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Nicotine Reverses Scopolamine-Induced Impairment of Performance in Passive Avoidance Task in Rats Through Its Action on the Dopaminergic Neuronal System

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NITTA, A., Y. KATONO, A. ITOH, T. HASEGAWA AND T. NABESHIMA. *Nicotine reverses scopolamine-induced impairment of performance in passive avoidance task in rats through its action on the dopaminergic neuronal system.* PHARMACOL BIOCHEM BEHAV **49**(4) 807–812, 1994.—Interest has recently focused on tobacco and/or nicotine in relation to senile dementia of the Alzheimer type because the population of patients with this disease among tobacco smokers is significantly smaller than in nonsmokers. We investigated whether, in relation to the dopaminergic neuronal system, nicotine was effective in ameliorating the impairment of performance in passive avoidance tasks in rats induced by scopolamine, an inhibitor of muscarinic acetylcholine receptors. Scopolamine and nicotine were coadministered to rats 30 min before the acquisition trial. Some rats received scopolamine alone; they showed much shorter step-through latency (STL) than the control group in the retention test. Nicotine significantly prolonged the decreased STL induced by scopolamine. The effects of nicotine were inhibited by the preadministration of mecamylamine, SCH 23390, and (−)sulpiride, which are nicotinic acetylcholine, D_1, and D_2 receptor antagonists, respectively. These results suggest that nicotine, by activating the nicotinic acetylcholinergic and dopaminergic neuronal systems, ameliorates the impairment of performance in the passive avoidance task induced by a muscarinic acetylcholine receptor blocker.

Nicotine Scopolamine Acetylcholine Dopaminergic neuron SCH 23390 Sulpiride
Learning and memory Passive avoidance task Rats

IN senile dementia of the Alzheimer type (SDAT), learning and memory are associated with dysfunction of the cholinergic neurons (18). Acetylcholine is one of the most important neuronal transmitters. Muscarinic acetylcholine receptors play an important role in learning and memory, as shown by finding that scopolamine, an inhibitor of these receptors, causes amnesia in both rodents and humans (16,21). In SDAT patients, nicotinic acetylcholine receptor is decreased (10). The relationship between nicotine intake and Alzheimer's disease (AD) has been attracting some interest because a recent epidemiological study demonstrated that the risk of AD decreased with the increased number of cigarettes smoked daily (19). Moreover, several reports in animals and humans indicate that nicotine, an agonist of nicotinic acetylcholine receptors, enhances learning and memory (5,11,13,17). However, the precise mechanism responsible for the enhancement of learning and memory by nicotine has not yet been elucidated.

Nicotine has been shown to induce dopamine release from striatal slices (6). In vivo studies using intracerebral voltammetry and dialysis have also shown that nicotine increases dopamine release and dopamine metabolism selectively in the nucleus accumbens (3,9). Dopaminergic neurons also play an important role in learning and memory, as shown by finding that dopamine depletion induced by 6-hydroxydopamine causes impairment of performance in maze learning and conditional discrimination (1,7).

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It is speculated that the role of cholinergic and dopaminergic neurotransmission in learning and memory is not exerted simply via their independent functioning, but, rather, by dynamic interaction between these two systems. The effects of nicotine on learning and memory may depend upon the interaction between cholinergic and dopaminergic neuronal systems. We demonstrated here that nicotine was effective in ameliorating the scopolamine-induced impairment of performance in a passive avoidance task, and also that these effects were blocked by SCH 23390 and (−)sulpiride, D_1- and D_2-selective antagonists, respectively.

METHOD

Animals

Male Kbl Wistar rats (Kitayama Laboratories Co. Ltd., Kyoto, Japan), weighing 280–320 g, were used. They were housed in groups of two or three in a temperature- and light-controlled room (23°C; 12 L : 12 D cycle starting at 0900 h). The rats had free access to food and water.

