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MK-801-induced learning impairments reversed by physostigmine and nicotine in zebrafish

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Previous studies have demonstrated that *N*-methyl-D-aspartate (NMDA) receptors and acetylcholine receptors are related to learning and memory in rat and mice. In this study, we examined the effects of MK-801, a non-competitive NMDA receptor antagonist, on learning and memory in zebrafish using a passive avoidance test. We further tested whether or not nicotine, a nicotinic acetylcholine receptor agonist, and physostigmine, an acetylcholinesterase inhibitor, reverse the effects of MK-801. Crossing time was increased significantly in the training and test sessions for the controls. When 20 μM MK-801 was administered prior to the training session, the crossing time did not increase in either session. The MK-801-induced learning deficit was rescued by pretreatment with 20 μM physostigmine, and crossing time was increased in the training and test sessions compared to the MK-801-treated zebrafish. Further, the MK-801-induced learning deficit was prevented by pretreatment with 20 μM nicotine, and crossing time was increased in the training session but not in the test session. These results show that MK-801 induced a learning deficit in zebrafish that was prevented by pretreatment with nicotine and physostigmine.

Keywords: zebrafish; MK-801; physostigmine; nicotine; avoidance response

Introduction

NMDA (*N*-methyl-D-aspartic acid) receptor antagonists are known to induce impairments in learning and memory by affecting synaptic plasticity including long-term potentiation. For example, MK-801, a non-competitive NMDA receptor antagonist, impairs conditional discrimination learning and T-maze performance in rats (Murray and Ridley 1997; Watson and Stanton 2009b). It also has been shown to prevent the expression and extinction of conditioned fear (Orsini and Maren 2009). Pre-training administration of ketamine (100 mg/kg), a non-competitive NMDA receptor antagonist, impairs both spatial and non-spatial recognition memory in object location and recognition tasks in rats (Pitsikas and Boultadakis 2009). In addition to non-competitive antagonists, intraseptal administration of DL-AP5, a competitive NMDA receptor antagonist, suppresses spatial and emotional learning in rats (Elvander-Tottie et al. 2006).

The cholinergic system is also critical to the learning and memory abilities of the brain. Anticholinergic drugs such as scopolamine and atropine have been shown to impair learning and memory in rodents during various behavioral tasks, including the passive avoidance and Morris water maze tests (Boccia et al. 2003; De-Mello and Carobrez 2002; Kwon et al. 2009). Contrarily, acetylcholinesterase inhibitors increase acetylcholine levels in the synaptic cleft and enhance the availability of cholinergic transmission, which improves learning and memory deficits. Physostigmine, an acetylcholinesterase inhibitor, has been shown to reverse memory deficits in a transgenic mouse model of Alzheimer's disease (Dong et al. 2005). Acute and chronic nicotine treatment also improves performance of different hippocampus-dependent tasks such as the Morris water maze and the radial arm maze, and contextual fear conditioning (Kenney and Gould 2008). Nicotinic acetylcholine receptors are known to be required for the rescue of scopolamine-induced memory deficits by cholinesterase inhibitor for the eight-arm radial maze and hippocampal theta activity in rats (Masuoka and Kamei 2009).

Our previous study demonstrated that long-term potentiation induced by a high dose of KCl is blocked by AP5 in isolated zebrafish brain (Nam et al. 2004). Physostigmine also generates spontaneous discharges in the adult and larval brains of zebrafish (Park et al. 2008). From a behavioral aspect, MK-801 prevents memory formation in zebrafish when applied after a one-trial avoidance training session in an inhibitory avoidance test (Blank et al. 2009). It also induces impairment of spatial memory of spatial maze cues in goldfish (Gómez et al. 2006). Nicotine at low doses improves memory formation during three-chamber delayed spatial alternation in zebrafish, but impairs memory at high doses (Levin and Chen 2004). In addition to these studies finding that glutamatergic and cholinergic transmission systems play roles in learning

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and memory in zebrafish, it has been reported that scopolamine-induced learning deficits can be prevented by pretreatment with physostigmine in passive avoidance tasks.

