Original Article

Activation of the Nitric-Oxide System in Nucleus Accumbens Inhibits the Nicotine Reversal Effects upon Ethanol-Induced Amnesia

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Abstract

The present study investigated the possible involvement of the nucleus accumbens' (NAc) nitric oxide system in nicotine's reversal effect upon ethanol-induced amnesia. The hypothesis was tested through ethanol state-dependent memory assessment in adult male Wistar rats. Bilateral chronic cannulae were implanted in the NAc and the animals were trained in a step-through type inhibitory avoidance memory task. The step-through latency was examined 24 h after animals' training. The pre-training or pre-test intraperitoneal (i.p.) injection of ethanol (0.9 g/kg) decreased the step-through latency, indicating an amnesic effect of the drug. Meanwhile, the pre-test administration of ethanol (0.6 and 0.9 g/kg) could reverse the pre-training ethanol (0.9 g/kg)-induced amnesia, suggesting a state-dependent effect. Similar to ethanol, the pre-test intra-NAc microinjection of nicotine (0.25 and 0.5 µg/rat) alone or nicotine (0.1, 0.25 and 0.5 µg/mouse, intra-NAc) in combination with an ineffective dose of ethanol (0.3 g/kg) could significantly reverse the (pre-training) ethanol-induced memory impairment. The ethanol (0.9 g/kg)-induced amnesia was similarly prevented following the pre-test intra-NAc administration of a nitric oxide synthase (NOS) inhibitor, L-NAME (0.4 and 0.8 µg/rat). Of note, the co-administration of L-NAME (0.04 and 0.08 µg/rat, intra-NAc) with an ineffective dose of nicotine (0.1 µg/rat, intra- NAc) could significantly potentiate the memory-improving effect of nicotine on ethanol-induced amnesia and resembled the effects of pre-test administration of a higher dose of nicotine. Furthermore, while the pre-test intra-NAc injection of L-NAME impaired the memory retrieval by itself, the pre-test intra-NAc administration of L-arginine, a nitric oxide precursor (0.3 and 0.6 µg/rat, intra-NAc), did not exert any effect either alone or in combination with an effective dose of nicotine (0.5 µg/rat, intra-NAc) on pre-training ethanol-induced memory impairment. Our findings indicated a possible role of the nucleus accumbens' nitric oxide system in the improving effects of nicotine on ethanol-induced amnesia and the related state-dependent learning.

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Introduction

Cigarette smoking is often accompanied by the use of ethanol (1, 2). Both ethanol and nicotine can potentially activate the mesolimbic dopaminergic system projecting from the ventral tegmental area to the nucleus accumbens, hippocampus, amygdala and the prefrontal cortex. These drugs have therefore an important role in reward and reward-related learning (3).The impairing effects of ethanol on learning and memory have been well-established in different experimental models(4-6)including the inhibitory avoidance(7, 8), working (9) and spatial memory (10-12). In agreement with some earlier reports (4, 13, 14), we noticed that ethanol, when administered both pre- and post-training, can impair inhibitory avoidance memory in a state-dependent manner, and the effect is reversible by pre-test ethanol treatment. A considerable body of evidence suggests a solid interaction between ethanol and nicotine in the central nervous system (Collins et al. 1993, 1996; Smith et al. 1999; Lê et al. 2003) in which the nicotinic acetylcholine receptors seem to have an important role for such interrelation(3, 15, 16).Former reports have indicated that the combination of alcohol and nicotine may produce state-dependent learning in humans(17). In addition, according to some later studies, the administration of nicotinic receptor agonists reversed the ethanol-induced amnesia in laboratory animals (7, 18-20).While nicotine may reverse the ethanol-induced amnesia (similar to pre-test ethanol), the drugs have some opposite effects on other cognitive functions (6, 8, 21). Where nicotine enhances learning either through a direct effect on attention or affecting the pre-synaptic nicotinic acetylcholine receptors, ethanol may potentially impair learning (4-6). Taken together, the opposite effects of ethanol and nicotine on cognitive functions (5, 8, 21) have made the interaction between them complex and hence not fully understood yet.

On the other hand, there exist some well-demonstrated interactions between nicotine and NO (22-24). Cumulating evidence has supported the hypothesis that some behavioral effects of nicotine and ethanol are mediated by NO (6, 23, 25). For instance, the inhibition of NOS has been reported to attenuate various nicotine-induced addictive behaviors including the dependence (26), sensitization (22), withdrawal (27) and reward (28). The dorsal hippocampal NO system has also been shown to play an important role in ethanol state-dependent learning (6). According to one of our recent reports, the intra-CA1 injection of nicotine restores the ethanol-induced amnesia, at least partly through the activation of the NO system in the dorsal hippocampus (7). Our data substantiated that the intra-CA1 microinjection of L-arginine potentiates the reversal effect of nicotine on ethanol-induced amnesia, while the intra-CA1 administration of L-NAME prevented the improving effect of nicotine on the same(7). Findings from a large body of research have suggested the modulatory effects of NO on different learning and memory processes, namely the inhibitory avoidance memory(29-32) and spatial learning (33-36). For example, systemic, intra cerebro-ventricular(i.c.v.) or local injection of NOS inhibitor, has led to impairments in object recognition (37), spatial learning (30, 38)and inhibitory avoidance (30, 39-41) tasks in rats. Moreover, NOS inhibitors are shown to potentially impair the memory performance in one-trial inhibitory avoidance (7)and spontaneous alternations in mice (36). Other studies, however, have shown no effects of NOS inhibition on learning and memory processes. According to Blokland et al. (42) and Bannerman et al. (43), the systemic or intra-hippocampal injections of NOS inhibitors did not impair the spatial learning. Bohme et al. also reported that L-NAME administration produces no significant effect on inhibitory avoidance memory in rats (44).

It has been proposed that the inhibitory avoidance paradigm, which is widely used in pharmacological studies on long term memory in rodents, mainly involves the dorsal hippocampus (45).However, the hippocampal memory processes are largely affected by several limbic nuclei such as the NAc and VTA (46). Recent investigations have suggested a functional loop between the hippocampus, NAc and VTA, which controls the entry of information into long-term memory. The upward arc of this loop comprises dopaminergic neurons projecting from the VTA to hippocampus and the downward arc includes the NAc and ventral pallidum (VP)(46). The VTA dopamine neuron activity can receive accumbal influence both though direct projections to the VTA and an indirect projection via the VP (47). These projections are shown to be GABA ergic pathways (48, 49).Based on some solid evidence, NOS is localized in the somata and dendrites of these GABAergic neurons which typically project from the nucleus accumbens (NAc) to the ventral tegmental area (VTA)(50, 51).Since such GABAergic neurons comprise almost 90% of the neuronal population in the NAc (52, 53), the downward arc of the aforementioned functional-loop may serve as an inhibitory control over the activity of VTA dopaminergic neurons.