Step-Through Passive Avoidance Task

The experimental apparatus consisted of two compartments (each 25 × 15 × 15 cm high), one illuminated, and one dark, equipped with a grid floor (14). The two compartments were separated by a guillotine door. In the acquisition trial, each rat was placed in the illuminated compartment; as soon as the rat entered the dark compartment, the door was closed and an inescapable foot shock (3.0 mA, 5 s) was delivered through the grid floor. In the retention test, the rat was again placed in the illuminated compartment, 24 h after the acquisition trial, and the time until it entered the dark compartment was measured as step through-latency (STL). When

TABLE 1

EFFECTS OF NICOTINE, MECAMYLAMINE, SCH 23390, AND SULPIRIDE ON STEP-THROUGH LATENCIES OF THE ACQUISITION TRIAL IN THE PASSIVE AVOIDANCE TASK

Drug			Step-Through Latency(s)
Saline	Saline	Saline	20.93 (11.11–44.47)
Saline	Scopolamine (1.5 mg/kg)	Saline	5.94 (3.18–18.61)
Saline	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	6.42 (3.00–12.76)
Mecamylamine (3 mg/kg)	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	17.09 (2.76–28.69)
Mecamylamine (10 mg/kg)	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	4.27 (1.29–12.98)
Saline	Saline	Saline	18.57 (6.43–30.82)
Saline	Scopolamine (1.5 mg/kg)	Saline	5.02 (2.33–21.58)
Mecamylamine (3 mg/kg)	Scopolamine (1.5 mg/kg)	Saline	6.94 (2.18–15.35)
Mecamylamine (10 mg/kg)	Scopolamine (1.5 mg/kg)	Saline	10.13 (2.80–15.49)
Saline	Saline	Saline	38.15 (19.12–45.84)
Mecamylamine (3 mg/kg)	Saline	Saline	14.22 (8.48–18.59)
Mecamylamine (10 mg/kg)	Saline	Saline	14.72 (2.54–39.53)
Saline	Saline	Saline	20.93 (11.11–44.47)
Saline	Scopolamine (1.5 mg/kg)	Saline	5.94 (3.18–18.61)
Saline	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	6.42 (3.00–12.76)
SCH 23390 (0.05 mg/kg)	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	7.10 (6.00–13.80)
SCH 23390 (0.1 mg/kg)	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	24.00 (5.26–40.12)
Saline	Saline	Saline	18.57 (6.43–30.82)
Saline	Scopolamine (1.5 mg/kg)	Saline	5.02 (2.33–21.58)
SCH 23390 (0.05 mg/kg)	Scopolamine (1.5 mg/kg)	Saline	7.53 (2.84–14.07)
SCH 23390 (0.1 mg/kg)	Scopolamine (1.5 mg/kg)	Saline	7.41 (2.97–36.55)
Saline	Saline	Saline	38.15 (19.12–45.84)
SCH 23390 (0.05 mg/kg)	Saline	Saline	5.66 (4.23–16.41)
SCH 23390 (0.1 mg/kg)	Saline	Saline	18.79 (2.80–45.23)
Saline	Saline	Saline	20.93 (11.11–44.47)
Saline	Scopolamine (1.5 mg/kg)	Saline	5.94 (3.18–18.61)
Saline	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	6.42 (3.00–12.76)
Sulpiride (5 mg/kg)	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	9.95 (3.00–20.40)
Sulpiride (10 mg/kg)	Scopolamine (1.5 mg/kg)	Nicotine (0.3 mg/kg)	12.08 (7.44–38.03)
Saline	Saline	Saline	18.57 (6.43–30.82)
Saline	Scopolamine (1.5 mg/kg)	Saline	5.02 (2.33–21.58)
Sulpiride (5 mg/kg)	Scopolamine (1.5 mg/kg)	Saline	11.12 (2.44–16.68)
Sulpiride (10 mg/kg)	Scopolamine (1.5 mg/kg)	Saline	10.63 (2.76–28.72)
Saline	Saline	Saline	38.15 (19.12–45.84)
Sulpiride (5 mg/kg)	Saline	Saline	6.72 (4.37–17.67)
Sulpiride (10 mg/kg)	Saline	Saline	6.66 (3.04–27.96)

Nicotine and scopolamine were coadministered 30 min before the acquisition trial. Mecamylamine, SCH 23390, and sulpiride were injected 5 min before the administration of nicotine and scopolamine.

