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Nitric oxide in the dorsal hippocampal area is involved on muscimol state-dependent memory in the step-down passive avoidance test

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ABSTRACT

In the present study, the effects of intra-dorsal hippocampal (intra-CA1) injections of nitric oxide (NO) agents on muscimol state-dependent memory were examined in mice. A single-trial step-down passive avoidance task was used for the assessment of memory retrieval in adult male NMRI mice.

Post-training intra-CA1 administration of a $GABA_A$ receptor agonist, muscimol (0.05 and 0.1 μg/mouse) dose dependently induced impairment of memory retention. Pre-test injection of muscimol (0.05 and 0.1 μg/mouse) induced state-dependent retrieval of the memory acquired under post-training muscimol (0.1 μg/mouse, intra-CA1) influence.

Pre-test injection of a NO precursor, L-arginine (1 and 2 μg/mouse, intra-CA1) improved memory retention, although the low dose of the drug (0.5 μg/mouse) did not affect memory retention.

Pre-test injection of an inhibitor of NO-synthase, L-NAME (0.5 and 1 μg/mouse, intra-CA1) impaired memory retention, although the low dose of the drug (0.25 μg/mouse) did not affect memory retention.

In other series of experiments, pre-test intra-CA1 injection of L-arginine (0.25 and 0.5 μg/mouse) 5 min before the administration of muscimol (0.1 μg/mouse, intra-CA1) dose dependently inhibited muscimol state-dependent memory. Pre-test intra-CA1 administration of L-arginine (0.125, 0.25 and 0.5 μg/mouse) by itself cannot affect memory retention.

Pre-test intra-CA1 injection of L-NAME (0.25 μg/mouse, intra-CA1) reversed the memory impairment induced by post-training administration of muscimol (0.1 μg/mouse, intra-CA1). Moreover, pre-test administration of L-NAME (0.125 and 0.25 μg/mouse, intra-CA1) with an ineffective dose of muscimol (0.025 μg/mouse, intra-CA1) significantly restored the retrieval and induced muscimol state-dependent memory. Pre-test intra-CA1 administration of L-NAME (0.0625, 0.125 and 0.25 μg/mouse) by itself cannot affect memory retention.

It may be suggested that the nitric oxide in the dorsal hippocampal area play an important role in muscimol state-dependent memory.

1. Introduction

Nitric oxide (NO) is an intercellular retrograde messenger in the central nervous systems which has been shown to involve in certain forms of long-term potentiation (LTP), expression and synaptic plasticity (Prast and Philippu, 2001; Domek-Łopacińska and Strosznajder, 2005; Koylu et al., 2005; Edwards and Rickard, 2007; Kleppisch and Feil, 2009; Cserép et al., 2011).

In the brain, NO is generated by a series of isoenzymes of the family of NO-synthases (NOS's) from L-arginine in low nanomolar concentrations under physiological conditions (Alderton et al., 2001; Burette et al., 2002; Stuehr et al., 2004; Szabadits et al., 2007; Garthwaite, 2008; Contestabile, 2008).

Neuronal NOS (nNOS) and endothelial (eNOS) are widely distributed in the brain, prominently in the cerebellum and CA1 region of the hippocampus, which is critical in memory formation (Rodrigo et al., 1994; Pepicelli et al., 2004; Ledo et al., 2004; Feil and Kleppisch, 2008; Harooni et al., 2009).

Experiments investigating the role of hippocampal NO in memory processes have shown that intra-hippocampal injections of NO donors induce LTP in CA1 region and consequently improve memory (Arancio et al., 1996; Huang, 1997; Prast and Philippu, 2001; Majlessi et al., 2008), while NOS inhibitors eliminate or partially block hippocampal LTP and consequently impair memory formation in various behavioral tasks (Blokland et al., 1998; Kopf et al., 2001; Prast and Philippu, 2001; Bon and Garthwaite, 2003; Khavandgar et al., 2003; Yildirim and Marangoz, 2004), whereby NO may have modulatory effects on learning and memory processes.

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system (Castellano et al., 1996) which plays a controlling role on the balance of excitability and inhibitory states in the cortex, hippocampus and the interneurons, and is involved in memory formation in the hippocampus (Paulsen and Moser, 1998).