Previous studies have demonstrated the dopaminergic system's critical role in the reversal effect of nicotine on amnesia induced by ethanol or morphine (54, 55). It is therefore possible that NO

agents influence the reversal effect of nicotine on ethanol-induced amnesia via the modulation of the GABAergic neurons, projecting from the NAc to VTA.

Based on our earlier investigation, the dorsal hippocampal NO system seems to be involved in the improving effect of nicotine on ethanol-induced amnesia(7). Meanwhile, the involvement of accumbal NO system in the effect of nicotine on ethanol-induced amnesia cannot be excluded. Considering the presence of NOS in the NAc as well as the well-discussed interactions between NO system and nicotine or ethanol effects (24, 56, 57), the aim of the present research was to investigate the role of NO system of the NAc in the reversal effect of nicotine upon ethanol-induced memory impairment in rats.

Materials and methods

- *Animals*

Adult male Wistar rats (Pasteur institute, Tehran, Iran) weighing 220– 270 g at the time of surgery were used. Animals were housed four per cage with access to food and water ad libitum and kept at (22 ± 2) ◦C under a 12/12 h light-dark cycle (lights on at 7:00 AM). All experiments were done during the light phase between 8:00 and 14:00. Each experimental group comprised eight animals and each animal was tested only once. Behavioral tests and animal care were conducted in accordance with the standard ethical guidelines (NIH, publication no. 85–23, revised 1985; European Communities Directive 86/609/EEC) and approved by the local ethical committee.

- *Surgery*

Animals were anesthetized using the intraperitoneal (i.p.)ketamine/ xylazine mixture (50 mg/kg ketamine, 5 mg/kg xylazine) and placed in a stereotaxic frame (David Kopf Instruments) in a flat-skull position [incisor bar -3.3 mm] relative to the inter-aural line (58). A midline incision was made with the skin and underlying periosteum retracted. Bilateral stainless steel guide cannulae (22 gauge) were implanted 2 mm above the NAc shell according to stereotaxic coordinates including AP:+1 mm forward of bregma, L: ± 1 mm from midline, V: -5.5 mm relative to dura (58), and anchored to the skull with dental cement. Stainless steel stylets (27 gauge) were inserted into the guide cannulae to maintain the patency. All animals were allowed one week to recover from surgery.

- *Drugs and microinjections*

The applied drugs were ETOH (Merck, Germany), L-NAME (NG-nitro-L-arginine methyl ester, a non-specific inhibitor of nitric oxide synthase), L-arginine (Sigma, St Louis, CA, USA) and nicotine hydrogen tartrate (Sigma, Poole, Dorset, UK). All drugs were dissolved in sterile saline except nicotine which was dissolved in sterile saline with the pH of the solution adjusted to 7.2 with NaOH (0.1 normal solution). The 1 g/kg dose of ethanol was made from a 12.6% ethanol in 0.9% saline (vol/vol) stock solution, made freshly for each experiment and then diluted to the required concentration (0.5 g/kg). Ethanol was injected i.p. at a volume of 1 ml/kg. Bilateral intra-NAc micro-infusions of L-arginine and L-NAME were at a volume of 0.6 µl (0.3 µl/side). To administer the intra-NAc doses, the 27-gauge infusion cannulae were lowered to extend 2 mm beyond the tip of the guide cannulae at the infusion sites. The infusion cannula was attached to a 1 µl Hamilton syringe via a polyethylene tubing. Infusions (0.3µl/side) were made over 60 s, first on one side then the other, and the infusion cannulae were left in place for an additional 30 s to facilitate drug diffusion. Control animals received either saline or vehicle. In experiments where animals received one or two injections, the control groups received one or two saline or vehicle injections. The timing between injections and the injection sequence were defined based on a pilot study and our previous findings (7, 40, 41, 59, 60).

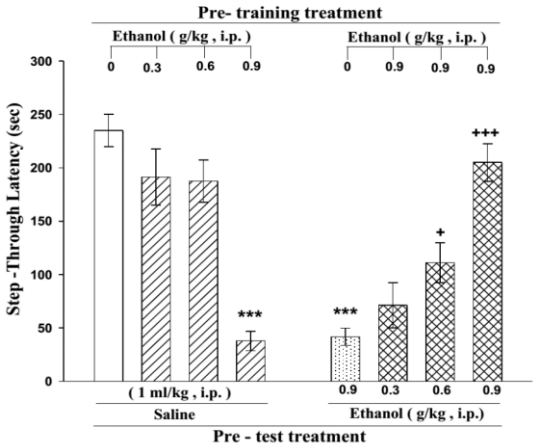
- *Inhibitory avoidance apparatus*

We used a step-through inhibitory avoidance apparatus consisting of two same-size compartments (20 × 20 × 30 cm3). A manually retractable guillotine door (7.9 cm2) isolated the two compartments at the middle of a dividing wall. The walls and the floor of one compartment were composed of white opaque resin and the walls of the other compartment were dark. Stainless steel bars (0.3 mm in diameter set in 1 cm intervals) constituted the floor of the dark compartment. Intermittent electric shocks (50 Hz, 3 s, and 1 mA intensity) were delivered to the grid floor of the dark compartment by an isolated stimulator.

- *Behavioral procedures*

Training was done based on our previous studies (61, 62). All animals were allowed to habituate in the experimental room for at least 30 min prior to the experiments. Each animal was then gently placed in the brightly lit compartment of the apparatus. After 5 s, the guillotine door was opened and the animal was allowed to enter the dark compartment. The latency after which the animal crossed into the dark compartment was recorded. Animals which spend over 100 s to cross to the dark

compartment were eliminated from the experiments. Once the animal crossed (with all four paws) to the next compartment, the guillotine door was closed and the rat was taken into its home cage. The trial was repeated after 30 min. Similar to the acquisition trial, the guillotine door was opened in 5 s and as soon as the animal crossed to the dark (shock) compartment the door was closed and a foot shock (50 Hz, 1 mA and3 s) was immediately delivered to the grid floor of the dark room. After 20 s, the rat was removed from the apparatus and temporarily placed into its home cage. Two minutes later, the procedure was repeated. In case the rat avoided entering the dark compartment within 120 s, a successful acquisition of inhibitory avoidance response was recorded. On the other hand, when the rat entered the dark compartment (within120 s) a second time, the door was closed and the animal received the same shock again. Twenty-four hours after training, each animal was gently placed in the light compartment for 20 s, the door was opened, and the step-through latency was measured for entering into the dark compartment. The testing session was ended once the animal entered the dark compartment or remained in the light compartment for 300 s (criterion for retrieval). During testing sessions, no electric shock was applied.



Experimental design

Experiment 1: In this experiment, the effect of pre-training and pre-test administration of ethanol on inhibitory avoidance response was examined in eight groups (n=8/group). Two groups received pre-training saline (1 ml/kg), others received either saline or ethanol (0.9 g/kg) before testing (pre-test) as control groups. The remaining three groups of animals received different doses (0.3, 0.6 and 0.9 g/kg, i.p.) of ethanol 30 min prior to training. On the test day, all of them received saline 30 min before the test (pre-test). The other three groups of animals received pre-training (0.9 g/kg of ethanol) and pre-test injections of ethanol (0.3, 0.6 and 0.9 g/kg, i.p.) (Figure1).