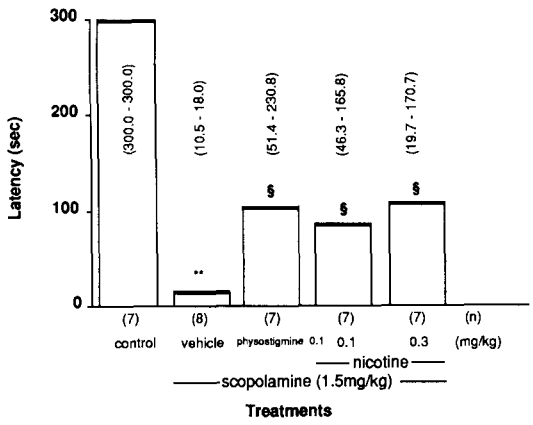

FIG. 1. Effects of nicotine on performance of the passive avoidance task in scopolamine-treated rats. Each value for step-through latency shows median (column) and interquartile range (numbers). Numbers in parentheses denote numbers of animal used. Significance levels: $**p < 0.01$ vs. control, $\S p < 0.05$ vs. vehicle group.

the rat did not enter for at least 300 s, a score of 300 s was assigned.

Drug Administration

All drugs were dissolved in saline and injected IP and SC, in a volume of 2 ml/kg body weight. (−)Nicotine (free base; 0.1 and 0.3 mg/kg, IP; Sigma, St. Louis, MO) and scopolamine hydrobromide (1.5 mg/kg, SC; Katayama, Tokyo, Japan) were coadministered 30 min before the acquisition trial. Mecamylamine (3 and 10 mg/kg, IP; Sigma), SCH 23390 (0.05 and 0.1 mg/kg, IP; Research Biochemical Inc. Massachusetts), and *S*-(−)sulpiride (5 and 10 mg/kg, IP; Research Biochemical Inc.) were injected 5 min before the administration of nicotine and scopolamine. Physostigmine hemisulfate, a positive control drug (0.1 mg/kg, IP; Sigma), was injected 15 min before the administration of nicotine and scopolamine. Control animals received an equivalent volume of saline, and one group of animals received scopolamine only (1.5 mg/kg).

Statistics

Statistical differences in STL between the drug-treated and control groups were first analyzed using the Kruskal-Wallis test and then the two-tailed Mann-Whitney *U*-test. Values of $p < 0.05$ were regarded as significant.

RESULTS

STL in the acquisition trial and general behavior were not changed by treatment with scopolamine, nicotine, mecamylamine, SCH 23390, and sulpiride. In the acquisition trial, the drugs, at the doses used in this study, had no significant effects on the STL (Table 1). There were no differences in the pain thresholds for electric foot shock (i.e., flinch, vocalization, and jump thresholds) among controls and drug-treated groups (data not shown).

Effects of Nicotine on Performance in the Passive Avoidance Task in Scopolamine-Treated Rats

In the retention trial, control rats showed a very long STL; in the scopolamine treated-rats, the STL was significantly less ($p < 0.01$). Physostigmine (0.1 mg/kg)- and nicotine (0.1 and 0.3 mg/kg)-treated rats showed significantly longer STL than that shown in the group treated with scopolamine alone ($p < 0.05$) (Fig. 1). Nicotine itself did not show any effect on the performance in the passive avoidance task (data not shown).

Antagonistic Effects of Mecamylamine on Nicotine-Induced Effects in Scopolamine-Treated Rats

Preadministration of mecamylamine (5 min before scopolamine and nicotine administration) shortened the increased STL induced by nicotine in scopolamine treated-rats ($p <$

