# ROLE OF CHOLINERGIC SYSTEM ON THE CONSTRUCTION OF MEMORY AND ITS INTERACTION WITH DOPAMINERGIC SYSTEM

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**Abstract-** The central cholinergic system has been associated with cognitive function and memory and acetylcholine plays an important role during the early stages of memory consolidation. In this study, mice were trained with one way active avoidance procedure. Different doses of arecoline and physostigmine, with and without scopolamine, were administrated at pre-training, post-training and retrieval phases. Avoidance retention was tested at 4, 8, 12, 16 and 24 hours after training. Results showed that muscarinic agonist arecoline can potentiate memory in post training and retrieval phases and reversible cholinesterase inhibitor physostigmine potentiated memory only in retrieval phase. Scopolamine disrupted acetylcholine potentiation only in retrieval phase. In the second part of this study, the effect of dopaminergic system was investigated. Low dose of apomorphine and $D_2$ agonist bromocriptine potentiated memory when administered in immediate post-training phase, and $D_2$ antagonist sulpiride impaired memory. When the cholinergic system was blocked by scopolamine in immediate post-training phase, apomorphine and bromocriptine potentiated memory and sulpiride impaired it. In conclusion, these results suggest that cholinergic system plays a critical role in retrieval phase. No interaction was found between cholinergic and dopaminergic systems in the post-training phase.

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**Key words:** Muscarinic receptor, consolidation**,** retrieval, active–avoidance, apomorphine, sulpiride

## INTRODUCTION

The role of cholinergic system in learning and memory was suggested for the first time by Carew *et al.* in 1973 (1). They demonstrated that hyoscine, a muscarinic receptor blocker, impairs cognition and memory (2).

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The hippocampus which plays an important role in learning and memory receives abundant cholinergic innervation from cholinergic neurons in basal forebrain nucleus (3, 4). Muscarinic cholinergic receptors (mChRs) are critical components in modulation of memory consolidation. Memory can also be affected by post-training activation of mChRs in the hippocampus, striatum, cortex and basolateral amygdale. mChRs activation is also involved in the storage of information in these brain regions (5-7). Immediate post-training intraperitoneal administration of the centrally acting

physostigmine showed that atropine, but not methylatropine, prevents the enhancement of physostigmine effect (8, 9).

Cholinergic system is also involved in Alzheimer disease pathophysiology. The degenerative changes in the basal forebrain are paralleled by the concomitant reduction of presynaptic cholinergic markers (synthesis, storage and release) of acetylcholine in the neocortex and hippocampus. Cognitive dysfunction in rat induced by ethanol treatment can be ameliorated by the pharmacological manipulation of central cholinergic neurotransmission with physostigmine, arecoline or nicotine (6).

The dopaminergic system plays a pivotal role in short-term (10) and long-term memory (11). Improvement in learning and memory by administration of dopamine agonists was demonstrated by Seeman in 1980 (12). Low and high doses of apomorphine as $D_1/D_2$ agonist respectively improved and impaired memory in the active–avoidance method and low dose of sulpiride ($D_2$ antagonist) impaired memory using single–trial passive–avoidance method (13). The stimulation of post-synaptic $D_2$ dopamine receptors impairs retrieval while activation of pre-synaptic $D_2$ or post-synaptic $D_1$ receptors improves memory retrieval (14). Interactive effect of $D_1$ and $D_2$ agonists with scopolamine on radial–maze performance represents critical role of two systems in memory (15).

Study of functions of different neurotransmitters in different phases of memory can help us prevent and threat deficits in learning and memory in Alzheimer disease, mental retardation and amnestic diseases. In this research, we studied the role of cholinergic system in three separate phases of memory and interactive effect of cholinergic with dopaminergic system only in post-training phase.

# MATERIALS AND METHODS

## Animals

Male albino mice weighing 20–25 gr were used. The animals were individually housed in a temperature controlled (20-30$^{\circ}$ C) environment with a 12-h light/dark cycle. Each animal was used only once and attention was paid to the ethical guidelines for investigation of experimental pain in conscious animals.