In this study, we determined whether MK-801, a NMDA receptor antagonist, impairs the acquisition of passive avoidance response in adult zebrafish as well as whether physostigmine and nicotine, which are an acetylcholinesterase inhibitor and nicotinic acetylcholine receptor agonist, respectively, antagonize the effect of MK-801 on learning and memory using a passive avoidance test in zebrafish.

Materials and methods

Animal maintenance

Adult zebrafish (around 2.5 cm long), purchased from a local fish shop, were maintained at 28.0 $\pm$ 1.0°C under a 14 h light – 10 h dark cycle in an aquarium container equipped with multistage filtration that contained a sediment filter, post-carbon filter, fluorescent UV light sterilizing filter and an aeration system (Zebrafish AutoSystem, Genomic Design, Seoul, Korea). Zebrafish were fed twice a day with flake food and *Artemia nauplia*.

Experimental chamber

The shuttle chamber (18.5 cm long $\times$ 7.0 cm wide $\times$ 10.0 cm high) consisted of two compartments divided by a wall containing a 3-cm-diameter opening that could be opened or closed with an adjoining sliding door. This chamber was composed of black acryl, except for the upper portion. One compartment remained dark while the other was lighted through a transparent window that was 3 cm in diameter and located opposite the sliding door, which allowed a signal of flashing light to pass into the compartment (Kim et al. 2009).

Passive avoidance test procedure

A zebrafish was placed in the dark compartment of the shuttle chamber. After 3 min of acclimation, the flashing light was activated on the side of the transparent window, and the sliding door was subsequently lifted to allow the zebrafish access to the light compartment. Three seconds after the zebrafish crossed the door, a small stone was dropped in front of the fish, which functioned as the noxious stimulus. The zebrafish was gently pushed back into the dark compartment with a fishnet, and the light was switched off. Every 3 min, the process was repeated two more times. Each crossing was considered a trial and each training session consisted of three trials. For each trial, the time from the moment the door was opened to the moment the fish swam through the door was measured using a stopwatch. In all experiments, the crossing time was measured up to 300 s. Zebrafish that did not cross the door within 300 s in the first trial were not included in further experiments. In order to assess the retention ability of the learned avoidance response, a test session was carried out 2 h after the termination of the training session. The fish was then reintroduced into the dark compartment, and after 3 min of acclimation, the sliding door was opened to allow the fish to cross the door. Only one trial was conducted without delivery of a noxious stimulus.

Drug treatment

In the first series of experiments, we attempted to determine whether or not physostigmine, an acetylcholinesterase inhibitor, nicotine, a nicotinic acetylcholine receptor agonist, and MK-801, an NMDA receptor antagonist, affect the learning of a passive avoidance task. Zebrafish were singly placed into a 250 ml beaker filled with drug-containing aquarium water for a given duration. Zebrafish were exposed to MK-801 (20 μM) for 30 min, physostigmine (10 and 30 μM) for 1 h, and nicotine (10 and 30 μM) for 2 h in the drug-containing beaker. The training session was conducted in the shuttle chamber immediately after termination of the drug treatment. Next, to determine whether or not physostigmine or nicotine antagonizes the effects of MK-801 on the learning of passive avoidance response, zebrafish were exposed to physostigmine (20 μM) or nicotine (20 μM) for 1 or 2 h during the last 30 min of MK-801 (20 μM) treatment. Either drug was present in the chamber during the training and test session but not during the 2 h interval term.

MK-801 (Sigma-Aldrich, St. Louis, MO, USA), physostigmine (Tocris, Bristol, UK) and nicotine (Sigma-Aldrich) were dissolved at high concentrations (20, 20 and 100 mM, respectively) in distilled water, and then diluted to final concentrations in aquarium water.