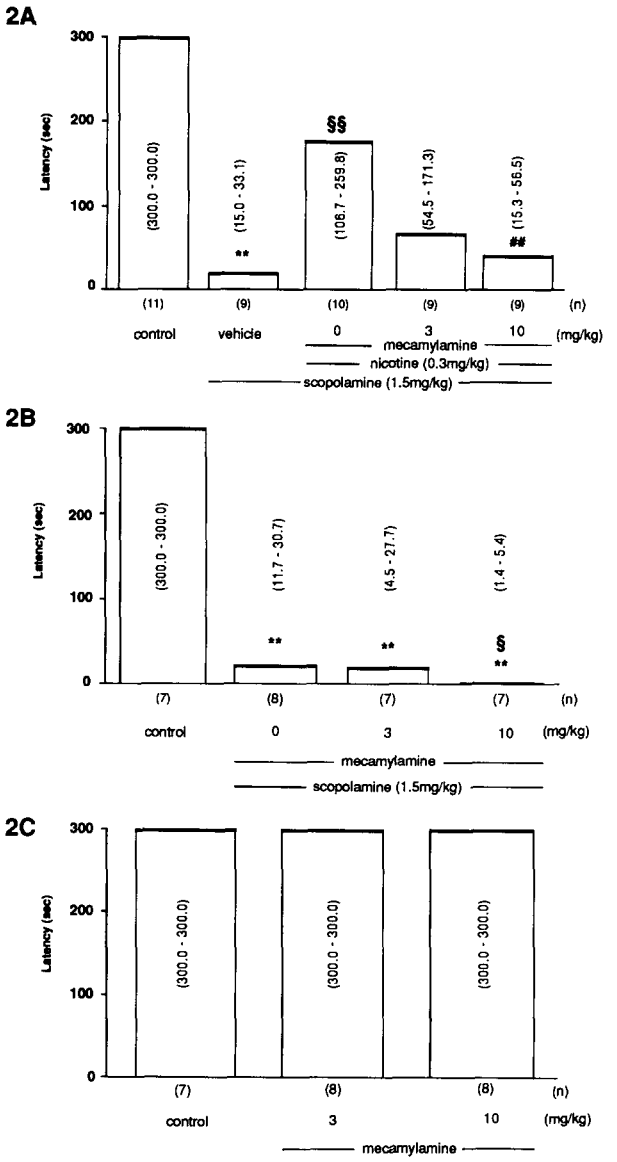

FIG. 2. Effects of mecamylamine on performance of the passive avoidance task in (A) scopolamine + nicotine-treated, (B) scopolamine-treated, and (C) normal rats. Each value for step-through latency shows median (column) and interquartile range (numbers). Numbers in parentheses denote numbers of animal used. Significance levels: $**p < 0.01$ vs. control, $\S p < 0.05$, $\S\S p < 0.01$ vs. vehicle, $\#\# p < 0.01$ vs. scopolamine + nicotine-treated group.