## Apparatus

Animals were trained in an avoidance apparatus consisting of two compartments, an aluminum V-shaped trough and a black safe chamber of plexiglass, 5×5×4 inch in size, separated by a gutine door.

Training was started by placing the animals in the V-shaped trough facing away from the door. After 5 s a conditioned stimulus (CS; flashing light 0.5 s on; 0.5 s off) was activated and the door raised, thus starting the latency timer. After 10 seconds the unconditioned stimulus (UCS, 0.6 mA electric shock) was turned on and when the animals had crossed into the safe chamber, both CS and UCS were terminated (16).

## Behavioral testing

One way active–avoidance method was used to assess avoidance retention. Mice were trained to a relatively weak criterion (3/5 avoidances) that showed relatively good retention 24 hour following the training. Mice were placed in a V-shaped trough and the same procedure employed during training was used, except for those animals that did not receive UCS. Mice failing to cross into the safe chamber within 60 s were given the maximum latencies (60 s) in five trials, each separated by a 30 s inter-trial interval. The mean latencies of the five trials were expressed as a value for each animal (14).

Four groups of mice were trained to a criterion of 3/5 avoidances and were tested 4, 8, 16 and 24 h after training. Non-shocked group was trained without UCS and the last group was not trained at all (untrained group).

## Drugs

The following drugs were used: arecoline (Nutritional Biochemicals Corporation, Cleveland Ohio USA), physostigmine (Sigma, USA), Scopolamine, aminoxide hydrobromide (sigma, USA), apomorphine hydrochloride (sigma, USA), bromocriptine (Ciba, Switzerland) and sulpiride (Sigma USA).

All drugs except for bromocriptine and sulpiride were dissolved in distilled water: arecoline (0.1

mg/kg), physostigmine (0/02 mg/kg), scopolamine (1, 2.5, 5 mg/kg) and atropine (5 mg/kg). Bromocriptine (4 mg/kg) was dissolved in water by using crystalline tartaric acid and one drop of alcohol and sulpiride (20 mg/kg) was dissolved in a drop of acetic acid and then diluted with distilled water. All the drugs were injected 30 min before testing except bromocriptine and sulpiride which were administrated 90 min before testing. The drugs were injected intraperitoneally (IP), except apomorphine (0.06 mg/kg) that was injected subcutaneously (SC). The control group received saline.

### Statistical analysis

SPSS 12 for window was used to perform statistical analysis. Analysis of variance (ANOVA) followed by Newman-Keuls tests were used to evaluate to significance of the results obtained.

## RESULTS

### Spontaneous memory loss of active avoidance learning

Analysis of data by two–way ANOVA indicated that there was a significant difference between non-shocked group, untrained group and trained group ($P < 0.01$, $P < 0.001$), but non-shocked group did not show any difference from the untrained group (Fig. 1).

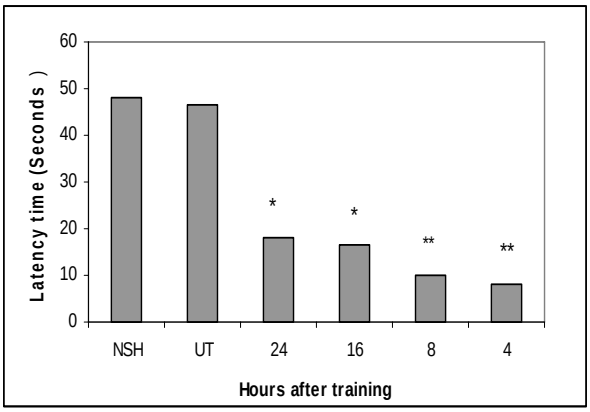


**Fig. 1**. Time related memory loss in trained, non-shocked (NS) and untrained (UT) mice. Trained animals were tested 4, 8, 16 and 24 h later and the mean ± SEM of each group of animals was recorded and compared with NS group. No difference was found between NS and UT groups (* $P < 0.01$, ** $P < 0.001$). There were 7 mice in each group.