Figure 1. The effects of pre-training or pre-test administration of ethanol on step-through latency

Experiment 2: This experiment examined the effects of pre-test administration of nicotine alone or in combination with ethanol on ethanol-induced amnesia in twelve groups (n=8/group). Four groups of animals received pre-training saline (1 ml/kg, i.p.). On the test day, animals of these groups received saline (1 ml/kg) 30 min before testing plus different doses of nicotine (0, 0.1, 0.25 and 0.5 µg/rat, intra-NAc) 5 min prior to the test. Other eight groups received pre-training ethanol (0.9 g/kg). During the test day, four groups of these animals received saline (1 ml/kg) 30 min before testing plus different doses of nicotine (0, 0.1, 0.25 and 0.5 µg/rat, intra-NAc), 5 min before testing. The other four groups received ethanol (0.3 g/kg) 30 min before testing plus different doses of nicotine (0, 0.1, 0.25 and 0.5 µg/rat, intra-NAc), 5 min prior to the test (Fig. 2).

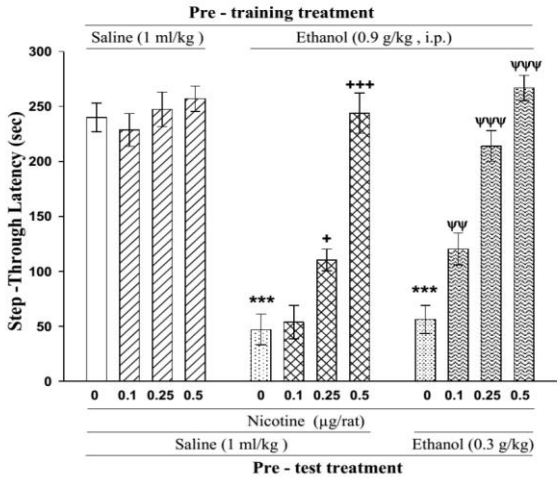


Figure 2. The effects of pre-test injection of nicotine in the presence or absence of ethanol on inhibitory avoidance memory.

Experiment 3: In this experiment, we assessed the effects of pre-test administration of L-NAME alone or in combination with ethanol on ethanol-induced amnesia in twelve groups (n=8/group). Four groups of animals received pre-training saline (1 ml/kg). During the test day, these animals received L-NAME (0, 0.4, 0.8 and 0.16 µg/rat, intra-NAc) and were injected with vehicle (0.6 µ1/rat, intra-NAc), 5 min later.Other eight groups of animals received a pre-training effective dose of ethanol (0.9 g/kg). Upon test, four groups of these animals received L-NAME (0, 0.4, 0.8 and 1.6 µg/rat, intra-NAc) and were similarly injected with vehicle (0.6 µ1/rat, intra-NAc),5 min later. The other four groups of animals received L-NAME (0, 0.4, 0.8 and 1.6 µg/rat, intra-NAc) and in 5 min, were injected with nicotine (0.1 µg/rat, intra-NAc). Step-through latency was measured 5 min after the last injection (Figure 3).

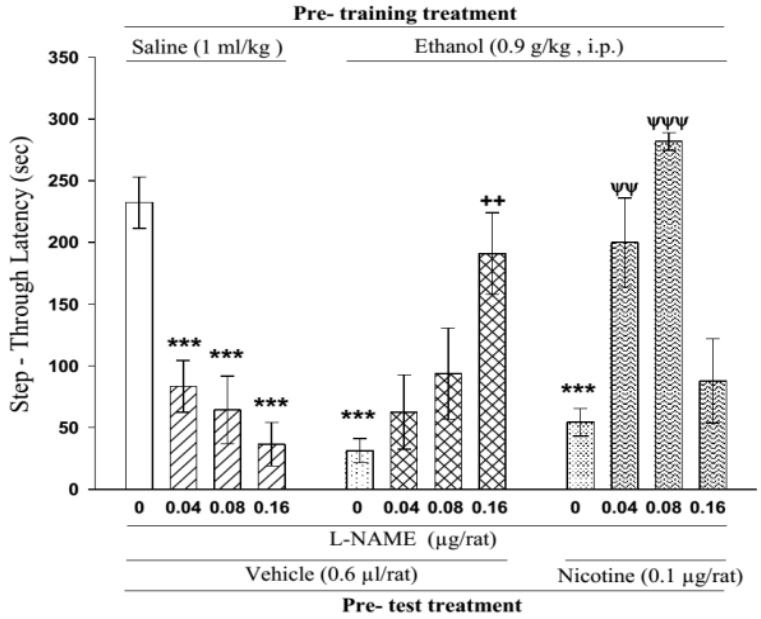


Figure 3. The effects of pre-test intra-NAc microinjection of L-NAME in the presence or absence of ethanol and/or nicotine on memory retrieval.

Experiment 4: we examined the effects of pre-test administration of L-arginine alone or in combination with nicotine on ethanol-induced amnesia in this experiment. The experiment included eight groups of animals (n=8/group) of which four groups received pre-training saline (1 ml/kg). During the test day, animals in these four groups received L-arginine (0, 0.15, 0.3 and 0.6 µg/rat, intra-NAc) and were injected with vehicle (0.6 µ1/rat, intra-NAc), 5 min later. The remaining four groups received a pre-training effective dose of ethanol (0.9 g/kg). On the test day, these animals received L-arginine (0, 0.15, 0.3 and 0.6 µg/rat, intra-NAc) and after 5 min, they were similarly injected with an effective dose of nicotine (0.5 µg/rat, intra-NAc). Step-through latency was measured 5 min after the last injection (Figure 4).

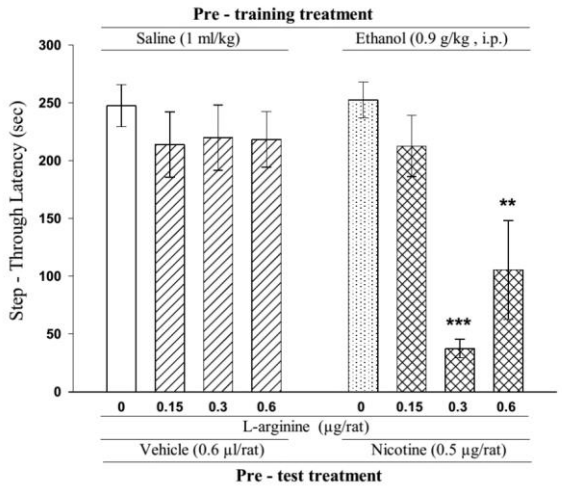


Figure 4. The effect of pre-test intra-NAc administration of L-arginine in the presence or absence of ethanol and nicotine on inhibitory avoidance memory

- *Histology*

Following the testing sessions, each rat was deeply anesthetized and 0.6 µl of a 4% methylene-blue solution was bilaterally infused into the NAc (0.3 µl/ side), as described in the drug section. Each animal was then decapitated with its brain removed and placed in formaldehyde (10%). After several days, the fixated brains were sliced and the sites of injections were verified according to the rat brain atlas by Paxinos and Watson (58). Although cannulae were implanted into the NAc of a total of 350 animals, only the data from 320 animals with correct cannulae implants were included in the statistical analyses.