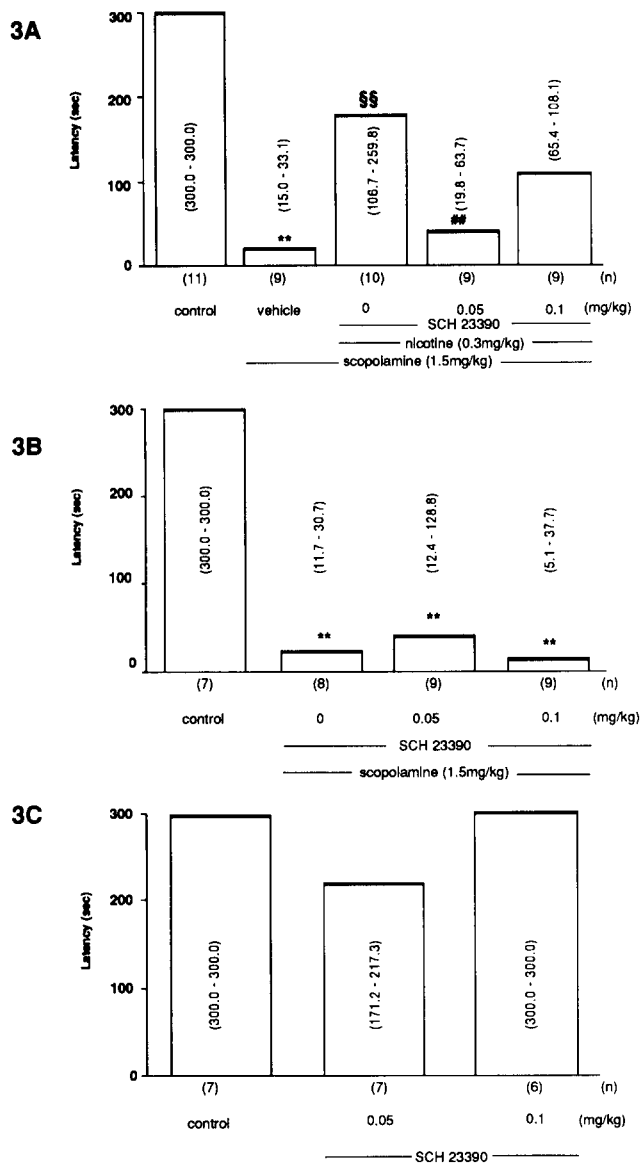

FIG. 3. Effects of SCH 23390 on performance of the passive avoidance task in (A) scopolamine + nicotine-treated, (B) scopolamine-treated, and (C) normal rats. Each value for step-through latency shows median (column) and interquartile range (numbers). Numbers in parentheses denote numbers of animal used. Significance levels: $^{**}p < 0.01$ vs. control, §§$p < 0.01$ vs. vehicle, ##$p < 0.01$ vs. scopolamine + nicotine-treated group.

0.01); these effects were dose dependent (Fig. 2A). Mecamylamine exacerbated the impairment of performance in the passive avoidance task in scopolamine-treated rats (Fig. 2B), but mecamylamine alone, at the doses used, failed to change this performance (Fig. 2C).

Antagonistic Effects of SCH 23390 on Nicotine-Induced Effects in Scopolamine-Treated Rats

Preadministration of SCH 23390 (5 min before scopolamine and nicotine administration) shortened the increased STL induced by nicotine in scopolamine-treated rats ($p <$ 0.01). However, these effects were not dose dependent (Fig. 3A). SCH 23390, at the doses used, did not affect the impairment of performance in scopolamine-treated rats or the performance in normal rats in the passive avoidance task (Fig. 3B,C).

Antagonistic Effects of Sulpiride on Nicotine-Induced Effects in Scopolamine-Treated Rats

As shown in Fig. 4A, preadministration of sulpiride (5 min before scopolamine and nicotine administration) shortened

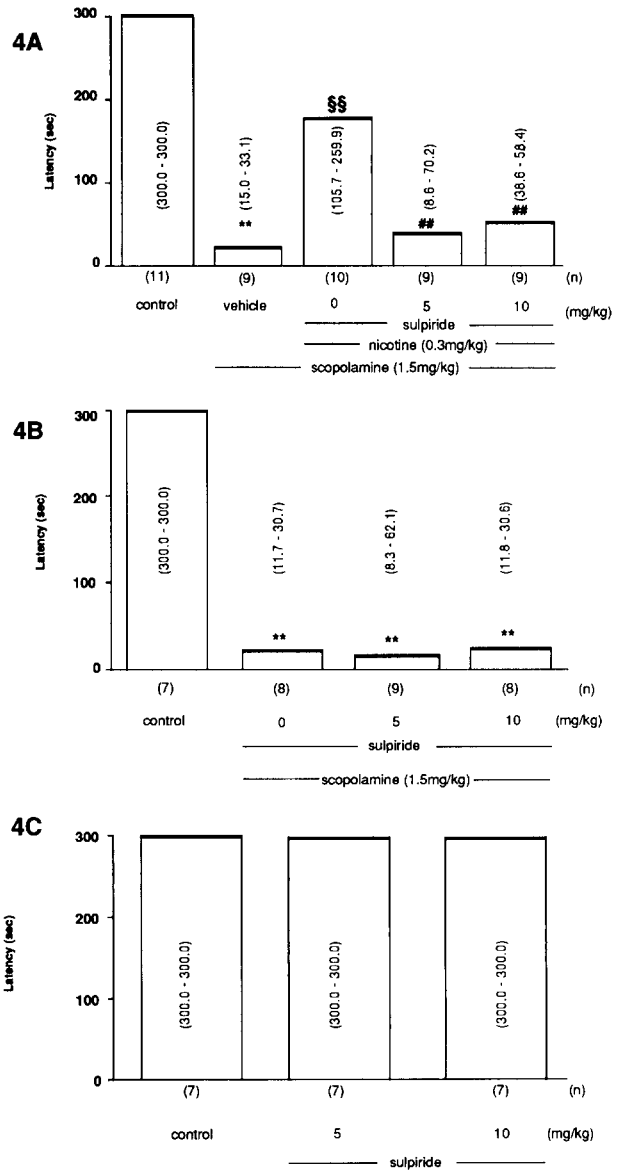

FIG. 4. Effects of sulpiride on performance of the passive avoidance task in (A) scopolamine + nicotine-treated, (B) scopolamine-treated, and (C) normal rats. Each value for step-through latency shows median (column) and interquartile range (numbers). Figures in parentheses denote numbers of animal used. Significance levels: $^{**}p < 0.01$ vs. control, §§$p < 0.01$ vs. vehicle, ##$p < 0.01$ vs. scopolamine + nicotine-treated group.