### Effect of arecoline and physostigmine in the presence and absence of cholinergic antagonist on trained mice

There was a significant difference between groups of animals which had been treated with saline, arecoline, physostigmine and arecoline plus scopolamine. Low dose of arecoline (0.1 mg/kg) in immediate post-training and in retrieval phases improved the memory ($P < 0.05$ and $P < 0.001$, respectively). When the animals were treated with different doses of physostigmine, only in retrieval phase low-dose physostigmine (0.02 mg/kg) caused significant memory improvement ($P < 0.001$) (Fig. 2). Administration of scopolamine as the antagonist of the cholinergic system in different doses (1, 2.5, 5 mg/kg) showed that only low-dose (1 mg/kg) of this drug in pre-retention phase had no significant effect and the other doses in three phases, especially in immediate post-training phase, had a very significant effect ($P < 0.001$) (Fig. 3). In the presence of arecoline (0.1 mg/kg) and scopolamine (5 mg/kg), scopolamine (5 mg/kg) only in retrieval phase did not antagonize arecoline, and latency-time was short (Fig. 3) (Table 1).

Intraperitoneal administration of scopolamine in doses of 2.5 and 5 mg/kg in three phases had a significant effect. Administration of 1 mg/kg scopolamine had no significant effect in retrieval phase. Coadministration of arecoline (0.1 mg/kg) and scopolamine (5 mg/kg) was examined in immediat post-training and pre-retrieval phases.

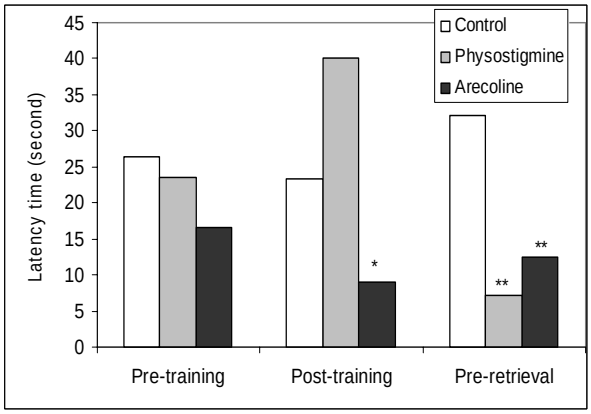


**Fig. 2**. Effect of arecoline (0.1 mg/kg) and physostigmine (0.02 mg/kg) in 3 phases (pre/post/pre-ret). Arecoline in immediate post-training and in retrieval phases improved the memory. When the animals were treated with physostigmine, only in retrieval phase low-dose physostigmine caused significant memory improvement. ** $P < 0.001$, * $P < 0.05$.

**Table 1.** Effects of cholinergic agonists and antagonists alone and in combination in three phases of memory in mice*

| | Latency time (sec) | | |
|---|---|---|---|
| **Drug** | **Pre-test** | **Post-test** | **Pre-retrieval** |
| Saline | 26.41 ± 6.4 | 23.4 ± 4.8 | 32.1 ± 2.9 |
| Arecoline (0.1mg/kg) | 16.5 ± 3.8 | 9.08 ± 1.17 | 12.5 ± 3.37 |
| Physostigmine (0.02 mg/kg) | 23 ± 6.41 | 40.9 ± 9.8 | 7.11 ± 0.28 |
| Scopolamine (1 mg/kg) | 38.45 ± 3.9 | 45.61 ± 5.12 | 42.7 ± 5.7 |
| Scopolamine (2.5 mg/kg) | 45.2 ± 6.7 | 43.6 ± 2.2 | 44.63 ± 6.9 |
| Scopolamine (5 mg/kg) | 48.66 ± 6.14 | 45.6 ± 3.17 | 49.45 ± 3.15 |
| Arecoline (0.1mg/kg) + scopolamine (5mg/kg) | --- | 20.05 ± 5.1 | 10.30 ± 2.13 |

*Data are given as mean ± SEM.