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GABA exerts its action by binding to specific membrane receptors that are divided into three major subclasses: $GABA_A$, $GABA_B$ and $GABA_C$ (Bormann, 2000; Semyanov and Kullmann, 2002; Emson, 2007; Olsen and Sieghart, 2009).

It is well documented that activation of $GABA_A$ receptors in the hippocampus impairs memory in inhibitory avoidance tasks (Farr et al., 2000; Amaral et al., 2007; Reis et al., 2009; Jafari-Sabet and Jannat-Dastjerdi, 2009; Makkar et al., 2010; Jafari-Sabet, 2011; Jafari-Sabet et al., 2013).

Our previous studies have shown that pre-training intra-dorsal hippocampal (intra-CA1) administration of the $GABA_A$ receptor agonist, muscimol induced memory impairment which was restored when the same dose of the drug was administered 24 h later in a pre-test session in the step-down passive avoidance task (Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011; Jafari-Sabet et al., 2013). This phenomenon has been named state-dependent learning (Izquierdo, 1980; Jafari-Sabet et al., 2005; Zarrindast et al., 2006).

These state-dependent effects are time- and dose-dependent and may be prevented or enhanced by activation of the dorsal hippocampal systems (Jafari-Sabet et al., 2005; Rezayof et al., 2008; Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011; Jafari-Sabet et al., 2013).

Interaction between GABAergic and the NO systems have been reported in some behavioral studies (Segovia et al., 1994; Getting et al., 1996; Casamenti et al., 1999; Prast and Philippu, 2001).

Furthermore, there is evidence that the release of GABA in hippocampus (Segovia et al., 1994), striatum (Guevara-Guzman et al., 1994; Segovia and Mora, 1998), and basal forebrain (Casamenti et al., 1999) is modulated by NO.

Also there are reports indicating that the release of GABA is biphasically (i.e., both excitatory and inhibitory), dependent on the NO concentration.

Ample evidence indicates that the CA1 region of the hippocampus is essential for memory formation of one-trial avoidance and is necessary to mediate the expression of place learning (Riedel et al., 1999; Compton, 2004; Izquierdo et al., 2006; Jafari-Sabet, 2006a, 2011; Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet et al., 2013).

One-trial avoidance has been widely used for the study of memory formation and corresponds to many important examples of learning in humans (Izquierdo et al., 2008).

One-trial step-down inhibitory (passive) avoidance in rodents has long been a favorite model for biochemical and pharmacological studies of memory (Izquierdo and Medina, 1997; McGaugh, 2000; Izquierdo and McGaugh, 2000; Szapiro et al., 2002) and induces LTP in CA1 region of the hippocampus (Whitlock et al., 2006).

However, memory formation requires not only LTP in the hippocampal CA1 region but also different sequences of the same or of related signaling pathways in other cortical regions and the amygdala (McGaugh et al., 1990; Izquierdo et al., 2006; Jafari-Sabet, 2006b).

Considering that nNOS is present in hippocampal GABAergic synapses and also NO can directly modify GABAergic synapses on hippocampal pyramidal cells in rodents (Szabadits et al., 2007; Zanelli et al., 2009), the main aim of the present study was to investigate the effects of intra-dorsal hippocampal (intra-CA1) microinjections of L-arginine (a NO precursor) and L-NAME (a non-specific inhibitor of nitric oxide synthase) on muscimol induced state-dependent memory retrieval in a passive avoidance task in mice.

2. Materials and methods

2.1. Animals

Male albino NMRI mice, weighing 24–30 g at the time of the surgery were used. The animals were kept in an animal house with a 12-h light/12-h dark cycle and controlled temperature (22 ± 2 °C). Food and water were available ad libitum. Animals were housed in groups of 10 in Plexiglas animal cages. Each animal was used once only. Ten animals were used in each group. Training and testing were done during the light phase of the cycle. All procedures were carried out in accordance with institutional guidelines for animal care and use. 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.