the increased STL induced by nicotine in scopolamine-treated rats ($p < 0.01$). At the doses used, sulpiride, like SCH 23390, did not affect the impairment of performance in scopolamine-treated rats on performance in normal rats in the passive avoidance task (Fig. 4B,C).

DISCUSSION

Several studies have demonstrated that nicotine has cognitive effects and increases learning ability in both experimental animals and humans (5,13,17,20). The present study confirmed that nicotine had antiamnesic effects in scopolamine-treated rats. Mecamylamine blocked the effects of nicotine in the scopolamine-induced impairment of performance in the passive avoidance task (Fig. 2A). Because scopolamine is an antagonist of muscarinic acetylcholine receptors and nicotine binds only nicotinic acetylcholine receptors, we speculate that nicotine might increase the extracellular level of acetylcholine in the brain, and that this increased acetylcholine might bind to muscarinic acetylcholine receptors, competing with scopolamine. Nicotine could then antagonize the effect of scopolamine in the performance of the passive avoidance task. Our speculation is supported by the findings of Nordberg et al. (15), who reported that nicotine increased acetylcholine release in vivo. Short-term administration of nicotine not only increases acetylcholine in vivo (15), but also increases in vivo extracellular levels of dopamine (3). Here, we found that the effects exerted by nicotine on scopolamine-induced impairment of performance were inhibited by dopamine receptor antagonists. Taken together, these findings indicate that the increases in dopamine, brought about by the action of nicotine, might bind dopamine receptors; the dopaminergic neuronal system might then stimulate the release of acetylcholine, an agent that could thus be responsible for the effects exerted by nicotine on the scopolamine-induced impairment of performance.

We have already demonstrated that SCH 23390 attenuates the acquisition of latent learning and suppresses exploratory behavior in the water finding test in mice (8). Further, it has been shown that pimozide, a dopamine D_2 receptor antagonist, enhances memory acquisition (8). These results suggest that the blocking of two dopamine receptor subtypes could possibly have functionally opposite effects on the acquisition stage of memory. Under our experimental conditions here, neither D_1 nor D_2 dopamine antagonists affected the performance of the passive avoidance task in normal rats (Figs. 3C and 4C). However, both these dopamine antagonists inhibited the effects of nicotine on scopolamine-induced impairment of performance of this task (Figs. 3A and 4A). Thus, in the context of these experimental conditions, both dopamine receptor subtypes played important roles in the mechanism of action of nicotine.

SCH 23390 did not have dose-dependent effects. This agent has 800 times higher affinity for D_1 than D_2 receptors, and selectively antagonizes the behavioral changes elicited by D_1 agonists (4). It represents a very useful tool, not only for gaining better understanding of the pharmacological relevance of the different subtypes of dopamine receptors but also for investigations of the importance of D_1 and D_2 sites in schizophrenia. We therefore used SCH 23390 as a D_1 receptor antagonist in this study. However, Bischoff et al. (2) have reported that SCH 23390 also binds with high affinity to serotonin 5-HT_2 receptors as an antagonist in rat brain (2). Although SCH 23390 (0.05 mg/kg) was effective on antagonistic actions of nicotine, SCH 23390 (0.1 mg/kg) was not. SCH 23390 (0.1 mg/kg) may affect serotonergic neurons, because the 5-HT_2 receptors are related to the learning impairment (12). Further study should be done to clarify this idea.

In conclusion, we found that nicotine, by activating the nicotinic acetylcholine receptors, possibly through the dopaminergic system, ameliorated the impairment of performance in a passive avoidance task induced by a muscarinic acetylcholine receptor blocker.

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