Statistics

The data were analysed via Friedman repeated-measures analysis of variance on ranks, followed by Student Newman-Keuls's multiple comparison test to determine significant differences among the crossing times in the training session. Post hoc Student Newman-Keuls tests were performed to measure the significant difference between trial 1 and trial 3 in the 'Results and discussion' section. The difference between the third trials of the first training session and test session was determined using the Wilcoxon rank sum test.

Results and discussion

Effects of different concentrations of physostigmine on passive avoidance response

For the controls, the crossing times were 35.7 ± 10.5 s, 138.9 ± 44.0 s and 216.6 ± 35.5 s in three consecutive trials of the training session, and 205.6 ± 35.9 s in the test session, which was conducted 2 h after the training session. The crossing time was increased along with the trials in the training session, and it was significantly longer in the third trial than in the first trial (Figure 1A, $F(2, 16) = 17.03$). Despite the 2 h interval, the crossing time in the test session was not reduced compared to that measured in the third trial of the training session (Wilcoxon rank sum test, $p = 0.859$). This result suggests that the zebrafish learned the avoidance response and maintained it.

Regarding zebrafish treated with 10 μM physostigmine, the crossing time was increased significantly during the training session; 34.4 ± 10.9 s, 190.8 ± 33.6 s and 235.4 ± 31.7 s in three consecutive trials (Figure 1B, $F(2, 14) = 20.71$). Crossing time was also maintained in the test session (212.6 ± 33.5 s) (Wilcoxon rank sum test, $p = 0.636$). In 30 μM physostigmine-treated zebrafish, the crossing times were 52.6 ± 8.9 s, 164.2 ± 36.6 s and 177.0 ± 35.8 s in the training session ($F(2, 16) = 7.19$) and 161.5 ± 46.2 s in the test session (Wilcoxon rank sum test, $p = 0.677$) (Figure 1C). Over the range 10–30 μM, physostigmine alone appeared neither to facilitate nor prevent the acquisition of the avoidance response.

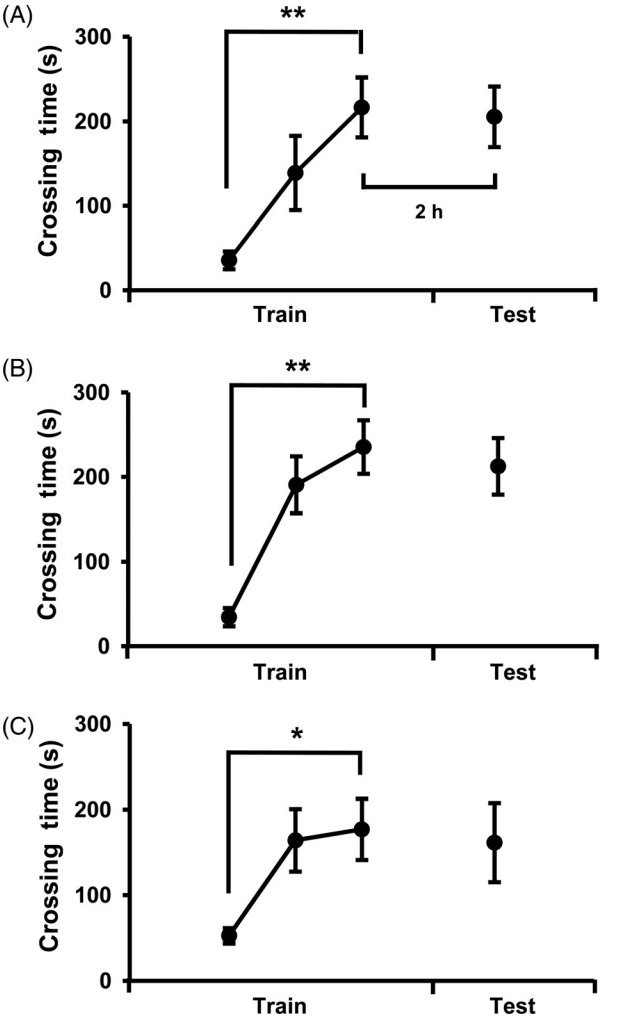

Figure 1. Effects of various concentrations of physostigmine on acquisition and retention of the avoidance response. (A) Increased crossing time was observed in the training session and was maintained after a 2 h interval in control fish. (B and C) Increased crossing time was observed in the training session and was maintained after a 2 h interval in physostigmine (10 and 30 μM)-treated zebrafish. * $p < 0.01$; ** $p < 0.001$.