- *Data analysis*

The data are expressed as mean ± S.E.M. The statistical analysis was performed using one-way and two-way analysis of variance (ANOVA). Post-hoc comparison of means was carried out using Tukey's test for multiple comparisons, when appropriate. The level of statistical significance was set at $P<0.05$. Calculations were performed using the SPSS statistical package.

Results

- *The effects of ethanol on inhibitory avoidance memory*

Figure 1 shows the effects of pre-training or pre-test administration of ethanol on step-through latency. One-way ANOVA revealed that pre-training or pre-test ethanol (0.9 g/kg, i.p.) impaired inhibitory avoidance memory on the test day, as compared to the saline-treated animals [$F(4, 35) = 29.01$, $P<0.001$]. In other groups, the pre-test ethanol administration (0.6 and 0.9 g/kg, i.p.) reversed the pre-training ethanol-induced amnesia (0.9 g/kg, i.p.) [$F(3, 28) = 17.19$, $P<0.001$].

- *The effects of pre-test nicotine administration with or without ethanol on inhibitory avoidance memory*

Figure 2 illustrates the effects of pre-test injection of nicotine in the presence or absence of ethanol on inhibitory avoidance memory. Two-way ANOVA results showed an interaction between the groups of animals with pre-training saline (1 ml/kg) and pre-test nicotine treatment (0.1, 0.25 and 0.5 µg/rat, intra-NAc) and those with pre-training ethanol (0.9 g/kg, i.p.) and pre-test nicotine treatment [for Treatment, $F(1,56)= 164.46$, $P<0.001$; Dose, $F(3,56)= 25.48$, $P<0.001$; and Treatment × Dose interaction, $F(3,56)= 16.09$, $P<0.001$] for their inhibitory avoidance memory. In addition, two-way ANOVA revealed a significant difference between the groups of animals with pre-training saline (1 ml/kg) and pre-test nicotine treatment and those with pre-training ethanol(0.9 g/kg, i.p.), followed by pre-test nicotine plus a lower dose of ethanol treatment (0.3 g/kg, i.p.) [for Treatment, $F(1,56)= 67.88$, $P<0.001$; Dose, $F(3,56)= 29.28$, $P<0.001$; and Treatment × Dose interaction, $F(3,56)= 19.82$, $P<0.001$] for their inhibitory avoidance memory. Furthermore, two-way ANOVA demonstrated a significant difference between the groups of animals which received pre-training ethanol (0.9 g/kg, i.p.) and pre-test nicotine and those which received pre-training ethanol (0.9 g/kg, i.p.), followed by pre-test nicotine plus a lower dose of ethanol (0.3 g/kg, i.p.) [for Treatment, $F(1,56)= 26.28$, $P<0.001$; Dose, $F(3,56)= 83.57$, $P<0.001$; and Treatment × Dose interaction, $F(3,56)= 4.76$, $P<0.01$] for their inhibitory avoidance memory. Moreover, post hoc analysis revealed that in the animals trained after saline treatment and tested following intra-NAc administration of nicotine (0.1, 0.25 and 0.5 µg/rat), no significant change was observed in the retention latencies as compared to the saline/saline control group [$F(3,28) = 0.74$, $P>0.05$] (Fig. 2, left panel). Where the pre-training administration of ethanol (0.9 g/kg) impaired inhibitory avoidance memory, the intra-NAc administration of nicotine (0.25 and 0.5 µg/rat), on the test day, significantly reversed the ethanol-

induced amnesia [F (3, 28) = 38.73, P<0.001] (Fig. 2, middle panel). Although the lower dose of the pre-test ethanol (0.3 g/kg) alone did not induce a significant ethanol state-dependent memory, the co-administration of different doses of nicotine (0.1, 0.25 and 0.5 µg/rat, intra-NAc) with 0.3 g/kg of ethanol significantly improved the memory retrieval and resembled the effects of pre-test administration of a higher dose ethanol [F(3,28)= 50.87, P<0.001] (Figure 2, right panel).

- *The effects of pre-test administration of L-NAME alone or in combination with nicotine on ethanol-induced amnesia*

The effects of pre-test intra-NAc microinjection of L-NAME in the presence or absence of ethanol and/or nicotine on memory retrieval has been demonstrated in Fig.3. Two-way ANOVA revealed an interaction between the groups of animals with pre-training saline (1 ml/kg) and pre-test L-NAME treatment (0, 0.04, 0.08 and 0.16 µg/rat, intra-NAc) and those which were treated with pre-training ethanol (0.9 g/kg, i.p.) and pre-test L-NAME [for Treatment, F(1,56)= 0.61, P>0.05; Dose, F(3,56)= 2.34, P>0.05; and Treatment ×Dose interaction, F(3,56)= 16.13, P<0.001] for their inhibitory avoidance memory. Two-way ANOVA also indicated a significant difference between the groups of animals which received pre-training saline (1 ml/kg) and pre-test L-NAME and those which received pre-training ethanol (0.9 g/kg, i.p.), followed by pre-test a lower dose of nicotine (0.1 µg/rat, intra-NAc) plus L-NAME [for Treatment, F(1,56)= 9.42, P<0.01; Dose, F(3,56)= 7.91, P<0.001; and Treatment ×Dose interaction, F(3,56)= 24.65, P<0.001] for their inhibitory avoidance memory. In addition, two-way ANOVA results showed a significant difference between the groups of animals which received pre-training ethanol (0.9 g/kg, i.p.) and pre-test L-NAME and those which received pre-training ethanol (0.9 g/kg, i.p.), followed by pre-test a lower dose of nicotine (0.1 µg/rat, intra-NAc) plus L-NAME [for Treatment, F(1,56)= 9.88, P<0.01; Dose, F(3,56)= 9.55, P<0.001; and Treatment ×Dose interaction, F(3,56)= 11.01, P<0.001] with regard to their inhibitory avoidance memory. Moreover, based on the post hoc analysis, the pre-test intra-NAc administration of L-NAME (0, 0.04, 0.08 and 0.16 µg/rat) reduced the step-through latency in the inhibitory avoidance task and appeared to induced amnesia [F(3, 28)= 15.93, P<0.001] (Fig. 3, left panel). Where the pre-training administration of ethanol (0.9 g/kg) impaired memory, administration of a higher dose of L-NAME (0.16 µg/rat, intra-NAc), on the test day, significantly reversed the ethanol-induced amnesia [F (3, 28) = 5.51, P<0.01] (Fig. 3, middle panel). Besides, the co-administration of L-NAME (0.04 and 0.08 µg/rat, intra-NAc) with 0.1 µg/rat of nicotine significantly potentiated the reversal effect of nicotine on ethanol-induced amnesia and mimicked the effects of the pre-test administration of a higher dose of ethanol or nicotine [F(3, 28)= 16.53, P<0.001] , (Figure 3, right panel).