Arecoline in pre-training phase had no significant effect and in this combination. Immediate post-training scopolamine (5 mg/kg) blocked arecoline (0.1 mg/kg), but the change was not significant (Fig. 4).In pre-retention phase, scopolamine (5 mg/kg) could not block arecoline (0.1 mg/kg) ($P < 0.001$), implying the critical role of the muscarinic receptor in retrieval phase (Fig. 5) (Table 1).

## Effect of apomorphine, bromocriptine and sulpiride

Results are shown in Fig. 6. Subcutaneous administration of apomorphine in 3 phases produced significant effect in immediate post-training and retrieval phases ($P < 0.05$). Administration of bromocriptine (4 mg/kg) and sulpiride (20 mg/kg) in immediate post-training phase improved ($P < 0.01$) and impaired ($P < 0.025$) memory, respectively. Results of coadministration of apomorphine, bromocriptine, sulpiride and scopolamine in immediate post-training phase are shown in Fig. 7. Administration of apomorphine (0.06 mg/kg) and scopolamine (5 mg/kg) in post training phase improved memory compared to saline treated trained mice and scopolamine could not block these improvements. In immediate post-training phase, a combination of apomorphine (0.06 mg/kg) and scopolamine (5 mg/kg) caused memory potentiation. Combinations of apomorphine (0.06 mg/kg), sulpiride (20 mg/kg) and scopolamine (5 mg/kg) caused memory destruction. Combination of bromocriptine (4 mg/kg), sulpiride (20 mg/kg) and scopolamine (5 mg/kg) impaired memory (Table 2).

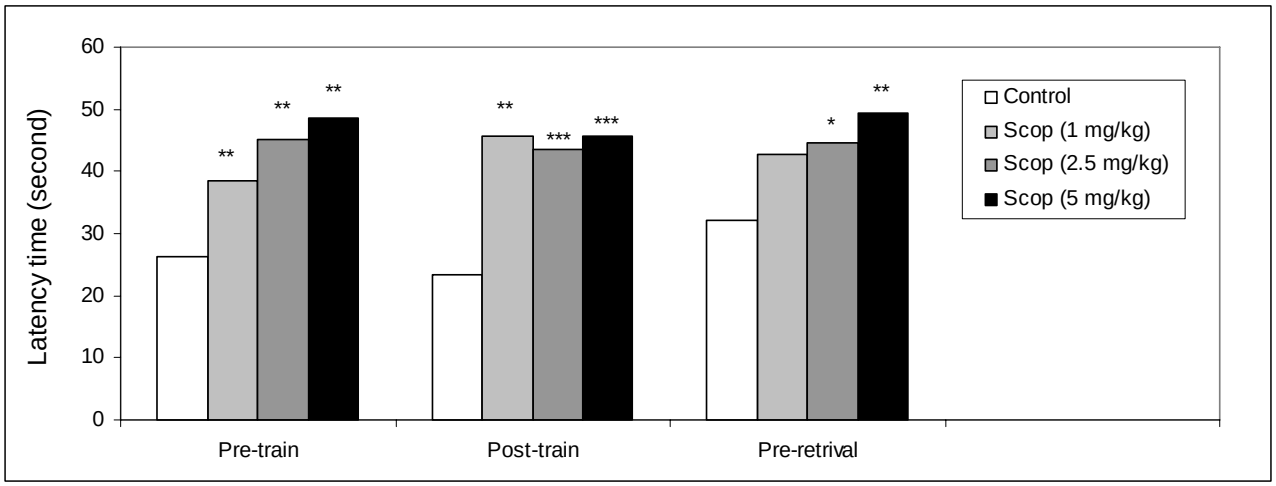


**Fig. 3**: Effect of Scopolamine (1, 2.5, 5 mg/kg) in three phases (pre/post/pre-ret.) *** $P < 0.005$, ** $P < 0.01$, * $P < 0.025$.