Effects of different concentrations of nicotine on passive avoidance response

The avoidance response was successfully acquired and maintained in the controls (Figure 2A, $F(2, 18) = 25.73$). In 10 μM nicotine-treated zebrafish, the crossing time was increased significantly during the training session; 58.2 ± 10.7 s, 143.5 ± 22.7 s and 173.2 ± 34.2 s in three consecutive trials (Figure 2B, $F(2, 22) = 10.65$). The increased crossing time (216.7 ± 32.6 s) was not reduced in the test session compared to that measured in the third trial of the training session (Wilcoxon rank sum test, $p = 0.371$). However, in 30 μM nicotine-treated zebrafish, the crossing times were not significantly different; 68.1 ± 8.0 s, 112.2 ± 24.5 s and 83.1 ± 25.7 s in the training session ($F(2, 22) = 2.19$) and 109.8 ± 32.0 s in the test session (Wilcoxon rank sum test, $p = 0.525$) (Figure 2C). Unlike physostigmine-treated zebrafish, the avoidance response was not learned in the 30 μM nicotine-treated zebrafish, although it was learned in the 10 μM nicotine-treated zebrafish (Figure 2B). Furthermore, 40 μM nicotine-treated zebrafish did not survive the training session. This dose dependency of the effects of nicotine on learning and memory has been shown in rats; a low dose (0.6 mg/kg) of nicotine improves working memory in the eight radial arms maze, whereas a high dose (1.2 mg/kg) of nicotine impairs memory function (Rezvani and Levin 2002).

Effects of physostigmine on MK-801-induced learning deficits

The avoidance response was successfully acquired and maintained in the controls (Figure 3A, $F(2, 24) = 15.14$). To test whether or not MK-801, an NMDA