- *The effects of pre-test administration of L-arginine alone or in combination with nicotine on ethanol-induced amnesia*

Figure 4 illustrates the effect of pre-test intra-NAc administration of L-arginine in the presence or absence of ethanol and nicotine on inhibitory avoidance memory. Two-way ANOVA indicated a significant difference between the effects of L-arginine (0, 0.15, 0.3 and 0.6 µg/rat, intra-NAc) alone and L-arginine plus nicotine (0.5 mg/kg) on inhibitory avoidance memory [for Treatment, F (1, 56) = 15.92, P<0.001; Dose, F (3, 56) = 8.64, P <0.001; and Treatment ×Dose interaction, F (3, 56) = 6.18, P<0.001]. One-way ANOVA also revealed that in the animals which were trained before saline treatment and tested following the intra-NAc administration of different doses of L-arginine (0.15, 0.3 and 0.6 µg/rat, intra-NAc), no significant change was observed in the retrieval latencies [F (3, 28) =0.37, P>0.05]. Furthermore, where pre-training administration of ethanol (0.9 g/kg) impaired inhibitory avoidance memory, the pre-test intra-NAc microinjection of L-arginine (0.3 and 0.6 µg/rat) could prevent the reversal effect of nicotine (0.5 µg/rat) on ethanol-induced amnesia [F (3, 28) = 13.59, P<0.001] (Figure 4, right panel).

Discussion

This study investigated the role of NAc NO system in the reversal effect of nicotine on ethanol-induced amnesia and ethanol state-dependent memory. While many reports have suggested the dorsal hippocampus as the main site for modulation of memory (59, 63), accumulating evidence have proposed that NAc or other sites of the brain may be involved in memory processes (7). According to the present data, the pre-training or pre-test injection of ethanol could decrease the step-through latency in a dose-dependent manner when animals were tested following 24 h. Other investigations have similarly shown that the pre-training ethanol inhibits the acquisition of memory in different paradigms such as inhibitory avoidance (7, 8), working (9) and

spatial memory (10-12).Our findings also showed that administration of the same dose of ethanol before retention, reverses the ethanol-induced amnesia. This phenomenon, called ethanol state-dependent learning, has previously been studied in our laboratory (6-8) and by others as well. Studies have proposed that the acquired information in one drug state is better remembered when the retrieval is tested in the same drug state (7, 8, 41, 64, 65).

According to our findings, the pre-test intra-NAc microinjection of nicotine reversed the memory impairment induced by pre-training systemic injection of ethanol. At the same time, , the co-administration of an ineffective dose of ethanol with a lower dose of nicotine before retention, significantly reversed the ethanol-induced amnesia and mimicked the effects of pre-test administration of a higher dose of ethanol or nicotine. In support of such findings, we have recently reported that the intra-CA1 (dorsal hippocampal) pre-test injection of nicotine is able to restore ethanol-induced amnesia in mice (5, 7, 8). Evidence has shown that the amnesic effects of ethanol on both reference and working memory can be blocked by nicotine pretreatment(20). The present data also are in agreement with those from other investigations, indicating an interaction between ethanol and central nicotinic receptors, both in vivo (3, 66, 67) and within neuronal cultures (68).

Both ethanol and nicotine increase the dopamine release in the NAc(3). The dopamine pathway may not be the only pathway accountable for the reversal effect of nicotine on memory and other neurotransmitter mechanisms may also be involved therein. Many of nicotine effects are possibly due to the ability of the drug to release various neurotransmitters (69). It has been postulated that stimulation of nicotinic receptors enhances the release of glutamate and NO production both in the VTA and NAc (70). Considering the functional interactions of ethanol and nicotine with NO (7, 40, 41) and that the NAc is a key structure in learning and memory (41, 65), we strived to examine the role of NO systems in the NAc in the reversal effect of nicotine on ethanol-induced amnesia. Our findings showed that the pre-test intra-NAc administration of L-NAME, but not L-arginine, impairs the inhibitory avoidance memory by itself. Such results are in line with other evidence indicating that the systemic, intra-CA1, intra-VTA or intra-NAc injection of L-NAME impairs memory (6, 7, 40, 41, 71-74).

Our data also demonstrated that the pre-test intra-NAc injection of L-NAME reverses the ethanol-induced amnesia. Likewise, the pre-test injection of an ineffective dose of nicotine in combination with the lower doses of L-NAME, which had no effect alone, synergistically restored the ethanol-induced amnesia. The above results may propose an interaction between the NO system and reversal effects of nicotine in the NAc upon restoring the ethanol-induced memory impairment. Along these lines, our previous studies have revealed that NO system and NMDA receptors of dorsal hippocampus involve in the reversal effect of nicotine on ethanol-induced amnesia (5, 7). Our earlier findings also indicated that NO system and NMDA receptors of the NAc involve in the reversal effect of nicotine on morphine amnesia(41, 65).The NAc can influence dopamine neuronal activity originating from the VTA (75). The medium spiny neurons, which project from the NAc to the VTA, are GABAergic(52, 53). Therefore, activation of theses spiny neurons can inhibit the VTA dopaminergic neurons. Convergent evidence indicates that NMDA receptors and NOS are expressed in the somata and dendrites of these GABAergic neurons (50,51). Therefore, it is possible that theL-NAME-related inhibition of NO system in the NAc increases dopamine release from the VTA, which may in turn modulate memory processes in the hippocampus and other target areas.

We have already reported that the intra-NAc injection of the NMDA receptor antagonist (MK-801) or NOS inhibitors (L-NAME) potentiates the reversal effect of nicotine on morphine-induced amnesia (41, 65). It has then been proposed that the blockade of GABAergic neurons (projecting from NAc to VTA)using MK-801 (65) or L-NAME (41) activates of VTA dopaminergic neurons and increases dopamine release in the NAc (76-80). There are many reports highlighting the role of dopamine as a key mediator for learning and memory (81-83). Evidence also indicates that dopamine mediates motivational effects of nicotine (84). As such, it seems possible that similar effects of nicotine and L-NAME on restoring ethanol- or morphine-induced amnesia during inhibitory avoidance memory task are modulated through the mesolimbic dopamine systems. Thus, an ineffective dose of nicotine plus lower doses of L-NAME, similar to an effective dose of nicotine or ethanol, seem to effectively activate the VTA dopaminergic neuron and restore the ethanol-induced amnesia. Meanwhile, further investigations are required to let this be fully understood. Another justification would be that the effects of a drug on memory retrieval, when given before retention test, simply depend on how well the information has been stored previously. As such, a drug which impairs the memory retrieval in animals with strong memory may enhance memory retrieval in animals with poor memory (53,85).

