilitatory role on memory processes. Until now, 11 different nicotinic acetylcholine receptors subtypes have been identified (Picciotto et al., 2000). One hippocampal neuron can express more than one nicotinic receptor subtype (Levin and Simon, 1998). The increase in both acetylcholine and glutamate release appears to be mediated through ą 7 subunit-containing nicotinic acetylcholine receptor as it can be blocked by . -bungarotoxin. Conversely, nicotine stimulates the firing of dopaminergic neurons (Picciotto et al;. 2000) as well as the release of dopamine from striatal sinaptosomes (Grady et al., 1992) through ą 42-containing nicotinic acetylcholine receptor.Identification of nicotinic acetylcholine receptor subtypes that are involved in cognitive functions requires future investigation.

CONCLUSIONS

On the basis of our results obtained in shuttle box task, we can conclude that nicotine could attenuate the impairment of learning and memory processes in the rats with muscarinic acetylcholine receptors blocked by scopolamine.

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