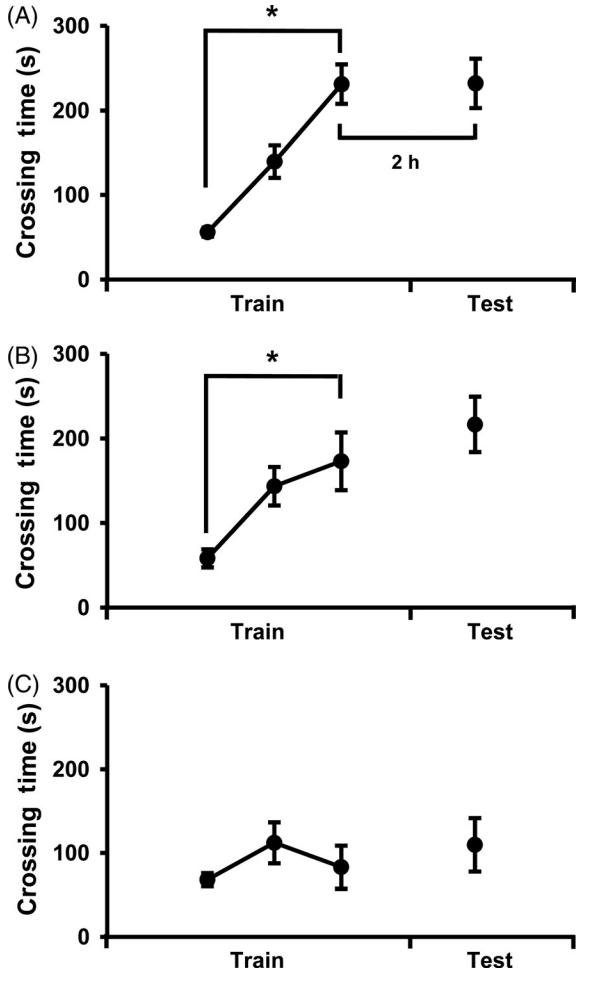

Figure 2. Effects of various concentrations of nicotine on acquisition and retention of the avoidance response. (A) Increased crossing time was observed in the training session and was maintained after a 2 h interval in control fish. (B) Increased crossing time was observed in the training session and was maintained after a 2 h interval in 10 μM nicotine-treated zebrafish. (C) The crossing time did not differ significantly between the training and test sessions in 30 μM nicotine-treated zebrafish. * $p < 0.001$.

receptor antagonist, affects the acquisition of the avoidance response, zebrafish were treated with 20 μM MK-801 for 30 min prior to the training session. The crossing time was not increased with the trials in the training session (Figure 3B, $F(2, 18) = 1.73$), suggesting that NMDA receptors were involved in acquisition of the passive avoidance response. These results are similar to other studies that showed MK-801-induced learning deficits in a variety of behavior tasks, such as the T-maze water maze tasks and passive avoidance test, in rats (Jafari-Sabet 2006; Nakamura et al. 2006; Watson and Stanton 2009a).

The crossing times were increased significantly during the training session; 46.4 ± 6.4 s, 100.5 ± 19.7 s and 178.7 ± 23.2 s in three consecutive trials in 20 μM physostigmine-treated zebrafish (Figure 3B, $F(2, 24) = 18.33$). The crossing time in the test session (161.1 ± 28.9 s) did not differ significantly from that measured in the third trial of the training session (Wilcoxon rank sum test, $p = 0.663$). However, the crossing times were 43.8 ± 7.4 s, 109.7 ± 15.8 s and 183.8 ± 28.9 s in the training session and 133.0 ± 31.0 s in the test session in both MK-801- and physostigmine-treated zebrafish (Figure 3C). In contrast with the results observed with the MK-801-treated zebrafish (Figure 3B), the crossing time was increased to a higher degree in the third trial than in the first trial ($F(2, 18) = 16.72$), thereby suggesting that MK-801-induced learning deficits were reversed by physostigmine treatment. Interestingly, the crossing time in the test session did not differ significantly from that measured in the third trial of the training session (Wilcoxon rank sum test, $p = 0.273$), showing that physostigmine improved MK-801-induced impairment of retention ability. These results are similar to the finding that physostigmine rescues scopolamine-induced impairment of acquisition and retention of passive avoidance responses in zebrafish (Kim et al. 2010) and further confirms the mnemonic effects of physostimine on NMDA receptor-mediated learning. Acetylcholinesterase inhibitors, such as physostigmine and donepezil, were shown to improve MK-801-induced deficits in spatial reversal learning as well as cued memory, and physostigmine also reduces hyper-locomotion by MK-801 in mice (Csernansky et al. 2005). An interactive effect between the cholinergic and glutamatergic systems was shown using a passive avoidance test in mice; while a low dose of physostigmine failed to improve the retention latency of passive avoidance response learning, co-treatment with NMDA, an NMDA receptor agonist, and physostigmine significantly improved the retention latency. Furthermore, the improving effects of physostigmine were blocked by MK-801 (Jafari-Sabet 2006).