2.2. Surgical and infusion procedures

Mice were anesthetized with intra-peritoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and placed in a stereotaxic apparatus. The skin was incised and the skull was cleaned. Two 27-gauge guide cannulae were placed (bilaterally) 1 mm above the intended site of injection according to the atlas of Paxinos and Franklin (2001). Stereotaxic coordinates for the CA1 regions of the dorsal hippocampi were AP: −2 mm from bregma, L: ±1.6 from the sagittal suture and V: −1.5 mm from the skull surface. The cannulae were secured to anchor jewelers' screws with dental acrylic. Stainless steel stylets (30-gauge) were inserted into the guide cannulae to keep them free of debris. All animals were allowed 1 week to recover from surgery and clear anesthetic.

For drug infusion, the animals were gently restrained by hand; the stylets were removed from the guide cannulae and replaced by 30-gauge injection needles (1 mm below the tip of the guide cannulae). The injector cannula was attached to a polyethylene tube fitted to a 2-μl Hamilton syringe. The injection solutions were administered in a total volume of 1 μl/mouse (0.5 μl in each side, intra-CA1) over a 60 s period. Injection needles were left in place for an additional 60 s to facilitate the diffusion of the drugs.

2.3. Passive avoidance apparatus

Animals were submitted to the behavioral procedure 7 days after surgery. The apparatus was a (30 cm × 30 cm × 40 cm high) wooden box; the floor of which consisted of parallel stainless steel bars (0.3 cm diameter spaced 1 cm apart). A wooden platform (4 cm × 4 cm × 4 cm) was placed on the center of the grid floor. In the training session the animals were placed on the platform and their latency to step down on the grid with all four paws was measured. Immediately after stepping down on the grid, animals received electric shocks (1 Hz, 0.5 s, 45 V DC) continuously for 15 s. The shocks were delivered to the grid floor by an isolated (Harvard Stimulator 6002, England) stimulator. If any animal stayed on the platform more than 20 s or stepped up to the platform before the end of 15 s of electric shocks, it was omitted from the experiments. Retention test session was carried out 24 h after training and was procedurally identical to training, except that no shock was delivered to the animals. Step-down latency was used as a measure of memory retention. An upper cut-off time of 300 s was set (Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011). The retention test was carried out between 8:00 a.m. and 3:00 p.m.

2.4. Drugs

The drugs used in the present study were muscimol (a $GABA_A$ receptor agonist), L-arginine (a nitric oxide precursor) and L-NAME (N^G-nitro-L-arginine methyl ester hydrochloride, a non-specific inhibitor of nitric oxide synthase) were purchased from Tocris (Cookson Ltd, UK). All drugs were dissolved in sterile 0.9% saline just before the experiments and were injected into the dorsal hippocampal CA1 regions (intra-CA1) 1 μl/mouse (0.5 μl per each side). Control animals received sterile 0.9% saline. The doses of muscimol were those used in our previous studies (Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011; Jafari-Sabet et al., 2013).

2.5. Experimental design

Ten animals were used in each experimental group. In experiments where the animals received one or two injections, the control groups also received one or two saline injections.

2.5.1. Experiment 1. The effects of muscimol on memory retrieval

The aim of this experiment was to produce muscimol-induced amnesia and state dependent memory. Seven groups of animals were used. The control group received saline (1 μl/mouse, intra-CA1) immediately after training (post-training) and 15 min before testing (pre-test). Three groups of animals received post-training muscimol (0.025, 0.05 and 0.1 μg/mouse, intra-CA1) immediately after training, followed by pre-test saline (1 μl/mouse, intra-CA1) 15 min before testing. Another three groups of animals received post-training muscimol (0.1 μg/mouse, intra-CA1) immediately after training, followed by pre-test administration of different doses of muscimol (0.025, 0.05 and 0.1 μg/mouse, intra-CA1) 15 min before testing.

2.5.2. Experiment 2. Effects of pre-test administration of L-arginine and L-NAME in mice trained under saline

In this experiment, eight groups of animals were used. First four groups of animals received saline (1 μl/mouse, intra-CA1) immediately after training (post-training). On the test day, one group of these animals received saline (1 μl/mouse, intra-CA1) and the other three groups received different doses of L-arginine (0.5, 1 and 2 μg/mouse, intra-CA1) 15 min before testing. The second four groups of animals received saline (1 μl/mouse, intra-CA1) immediately after training. On the test day, one group of these animals received saline (1 μl/mouse, intra-CA1) and the other three groups received different doses of L-NAME (0.25, 0.5 and 1 μg/mouse, intra-CA1) 15 min before testing.