Based on the present report, the pre-test co-administration of L-arginine with an effective dose of nicotine blocked the reversal effect of nicotine on

ethanol-induced amnesia. The results obtained by L-arginine injection may further support the hypothesis that the NAc NO system plays a key part in the reversal effect of nicotine on ethanol-induced amnesia. The effect of L-arginine may be due to the influence on GABAergic projections from the NAc to the VTA, which favors dopamine release. In contrast with the present data, our recent report showed that the pre-test intra-CA1 injection of L-arginine or ineffective doses of L-arginine plus an ineffective dose of nicotine can restore ethanol-induced amnesia, while the co-administration of L-NAME with an effective dose of nicotine before retention test, blocked the reversal effect of nicotine on ethanol-induced amnesia(7). Such discrepancy in results could partly be explained by differences in the brain sites in which NO-related compounds were infused. It could be inferred from these results that the intra-CA1 injection of L-arginine, similar to nicotine, increases the dorsal hippocampal dopamine release. On the contrary, the intra-CA1 injection of L-NAME injection is shown to decrease the release of dopamine in the dorsal hippocampus (7).Moreover, the intra-NAc injection of L-arginine is shown not only to inhibit the VTA dopaminergic neurons via the activation of NAc to VTA GABAergic projections but also to decrease dopamine release in the target area of mesolimbic dopamine pathway such as NAc and hippocampus. Meanwhile, the intra-NAc injection of L-NAME has been shown to activate the VTA dopaminergic neurons via the inhibition of descending GABAergic neurons projecting from NAc to VTA and increased the release of dopamine in the dorsal hippocampus (41, 76-80).

Such an apparent discrepancy in the obtained results could at least be partly attributed to the neuromodulatory role of NO in different sites of the brain. Our present data are consistent with previous findings showing that the intra-NAc infusion of NMDA receptor antagonist or NOS inhibitors potentiate the reversal effect of nicotine on morphine-induced amnesia while the intra-NAc injection of NMDA or NO precursor block the reversal effect of nicotine on memory impairment induced by morphine pretreatment (41, 65).

Conclusion

In conclusion, the blockade or activation of the NO system of NAc potentiates or decreases the reversal effect of nicotine upon ethanol-induced amnesia, respectively.

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References

1. Bien TH, Burge R. Smoking and drinking: a review of the literature. Int J Addict. 1990;25(12):1429-54.
2. Batel P, Pessione F, Maitre C, Rueff B. Relationship between alcohol and tobacco dependencies among alcoholics who smoke. Addiction. 1995;90(7):977-80.
3. Larsson A, Engel JA. Neurochemical and behavioral studies on ethanol and nicotine interactions. Neurosci Biobehav Rev. 2004;27(8):713-20.
4. Rezayof A, Sharifi K, Zarrindast MR, Rassouli Y. Modulation of ethanol state-dependent learning by dorsal hippocampal NMDA receptors in mice. Alcohol. 2008;42(8):667-74.
5. Rezayof A, Shirazi-Zand Z, Zarrindast MR, Nayer-Nouri T. Nicotine improves ethanol-induced memory impairment: the role of dorsal hippocampal NMDA receptors. Life Sci. 2010;86(7-8):260-6.
6. Rezayof A, Zare-Chahoki A, Zarrindast MR, Rassouli Y. Inhibition of dorsal hippocampal nitric oxide synthesis potentiates ethanol-induced state-dependent memory in mice. Behav Brain Res. 2010;209(2):189-95.
7. Raoufi N, Piri M, Moshfegh A, Shahin MS. Nicotine improves ethanol-induced impairment of memory: possible involvement of nitric oxide in the dorsal hippocampus of mice. Neuroscience. 2012.
8. Rezayof A, Alijanpour S, Zarrindast MR, Rassouli Y. Ethanol state-dependent memory: involvement of dorsal hippocampal muscarinic and nicotinic receptors. Neurobiol Learn Mem. 2008;89(4):441-7.
9. Melchior CL, Glasky AJ, Ritzmann RF. A low dose of ethanol impairs working memory in mice in a win-shift foraging paradigm. Alcohol. 1993;10(6):491-3.
10. Matthews DB, Simson PE, Best PJ. Acute ethanol impairs spatial memory but not stimulus/response memory in the rat. Alcohol Clin Exp Res. 1995;19(4):902-9.
11. Chin VS, Van Skike CE, Berry RB, Kirk RE, Diaz-Granados J, Matthews DB. Effect of acute ethanol and acute allopregnanolone on spatial memory in adolescent and adult rats. Alcohol. 2011;45(5):473-83.
12. Berry RB, Matthews DB. Acute ethanol administration selectively impairs spatial memory in C57BL/6J mice. Alcohol. 2004;32(1):9-18.
13. Nakagawa Y, Iwasaki T. Involvement of benzodiazepine/GABA-A receptor complex in ethanol-induced state-dependent learning in rats. Brain Res. 1995;686(1):70-6.
14. Nakagawa Y, Iwasaki T. Ethanol-induced state-dependent learning is mediated by 5-hydroxytryptamine3 receptors but not by N-methyl-D-aspartate receptor complex. Brain Res. 1996;706(2):227-32.
15. Larsson A, Svensson L, Soderpalm B, Engel JA. Role of different nicotinic acetylcholine receptors in mediating behavioral and neurochemical effects of ethanol in mice. Alcohol. 2002;28(3):157-67.
16. Narahashi T, Aistrup GL, Marszalec W, Nagata K. Neuronal nicotinic acetylcholine receptors: a new target site of ethanol. Neurochem Int. 1999;35(2):131-41.
17. Lowe G. State-dependent learning effects with a combination of alcohol and nicotine. Psychopharmacology (Berl). 1986;89(1):105-7.
18. Gould TJ, Collins AC, Wehner JM. Nicotine enhances latent inhibition and ameliorates ethanol-induced deficits in latent inhibition. Nicotine Tob Res. 2001;3(1):17-24.
19. Gulick D, Gould TJ. Interactive effects of ethanol and nicotine on learning in C57BL/6J mice depend on both dose and duration of treatment. Psychopharmacology (Berl). 2008;196(3):483-95.
20. Tracy HA, Jr., Wayner MJ, Armstrong DL. Nicotine blocks ethanol and diazepam impairment of air righting and ethanol impairment of maze performance. Alcohol. 1999;18(2-3):123-30.
21. Dawson DA. Drinking as a risk factor for sustained smoking. Drug Alcohol Depend. 2000;59(3):235-49.
22. Shim I, Kim HT, Kim YH, Chun BG, Hahm DH, Lee EH, et al. Role of nitric oxide synthase inhibitors and NMDA receptor antagonist in nicotine-induced behavioral sensitization in the rat. Eur J Pharmacol. 2002;443(1-3):119-24.
23. Sahraei H, Falahi M, Zarrindast MR, Sabetkasaei M, Ghoshooni H, Khalili M. The effects of nitric oxide on the acquisition and expression of nicotine-induced conditioned place preference in mice. Eur J Pharmacol. 2004;503(1-3):81-7.