**Table 2.** Effects of dopaminergic agonists and antagonists in three phases of memory in mice*

| | Latency time (second) | | |
|---|---|---|---|
| **Drug** | **Pre-train** | **Post-train** | **Pre-retrieval** |
| Saline | 26.41 ± 4.6 | 23.4 ± 6.8 | 32.1 ± 2.9 |
| Apomorphine (0.06 mg/kg) | 26.6 ± 4.09 | 14.56 ± 4.46* | 16.2 ± 5.52 |
| Bromocriptine (4 mg/kg) | ----- | 12.4 ± 1.8*** | ----- |
| Sulpiride (20 mg/kg) | ----- | 41 ± 2.32** | ----- |
| Apomorphine (0.06 mg/kg) + scopolamine (5 mg/kg) | ----- | 8.9 ± 0.80** | ----- |
| Apomorphine (0.06 mg/kg) + scopolamine (5 mg/kg) + sulpiride (20 mg/kg) | ----- | 48 ± 3.70** | ------ |
| Bromocriptine (4 mg/kg) + scopolamine (5 mg/kg) + sulpiride (20 mg/kg) | ----- | 44.9 ± 2.98* | ------ |

* Data are given as mean ± SEM. *** $P < 0.005$, ** $P < 0.01$, * $P < 0.025$.

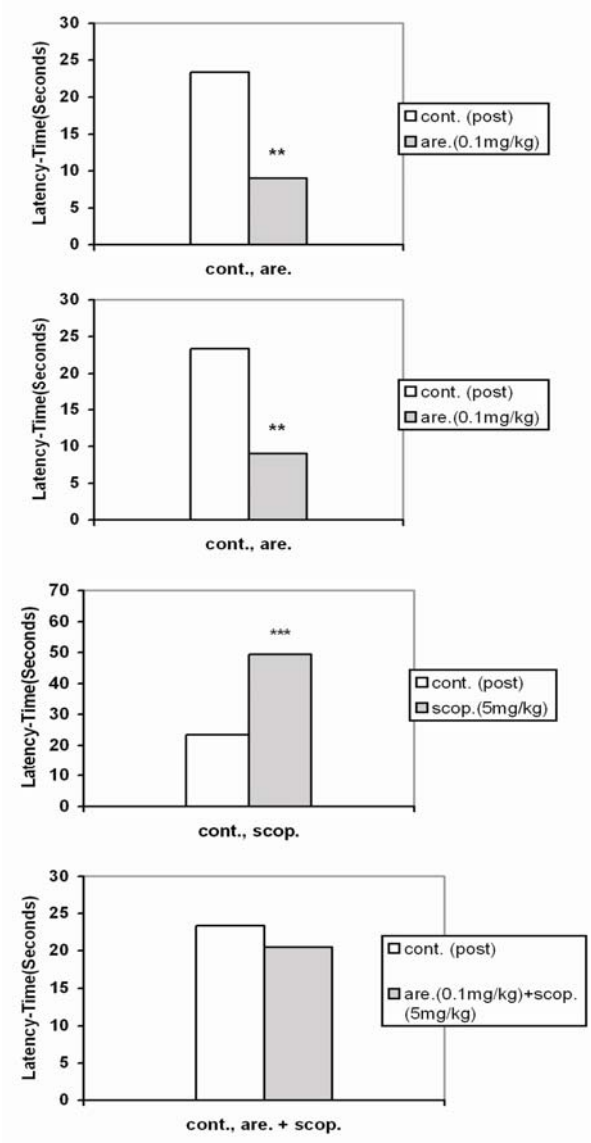


**Fig. 4**: Effect of arecoline (0.1 mg/kg) and scopolamine (5 mg/kg) and its coadministration in post training phase (** $P < 0.05$, *** $P < 0.01$).

