

THE EFFECTS OF CHRONIC NICOTINE TREATMENT ON PERFORMANCE IN RADIAL – ARM MAZE TASK IN RATS

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Abstract: Chronic (21 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). The benefic role of nicotinic acetylcholine receptors on memory performance is attributed to the interaction with dopaminergic and NMDA receptors.

INTRODUCTION

Although studies regarding the implication of cholinergic system in learning and memory began long time 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 (for review see Dutar et al. 1995; Van der Zee and Luiten, 1999). Muscarinic and nicotinic acetylcholine receptors mediate the action of acetylcholine. Clinical investigation on Alzheimer's disease patients does not indicate changes in number and function of muscarinic acetylcholine receptors. However, a significant decrease in nicotinic acetylcholine receptors density was reported in the cerebral cortex and hippocampus, two major areas which are involved in learning and memory process (James and Nordberg, 1995).

Concerning the influence of nicotine, a specific acetylcholine receptor stimulus, experimental studies in animals and human have shown contradictory results (Levin and Simon 1998). In the present study we examined the effects of chronic nicotine treatment on working and reference memory performance of rats in a radial arm – maze task.

MATERIAL AND METHODS

Radial arm -maze task

The maze used in the present study consisted of eight arms, numbered from 1 to 8 (48x12 cm) extending radially from a central area (32 cm in diameter). The floor of the arms and central area was painted in black. The apparatus was placed 40 cm above the floor, and surrounded by various extramaze cues placed at the same position during the study. At the end of each arm there was a food cup that held a single 50-mg food pellet. Prior to the performance of the maze task, the animals were kept on a 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. Following this shaping period, each animal was placed individually in the center of the maze and subjected to working and reference memory tasks, in which same five arms (No. 1, 2, 4, 5 and 7) were baited in

each daily training trial. The other three arms were never baited. The training trial continued until all five baits had been consumed or until 5 min had elapsed. An arm entry was counted when all four limbs of the rat were within an arm. Measures were made of the number of working memory errors (entering an arm containing food but previously consumed), reference memory errors (entering an arm that was not baited), the total number of errors to sample all five baited arms. 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 training trial each day.

DRUG ADMINISTRATION

The nicotine (free base, 0.3 mg/kg b.w., i.p.) was administered daily 30 minutes before training during 21 days. Before starting the experiments the rats used in radial-maze arm tasks were treated previously 14 days with nicotine.

Statistical analysis

Results were expressed as mean \pm 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

1. Effects of chronic nicotine treatment on memory performance in rats.

The experimental data are shown in Fig. 1-4. Chronic nicotine 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.

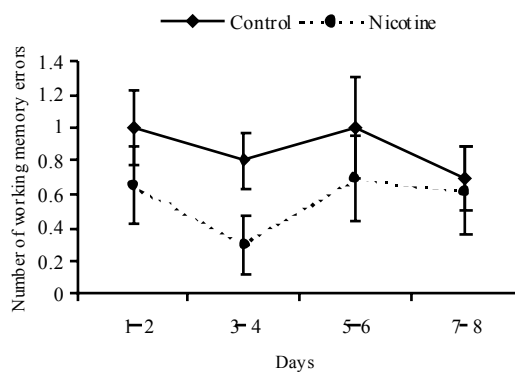


Fig.1 Effects of chronic nicotine treatment on spatial working memory formation in rats during eight days training. The values are mean \pm S.E.M. for two successive days.

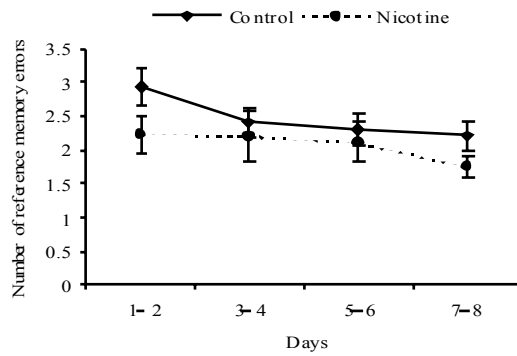


Fig.2 Effects of chronic nicotine treatment on reference memory formation in rats during eight days training. The values are mean \pm S.E.M. for two successive days. Legend as in Fig.1.

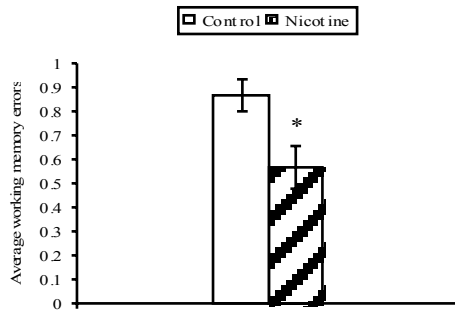


Fig.3 Average working memory errors during eight days training of rats treated with nicotine. The values are mean \pm S.E.M. * p < 0.05 vs. control.