24. Schilstrom B, Mameli-Engvall M, Rawal N, Grillner P, Jardemark K, Svensson TH. Nitric oxide is involved in nicotine-induced burst firing of rat ventral tegmental area dopamine neurons. Neuroscience. 2004;125(4):957-64.
25. Piri M, Zarrindast MR. Nitric oxide in the ventral tegmental area is involved in retrieval of inhibitory avoidance memory by nicotine. Neuroscience. 2011.
26. Tayfun Uzbay I, Oglesby MW. Nitric oxide and substance dependence. Neurosci Biobehav Rev. 2001;25(1):43-52.
27. Loh HH, Liu HC, Cavalli A, Yang W, Chen YF, Wei LN. mu Opioid receptor knockout in mice: effects on ligand-induced analgesia and morphine lethality. Brain Res Mol Brain Res. 1998;54(2):321-6.
28. Martin JL, Itzhak Y. 7-Nitroindazole blocks nicotine-induced conditioned place preference but not LiCl-induced conditioned place aversion. Neuroreport. 2000;11(5):947-9.
29. Khavandgar S, Homayoun H, Zarrindast MR. The effect of L-NAME and L-arginine on impairment of memory formation and state-dependent learning induced by morphine in mice. Psychopharmacology (Berl). 2003;167(3):291-6.
30. Qiang M, Chen YC, Wang R, Wu FM, Qiao JT. Nitric oxide is involved in the formation of learning and memory in rats: studies using passive avoidance response and Morris water maze task. Behav Pharmacol. 1997;8(2-3):183-7.
31. Telegdy G, Kokavszky R. The role of nitric oxide in passive avoidance learning. Neuropharmacology. 1997;36(11-12):1583-7.
32. Zarrindast MR, Shendy MM, Ahmadi S. Nitric oxide modulates state dependency induced by lithium in an inhibitory avoidance task in mice. Behav Pharmacol. 2007;18(4):289-95.
33. Choopani S, Moosavi M, Naghdi N. Involvement of nitric oxide in insulin induced memory improvement. Peptides. 2008;29(6):898-903.
34. Kendrick KM, Guevara-Guzman R, Zorrilla J, Hinton MR, Broad KD, Mimmack M, et al. Formation of olfactory memories mediated by nitric oxide. Nature. 1997;388(6643):670-4.
35. Majlessi N, Kadkhodaee M, Parviz M, Naghdi N. Serotonin depletion in rat hippocampus attenuates L-NAME-induced spatial learning deficits. Brain Res. 2003;963(1-2):244-51.
36. Yamada K, Noda Y, Hasegawa T, Komori Y, Nikai T, Sugihara H, et al. The role of nitric oxide in dizocilpine-induced impairment of spontaneous alternation behavior in mice. J Pharmacol Exp Ther. 1996;276(2):460-6.
37. Blokland A, Prickaerts J, Honig W, de Vente J. State-dependent impairment in object recognition after hippocampal NOS inhibition. Neuroreport. 1998;9(18):4205-8.
38. Ingram DK, Spangler EL, Kametani H, Meyer RC, London ED. Intracerebroventricular injection of N omega-nitro-L-arginine in rats impairs learning in a 14-unit T-maze. Eur J Pharmacol. 1998;341(1):11-6.
39. Fin C, da Cunha C, Bromberg E, Schmitz PK, Bianchin M, Medina JH, et al. Experiments suggesting a role for nitric oxide in the hippocampus in memory processes. Neurobiol Learn Mem. 1995;63(2):113-5.
40. Piri M, Zarrindast MR. Nitric oxide in the ventral tegmental area is involved in retrieval of inhibitory avoidance memory by nicotine. Neuroscience. 2011;175:154-61.
41. Zarrindast MR, Piri M, Nasehi M, Ebrahimi-Ghiri M. Nitric oxide in the nucleus accumbens is involved in retrieval of inhibitory avoidance memory by nicotine. Pharmacol Biochem Behav. 2012;101(1):166-73.
42. Blokland A, de Vente J, Prickaerts J, Honig W, Markerink-van Ittersum M, Steinbusch H. Local inhibition of hippocampal nitric oxide synthase does not impair place learning in the Morris water escape task in rats. Eur J Neurosci. 1999;11(1):223-32.
43. Bannerman DM, Chapman PF, Kelly PA, Butcher SP, Morris RG. Inhibition of nitric oxide synthase does not impair spatial learning. J Neurosci. 1994;14(12):7404-14.
44. Bohme GA, Bon C, Lemaire M, Reibaud M, Piot O, Stutzmann JM, et al. Altered synaptic plasticity and memory formation in nitric oxide synthase inhibitor-treated rats. Proc Natl Acad Sci U S A. 1993;90(19):9191-4.
45. Izquierdo I, Bevilaqua LR, Rossato JI, Bonini JS, Medina JH, Cammarota M. Different molecular cascades in different sites of the brain control memory consolidation. Trends Neurosci. 2006;29(9):496-505.
46. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron. 2005;46(5):703-13.
47. Zahm DS, Heimer L. Two transpallidal pathways originating in the rat nucleus accumbens. J Comp Neurol. 1990;302(3):437-46.
48. Kalivas PW, Churchill L, Klitenick MA. GABA and enkephalin projection from the nucleus accumbens and ventral pallidum to the ventral tegmental area. Neuroscience. 1993;57(4):1047-60.
49. Steffensen SC, Svingos AL, Pickel VM, Henriksen SJ. Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. J Neurosci. 1998;18(19):8003-15.
50. Gracy KN, Pickel VM. Ultrastructural localization and comparative distribution of nitric oxide synthase and N-methyl-D-aspartate receptors in the shell of the rat nucleus accumbens. Brain Res. 1997;747(2):259-72.
51. Afanas'ev I, Ferger B, Kuschinsky K. The associative type of sensitization to d-amphetamine is expressed as an NO-dependent dramatic increase in extracellular dopamine in the nucleus accumbens. Naunyn Schmiedebergs Arch Pharmacol. 2000;362(3):232-7.
52. Oorschot DE. Total number of neurons in the neostriatal, pallidal, subthalamic, and substantia nigral nuclei of the rat basal ganglia: a stereological study using the cavalieri and optical disector methods. J Comp Neurol. 1996;366(4):580-99.
53. Ahmadi S, Zarrindast MR, Nouri M, Haeri-Rohani A, Rezayof A. N-Methyl-D-aspartate receptors in the ventral tegmental area are involved in retrieval of inhibitory avoidance memory by nicotine. Neurobiol Learn Mem. 2007;88(3):352-8.
54. Azizbeigi R, Ahmadi S, Babapour V, Rezayof A, Zarrindast MR. Nicotine restores morphine-induced memory deficit through the D1 and D2 dopamine receptor mechanisms in the nucleus accumbens. J Psychopharmacol. 2011;25(8):1126-33.
55. Rezayof A, Motevasseli T, Rassouli Y, Zarrindast MR. Dorsal hippocampal dopamine receptors are involved in mediating ethanol state-dependent memory. Life Sci. 2007;80(4):285-92.
56. Schilstrom B, Nomikos GG, Nisell M, Hertel P, Svensson TH. N-methyl-D-aspartate receptor antagonism in the ventral tegmental area diminishes the systemic nicotine-induced dopamine release in the nucleus accumbens. Neuroscience. 1998;82(3):781-9.
57. Schilstrom B, Svensson HM, Svensson TH, Nomikos GG. Nicotine and food induced dopamine release in the nucleus accumbens of the rat: putative role of alpha7 nicotinic receptors in the ventral tegmental area. Neuroscience. 1998;85(4):1005-9.
58. Paxinos G, & Watson, C. The rat brain in stereotaxic coordinatesed r, editor. San Diego: Academic Press; 1997.
59. Azami NS, Piri M, Oryan S, Jahanshahi M, Babapour V, Zarrindast MR. Involvement of dorsal hippocampal alpha-adrenergic receptors in the effect of scopolamine on memory retrieval in inhibitory avoidance task. Neurobiol Learn Mem. 2010;93(4):455-62.
60. Nasehi M, Piri M, Jamali-Raeufy N, Zarrindast MR. Influence of intracerebral administration of NO agents in dorsal hippocampus (CA1) on cannabinoid state-dependent memory in the step-down passive avoidance test. Physiol Behav. 2010;100(4):297-304.
61. Zarrindast MR, Eidi M, Eidi A, Oryan S. Effects of histamine and opioid systems on memory retention of passive avoidance learning in rats. Eur J Pharmacol. 2002;452(2):193-7.
62. Zarrindast MR, Farajzadeh Z, Rostami P, Rezayof A, Nourjah P. Involvement of the ventral tegmental area (VTA) in morphine-induced memory retention in morphine-sensitized rats. Behav Brain Res. 2005;163(1):100-6.
63. Davis JA, Kenney JW, Gould TJ. Hippocampal alpha4beta2 nicotinic acetylcholine receptor involvement in the enhancing effect of acute nicotine on contextual fear conditioning. J Neurosci. 2007;27(40):10870-7.
64. Manago F, Castellano C, Oliverio A, Mele A, De Leonibus E. Role of dopamine receptors subtypes, D1-like and D2-like, within the nucleus accumbens subregions, core and shell, on memory consolidation in the one-trial inhibitory avoidance task. Learn Mem. 2009;16(1):46-52.
65. Ahmadi S, Zarrindast MR, Haeri-Rohani A, Rezayof A, Nouri M. Nicotine improves morphine-induced impairment of memory: possible involvement of N-methyl-D-aspartate receptors in the nucleus accumbens. Dev Neurobiol. 2007;67(8):1118-27.
66. Criswell HE, Simson PE, Duncan GE, McCown TJ, Herbert JS, Morrow AL, et al. Molecular basis for regionally specific action of ethanol on gamma-aminobutyric acidA receptors: generalization to other ligand-gated ion channels. J Pharmacol Exp Ther. 1993;267(1):522-37.
67. Yang X, Criswell HE, Breese GR. Action of ethanol on responses to nicotine from cerebellar interneurons and medial septal neurons: relationship to methyllycaconitine inhibition of nicotine responses. Alcohol Clin Exp Res. 1999;23(6):983-90.
68. Marszalec W, Aistrup GL, Narahashi T. Ethanol-nicotine interactions at alpha-bungarotoxin-insensitive nicotinic acetylcholine receptors in rat cortical neurons. Alcohol Clin Exp Res. 1999;23(3):439-45.
69. Wonnacott S. Presynaptic nicotinic ACh receptors. Trends Neurosci. 1997;20(2):92-8.
70. McGehee DS, Heath MJ, Gelber S, Devay P, Role LW. Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science. 1995;269(5231):1692-6.