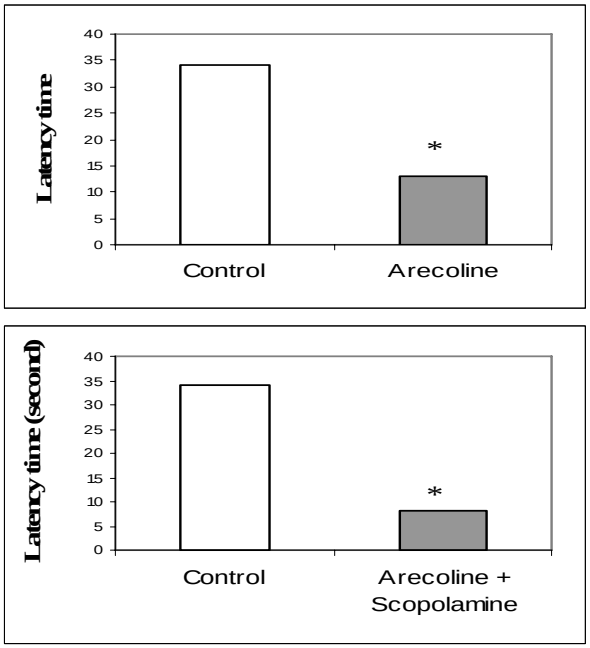


**Fig. 5**: Effect of arecoline (0.1 mg/kg) and its coadministration with scopolamine (5 mg/kg) in retrieval phase (* $P < 0.001$).

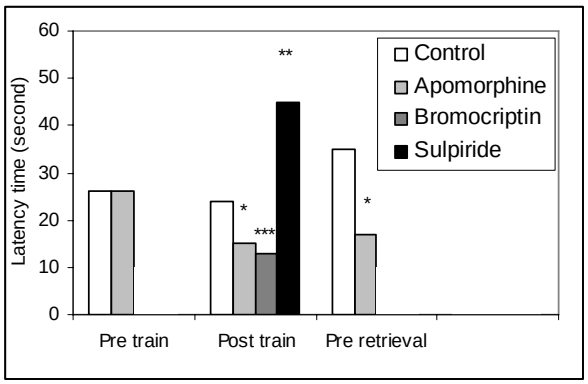


**Fig. 6**: Effect of apomorphine (0.06 mg/kg) in 3 phases (pre/post/pre-ret.), with bromocriptine and sulpiride in post-train phase (* $P < 0.05$, ** $P < 0.025$, *** $P < 0.01$).

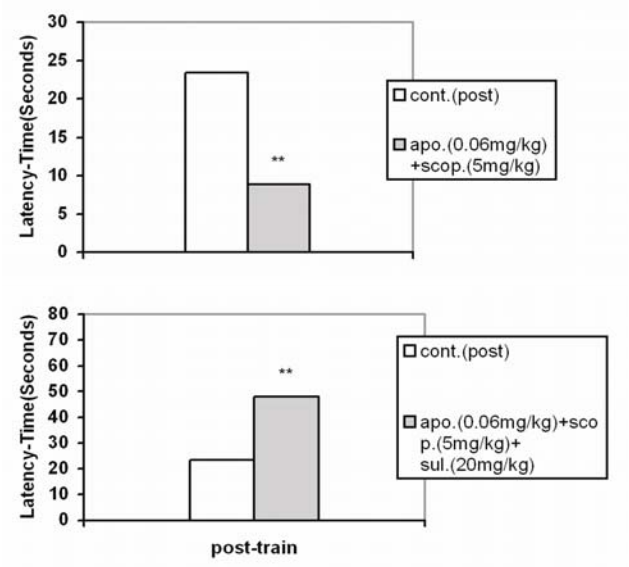


**Fig. 7**: Effect of coadministration of apo. (0.06 mg/kg) + scop. (5 mg/kg), apo. (0.06 mg/kg) + sulpiride (20mg/kg) + scop. (5 mg/kg) and bromocriptine (4 mg/kg) + sulpiride (20 mg/kg) + scop. (5 mg/kg) in post-train ($P < 0.025$).