2.5.3. Experiment 3. Effects of pre-test intra-CA1 administration of L-arginine alone or with muscimol (0.1 μg/mouse) in mice trained under saline or muscimol (0.1 μg/mouse) on memory retrieval

In this experiment, eight groups of animals were used. The animals received post-training saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) immediately after training. On the testing day, they received different doses of a NO precursor, L-arginine (0, 0.125, 0.25 and 0.5 μg/mouse) 5 min before saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1). All animals were tested 15 min after the last injection.

2.5.4. Experiment 4. Effects of pre-test intra-CA1 administration of L-NAME alone or with muscimol (0.025 μg/mouse) in mice trained under saline or muscimol (0.1 μg/mouse) on memory retrieval

In this experiment, twelve groups of animals were used. Four groups received saline (1 μl/mouse, intra-CA1) immediately after training (post-training) and also different doses of an inhibitor of NO synthase, L-NAME (0, 0.0625, 0.125 and 0.25 μg/mouse, intra-CA1) plus saline (1 μl/mouse) 15 min before testing. Another four groups received post-training muscimol (0.1 μg/mouse, intra-CA1), and were tested 24 h later, 15 min after pre-test administration of L-NAME (0, 0.0625, 0.125 and 0.25 μg/mouse, intra-CA1) plus saline (1 μl/mouse, intra-CA1). Further four groups received post-training muscimol (0.1 μg/mouse, intra-CA1) and were tested 24 h later, 15 min after pre-test administration of L-NAME (0, 0.0625, 0.125 and 0.25 μg/mouse, intra-CA1) plus muscimol (0.025 μg/mouse, intra-CA1).

2.6. Verification of cannulae placements

After completion of the experimental sessions, each animal was killed with an overdose of chloroform. Animals received bilateral intra-CA1 injection of ink (0.5 μl/side; 1% aquatic methylene blue solution). The brains were then removed and fixed in a 10% formalin solution for 10 days before sectioning. Sections were examined to determine the location of the cannulae aimed for the CA1 regions. The cannulae placements were verified using the atlas of Paxinos and Franklin (2001). Data from animals with injection sites located outside the CA1 regions were not used in the analysis.

2.7. Statistical analysis

Because of wide variations of the data in experimental models of memory study, the retention latencies were expressed as the median and interquartile range. The data were analyzed using the Kruskal–Wallis non-parametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann–Whitney's *U*-test, then Holm's Bonferroni correction for the paired comparisons. In all statistical evaluations, $P < 0.05$ was used as the criterion for statistical significance.

3. Results

3.1. The effects of muscimol on memory retrieval

As shown in Fig. 1, post-training administration of different doses of $GABA_A$ receptor agonist, muscimol (0.05 and 0.1 μg/mouse, intra-CA1) altered retrieval of inhibitory avoidance memory on the test day, compared with saline-treated animals. Lower doses of muscimol (0.025 μg/mouse) had no significant effect on retrieval of inhibitory avoidance memory, while the higher doses of muscimol (0.05 and 0.1 μg/mouse) significantly impaired retrieval of inhibitory avoidance memory on the test day (Kruskal–Wallis non-parametric ANOVA, $H(3) = 17.91$, $P < 0.001$). The greatest response was obtained with 0.1 μg/mouse of drug. In the other group, post-training administration of muscimol (0.1 μg/mouse, intra-CA1) impaired retrieval of inhibitory avoidance memory on the test day but was restored when muscimol (0.05 and 0.1 μg/mouse, intra-CA1) was administered as pre-test treatment (muscimol state-dependent memory) (Kruskal–Wallis non-parametric ANOVA, $H(3) = 20.28$, $P < 0.001$). The greatest response was obtained with 0.1 μg/mouse of drug. The results indicate that post-training injection of muscimol induced memory impairment which was