Effects of nicotine on MK-801-induced learning deficits

As shown in Figure 3, zebrafish learned and maintained the avoidance response, which was impaired by MK-801 treatment (Figure 4A, B). In nicotine-treated zebrafish, the crossing times were 51.2 ± 8.7 s, 131.0 ± 27.0 s and 171.8 ± 26.4 s in the training session ($F(2, 36) = 16.46$) and 152.3 ± 25.5 s in the test session, and they did not differ significantly from that measured in the third trial of the training session (Wilcoxon rank sum test, $p = 0.549$) (Figure 4B). The crossing times were 55.6 ± 5.5 s, 151.4 ± 17.9 s and 195.0 ± 21.1 s in the training session and 117.7 ± 21.4 s in the test

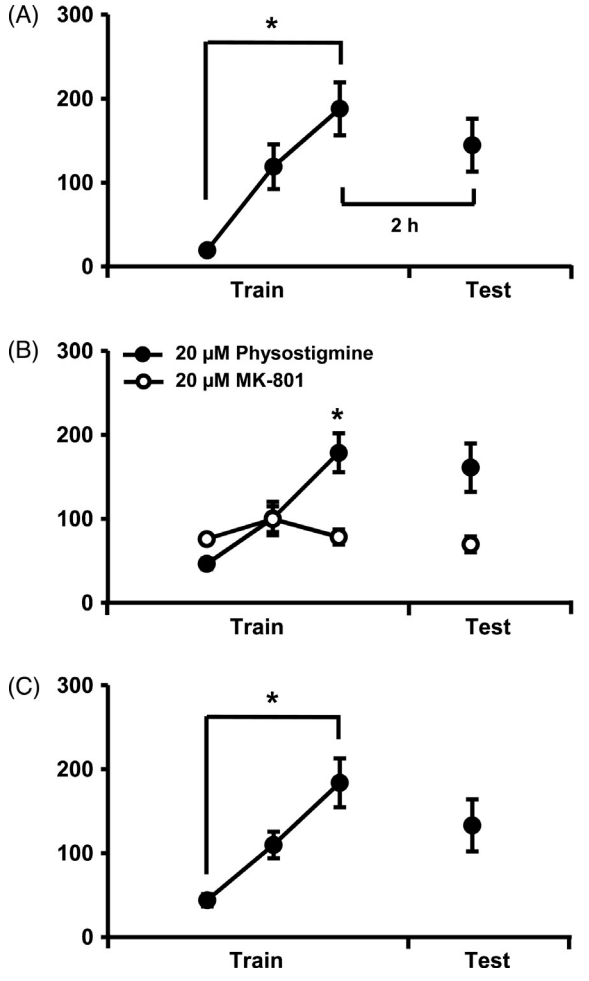

Figure 3. Effects of MK-801 and physostigmine on the avoidance response in zebrafish. (A) The crossing time was increased gradually in the training session and was maintained in the test trial after a 2 h interval in control fish (n = 13). (B) An increase in crossing time was not observed in 20 μM MK-801-treated zebrafish (n = 10), but did occur in zebrafish treated with 20 μM physostigmine (n = 13). (C) The crossing time was increased in the training and test trials after a 2 h interval upon pretreatment with 20 μM physostigmine for 1 h prior to treatment with 20 μM MK-801 (n = 10). * $p < 0.001$.