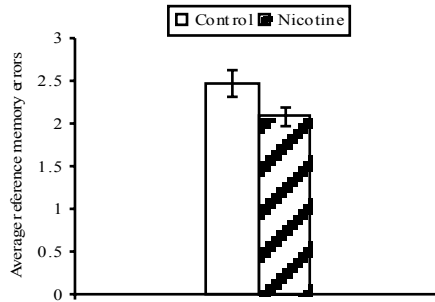


Fig.4 Effects of chronic nicotine treatment on average reference memory errors in rats. The values are mean ± S.E.M.

2. Effects of chronic nicotine treatment on time taken to consume all five baits in radial – arm task.

The experimental data are shown in Fig. 5-6. The chronic nicotinic treatment decrease the time taken to consume all baits which parallels the retention of working and reference memory errors.

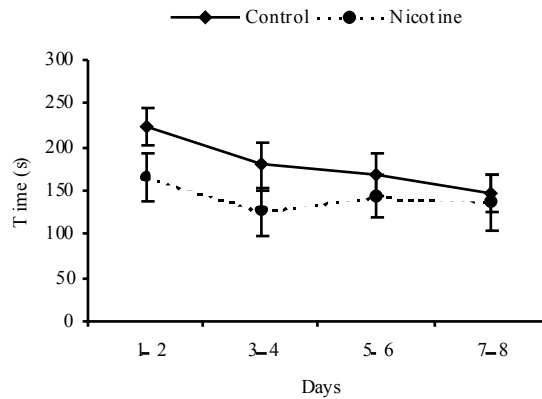


Fig.5 Effects of nicotine on time taken to consume all five baits during eight days training. Legend as in Fig.1.

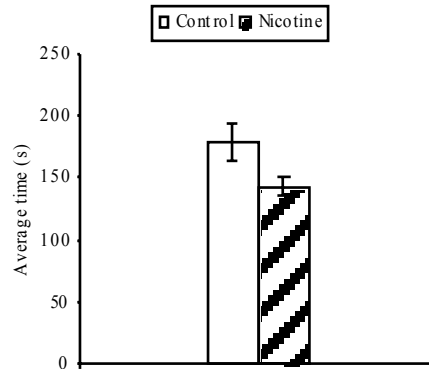


Fig.6 Average time taken to consume all five baits during eight days training of rats treated with nicotine (0.3 mg/kg/day).

DISCUSSIONS

Our experimental results showed that chronic cholinergic nicotine receptors stimulation with nicotine, administered chronic (21 consecutive days), has a facilitating effect on both short – term memory performance, evidenced by the number of working memory errors, and long – term memory performance evidenced by reference memory performance; the effect on short – term memory being more prominent than on long – term memory.

About the role of nicotine 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) 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, duration on drug treatment, animal strains or different tests used for memory evaluation.

Our present data show that nicotine administered chronic during three weeks (0.3 mg/ kg b.w./ day) has a facilitatory effect on working and reference memory performance. 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).

Nicotine induces the release of a variety of neurotransmitters including acetylcholine, dopamine, norepinephrine, GABA, serotonin and glutamate (Levin and Simon, 1998; Yin and French, 2000).

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, 2000). Nicotinic acetylcholine receptor (nAChR's) on dopaminergic

neurons in the ventral tegmental area (VTA) are thought to be a prime target for nicotine's stimulatory effects. Nicotine stimulates the firing rate of VTA dopamine neurons (White et al., 1995; Yin and French, 2000). Stimulation of VTA at frequency known to evoke dopamine overflow in the prefrontal cortex produces a long - lasting enhancement of the magnitude of the hippocampal – prefrontal cortex (PFC) long – term potentiation (Gurden, 1999), a putative cellular mechanism underlying plasticity (Bao et al., 2001). The existence of a direct monosynaptic pathway from the ventral CA₁ region of the hippocampus and subiculum to specific areas of the PFC provides useful model for conceptualizing the operations of hippocampal – PFC communication in learning and memory. Dopamine by means of D₁ dopamine receptors is crucial for control of NMDA receptor – mediated by synaptic response on a specific excitatory input to the prefrontal cortex. The interaction of D₁ dopamine receptor and NMDA receptor may play a crucial role in the storage and transfer of hippocampal information in the prefrontal cortex (Gurden et al., 2000).

CONCLUSIONS

On the basis of our results obtained by chronic stimulation of nicotinic acetylcholine receptors, we can conclude that nAChR's facilitate the retention of working and reference memory, which are a form of short – term and respectively long – term memory. The effects of nAChR's can be attributed to some degree to interaction with dopamine receptors and NMDA receptors.

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