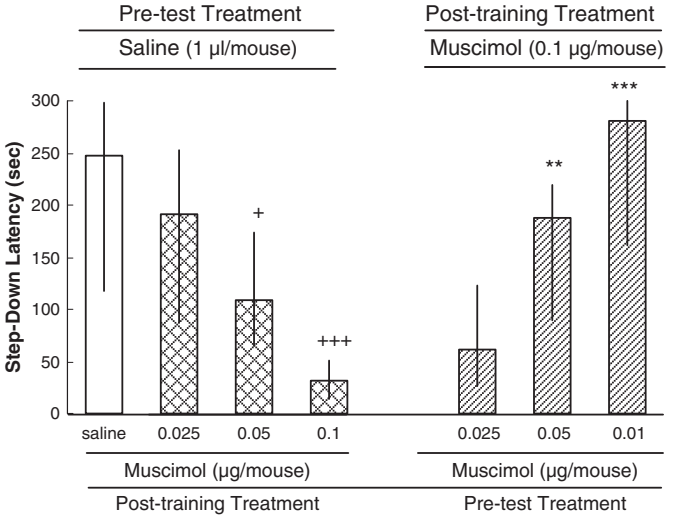

Fig. 1. The effects of post-training and pre-test administration of muscimol or saline on step-down latencies in mice. The control group was administered post-training and pre-test saline (1 μl/mouse, intra-CA1). Three groups of animals were trained before muscimol administration (0.025, 0.05 and 0.1 μg/mouse, intra-CA1) and were tested 15 min after receiving saline. Another three groups of animals were trained before muscimol administration (0.1 μg/mouse, intra-CA1) and were tested 15 min after receiving different doses of muscimol (0.025, 0.05 and 0.1 μg/mouse, intra-CA1). Each value represents the median and interquartile ranges for 10 mice. $^{+}P < 0.05$, $^{+++}P < 0.001$ different from post-training saline/pre-test saline group. $^{**}P < 0.01$, $^{***}P < 0.001$ different from post-training muscimol (0.1 μg/mouse)/pre-test saline group.

restored when the same dose of the drug was administered 24 h later in a pre-test session.

3.2. Effects of pre-test administration of L-arginine and L-NAME in mice trained under saline

Fig. 2 indicates that in animals trained before saline treatment and tested following the administration of three different doses of a NO precursor, L-arginine (0.5, 1 and 2 μg/mouse, intra-CA1) altered the memory retrieval on the test day, compared with saline-saline control group. Lower dose of L-arginine (0.5 μg/mouse) had no significant effect on memory retrieval, while the higher doses of L-arginine (1 and 2 μg/mouse) significantly improved the memory retrieval on the test day (Kruskal–Wallis non-parametric ANOVA, $H(3) = 19.68$, $P < 0.001$). The greatest response was obtained with 1 μg/mouse of drug.

However, in the animals which trained before saline treatment and tested following the administration of three different doses of an inhibitor of NO-synthase, L-NAME (0.25, 0.5 and 1 μg/mouse, intra-CA1) altered the memory retrieval on the test day, compared with saline–saline control group. Lower doses of L-NAME (0.25 μg/mouse) had no significant effect on memory retrieval, while the higher doses of L-NAME (0.5 and 1 μg/mouse) significantly impaired the memory retrieval on the test day (Kruskal–Wallis non-parametric ANOVA, $H(3) = 23.72$, $P < 0.001$).

3.3. Effects of pre-test intra-CA1 administration of L-arginine alone or with muscimol (0.1 μg/mouse) in mice trained under saline or muscimol (0.1 μg/mouse) on memory retrieval

Fig. 3, indicates that in animals trained before saline treatment and tested following the administration of three different doses of L-arginine (0.125, 0.25 and 0.5 μg/mouse, intra-CA1), no significant change was observed in the retention latencies compared to the saline–saline control group [Kruskal–Wallis non-parametric ANOVA, $H(3) = 0.76$, $P > 0.05$]. However, in the animals which received post-training and pre-test administration of muscimol (0.1 μg/mouse, intra-CA1), pre-test administration of L-arginine (0.25 and 0.5 μg/mouse intra-CA1) decreased the improvement of memory retrieval by pre-test muscimol (0.1 μg/mouse, intra-CA1) treatment [Kruskal–Wallis non-parametric ANOVA, $H(3) = 22.65$, $P < 0.001$].