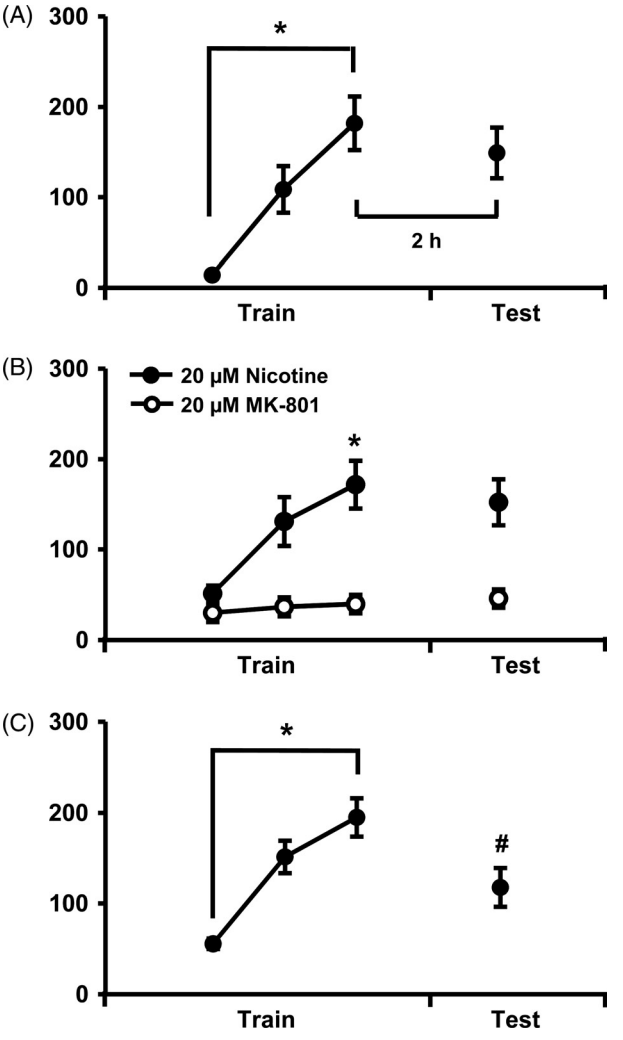

Figure 4. Effects of MK-801 and nicotine on the avoidance response in zebrafish. (A) The crossing time was increased gradually in the training session and was maintained in the test trial after a 2 h interval in control fish (n = 17). (B) An increase in crossing time was not observed in 20 μM MK-801-treated zebrafish (n = 10), but did occur in 20 μM nicotine-treated zebrafish (n = 18). (C) Pretreatment with 20 μM nicotine for 2 h prior to treatment with 20 μM MK-801 resulted in an increased crossing time in the training session that was not maintained in the test trial after a 2 h interval (n = 28). * $p < 0.001$; # $p < 0.05$.

session in the nicotine- and MK-801-treated zebrafish (Figure 4C). In contrast with the results observed with the MK-801-treated zebrafish, the crossing time was significantly increased in the third trial compared to the first trial in the training session ($F(2, 54) = 26.83$). However, the crossing time in the test session was reduced significantly compared to the third trial of the training session (Wilcoxon rank sum test, $p < 0.05$). These results again imply a connection between the activation of nicotinic acetylcholine receptors and glutamatergic receptors in zebrafish. A previous study indicated that pretrial nicotine administration in rats attenuates both working and reference memory deficits caused by dizocilpine in a radial-arm maze. These results suggest a functional interaction between nicotinic and NMDA systems in the brain (Levin et al. 1998). For example, the selective nicotine agonist RJR-2403 reversed MK-801-induced learning deficits, which was mediated by activation of presynaptic nicotinic receptors, which increased glutamate release in the hippocampal area of mice (Rodríguez-Moreno et al. 2006). Further, anabasine, a α7-nicotinic acetylcholine

receptor agonist, attenuated MK-801-elicited mouse popping behaviors (Mastropaolo et al. 2004). A recent study also showed that NMDA receptor activation in the CA1 region of the hippocampus is required for the improving effect of nicotine on ethanol-induced memory deficits (Rezayof et al. 2010).

It is noteworthy that physostigmine was more effective compared to nicotine in rescuing learning deficits induced by MK-801; retention of the avoidance response was not complete upon a low dose of nicotine and learning of the avoidance response was impaired at a higher dose of nicotine. This may have been due to the fact that the effects of physostigmine are mediated via activation of muscarinic receptors as well as nicotinic receptors. Accumulated results have demonstrated that muscarinic receptors play roles in learning and consolidation of learned responses (Power et al. 2003; Herrera-Morales et al. 2007). Activation of muscarinic receptor is known to induce synaptic modification of glutamatergic receptors, which leads to long-term depression or potentiation (Fernández de Sevilla and Buño 2010; Jo et al. 2010)

In conclusion, our study has shown that MK-801 treatment in zebrafish impaired the acquisition and retention of the avoidance response, which was improved by activation of the cholinergic system either through inhibition of acetylcholinesterase (AChE) or activation of nicotinic receptors.

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