## DISCUSSION

Experimental evidence has shown that the central cholinergic system is involved integrally in cognitive function (17-27) and drugs affecting this system have been shown either to enhance or to hinder performance in tests of learning and memory. Acetylcholinesterase inhibitor physostigmine is classified among the putative cholinomimetic cognition enhancers (21, 22). It facilitates learning in laboratory animals (19), but only in some experimental tasks and in a narrow range of doses (23). The present study showed that a low dose (0.02 mg/kg) of physostigmine administered 30 min before retention testing, improved Shuttle-Box avoidance acquisition in mice and potentiated memory only in retrieval phase (18, 19). Different doses of the centrally acting cholinergic antagonist scopolamine (1, 2.5, 5 mg/kg) when administered before pre/post-training and before retention testing impaired memory in a dose-dependent manner. Immediate post-training scopolamine at doses of 2.5 and 5 mg/kg had a very significant effect, thus in this phase, scopolamine was a powerful blocker. Coadministration of arecoline (0.1 mg/kg) and scopolamine (5 mg/kg) enhanced memory only in retrieval testing which indicates the critical action of muscarinic receptor of cholinergic system on retrieval phase (28, 29).

Anatomical sites and evidence from lesion studies suggest that pathways derived from the basal nuclear complex of the forebrain are critical for the cholinergic modulation of learning and memory. Most of the studies have focused on the septohippocampal projection (30, 31). The integrity and functionality of mChRs are fundamental in the modulation of memory process (32). The striatum is another site that contains the highest concentration of acetylcholine in the brain. This structure expresses two different forms of synaptic plasticity, long term depression (LTD) and long-term potentiation (LTP), which may contribute to the storage of motor skills and some cognitive processes (33). Current evidence appoints a central role to cholinergic interneurons in modulating striatal function, because LTP of synaptic transmission has been reported to occur in these neurons that have critical role in motor learning and motor control in songbirds for song learning (34, 35).

Results of the second part of this study showed that low-dose of $D_1/D_2$ agonist apomorphine (0.06 mg/kg) in two phases, immediate post-training and retrieval, could potentiate memory. Study on memory consolidation by using a passive avoidance task in the day-old chick showed that dopaminergic system is involved in the later stages of the memory formation process (36). Administration of the $D_2$ receptor agonist bromocriptine (4 mg/kg) in mice improved memory in immediate post-training phase (37, 38) and sulpiride (20 mg/kg) antagonized the improvement induced by bromocriptine that may act on pre or post synaptic dopamine receptors, respectively. It has been shown that activation of post-synaptic $D_2$ receptors impairs retrieval in trained mice (14) and in healthy volunteers (39).

The cholinergic-dopaminergic link and modulatory role of apomorphine have been showed earlier by Baratti (40) and McGurk (41). These researches reported this effect by radial arm maze with a balance between two systems. The neuronal circuits for this interaction show that dopaminergic system has been activated by cholinergic system and memory loss in Alzheimer disease is due to malfunction of cholinergic system, that causes a

decrease in dopaminergic system activity (13). This effect is most likely mediated via impairment of interneurons in area CA3 of rat hippocampus by activation of $D_1$-like dopamine receptors (42). In memory retrieval phase, this interaction is strongly modulated by dopamine $D_1$ and muscarinic cholinergic receptors (43, 44) and in post-training phase intrabasolateral amygdale, activation of both $D_1$ and $D_2$ receptors and concurrent activation of cholinergic system is involved (45).

Our results indicate that mChRs are involved in immediate post-training and retrieval phases and this system is critical for retrieval phase. Interaction with dopaminergic system in immediate post-training phase showed that action of $D_2$ receptors is independent of cholinergic system.

## Conflict of interests

The authors declare that they have no competing interests.

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