71. Harooni HE, Naghdi N, Sepehri H, Rohani AH. The role of hippocampal nitric oxide (NO) on learning and immediate, short- and long-term memory retrieval in inhibitory avoidance task in male adult rats. Behav Brain Res. 2009;201(1):166-72.
72. Baratti CM, Boccia MM, Blake MG, Acosta GB. Reactivated memory of an inhibitory avoidance response in mice is sensitive to a nitric oxide synthase inhibitor. Neurobiol Learn Mem. 2008;89(4):426-40.
73. Pitsikas N, Rigamonti AE, Bonomo SM, Cella SG, Muller EE. Molsidomine antagonizes L-NAME-induced acquisition deficits in a recognition memory task in the rat. Pharmacol Res. 2003;47(4):311-5.
74. Cobb BL, Ryan KL, Frei MR, Guel-Gomez V, Mickley GA. Chronic administration of L-NAME in drinking water alters working memory in rats. Brain Res Bull. 1995;38(2):203-7.
75. Heimer L, Alheid GF, de Olmos JS, Groenewegen HJ, Haber SN, Harlan RE, et al. The accumbens: beyond the core-shell dichotomy. J Neuropsychiatry Clin Neurosci. 1997;9(3):354-81.
76. Johnson SW, Mercuri NB, North RA. 5-hydroxytryptamine1B receptors block the GABAB synaptic potential in rat dopamine neurons. J Neurosci. 1992;12(5):2000-6.
77. Leone P, Pocock D, Wise RA. Morphine-dopamine interaction: ventral tegmental morphine increases nucleus accumbens dopamine release. Pharmacol Biochem Behav. 1991;39(2):469-72.
78. Olmstead MC, Franklin KB. The development of a conditioned place preference to morphine: effects of microinjections into various CNS sites. Behav Neurosci. 1997;111(6):1324-34.
79. Olmstead MC, Franklin KB. The development of a conditioned place preference to morphine: effects of lesions of various CNS sites. Behav Neurosci. 1997;111(6):1313-23.
80. Manzanedo C, Aguilar MA, Rodriguez-Arias M, Minarro J. Effects of dopamine antagonists with different receptor blockade profiles on morphine-induced place preference in male mice. Behav Brain Res. 2001;121(1-2):189-97.
81. Hefco V, Yamada K, Hefco A, Hritcu L, Tiron A, Nabeshima T. Role of the mesotelencephalic dopamine system in learning and memory processes in the rat. Eur J Pharmacol. 2003;475(1-3):55-60.
82. Seamans JK, Floresco SB, Phillips AG. D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. J Neurosci. 1998;18(4):1613-21.
83. Myhrer T. Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. Brain Res Brain Res Rev. 2003;41(2-3):268-87.
84. Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur J Pharmacol. 2000;393(1-3):295-314.
85. Yang Y, Cao J, Xiong W, Zhang J, Zhou Q, Wei H, et al. Both stress experience and age determine the impairment or enhancement effect of stress on spatial memory retrieval. J Endocrinol. 2003;178(1):45-54.