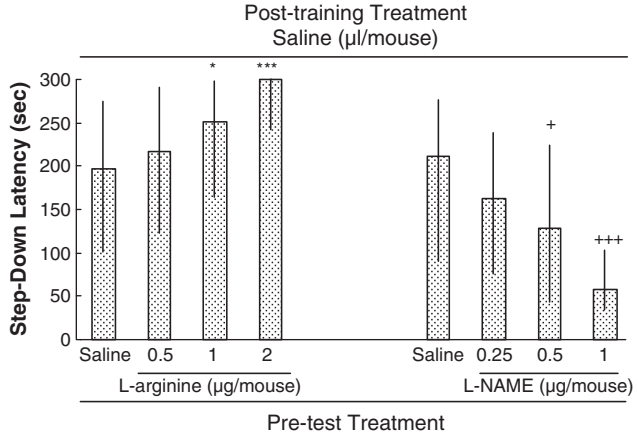

Fig. 2. The effects of pre-test administration of L-arginine and L-NAME on the step-down latencies in mice. The control group was administered post-training and pre-test saline (1 μl/mouse, intra-CA1). The other animals in each group were trained before saline administration (1 μl/mouse, intra-CA1) and were tested 15 min after receiving different doses of L-arginine (0.5, 1 and 2 μg/mouse, intra-CA1) or L-NAME (0.25, 0.5 and 1 μg/mouse, intra-CA1). Each value represents the median ± quartiles for 10 animals. *P < 0.05 and ***P < 0.001 compared with saline–saline group. $^{+}P < 0.05$ and $^{+++}P < 0.001$ compared with saline–saline group.

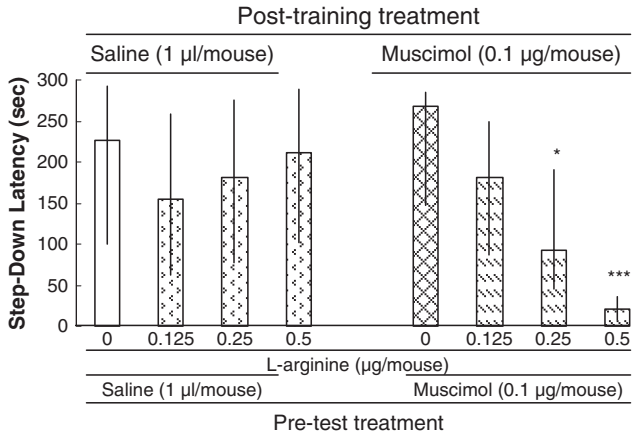

Fig. 3. The effects of pre-test administration of L-arginine following post-training treatment with saline or muscimol. All animals received saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) immediately after training. On the testing day, they received L-arginine (0, 0.125, 0.25 and 0.5 μg/mouse) and after 5 min, were injected with saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) 15 min before testing. Each value represents the median and interquartile ranges for 10 mice. *P < 0.05, ***P < 0.001 different from post-training muscimol/pre-test muscimol group.

3.4. Effects of pre-test intra-CA1 administration of L-NAME alone or with muscimol (0.025 μg/mouse) in mice trained under saline or muscimol (0.1 μg/mouse) on memory retrieval

As shown in Fig. 4, in animals trained before saline treatment and tested following administration of three different doses of L-NAME (0.0625, 0.125 and 0.25 μg/mouse, intra-CA1), no significant change was observed in the retention latencies as compared with saline–saline control group [Kruskal–Wallis non-parametric ANOVA, $H(3) = 5.9$, $P > 0.05$]. In the animals that post-training administration of muscimol (0.1 μg/mouse, intra-CA1) impaired memory retrieval, administration of L-NAME (0.25 μg/mouse, intra-CA1), on the test day, improved the memory retrieval significantly [Kruskal–Wallis, non-parametric ANOVA, $H(3) = 16.21$, $P < 0.05$]. Pre-test administration of L-NAME (0.125 and 0.25 μg/mouse, intra-CA1) in combination with muscimol (0.025 μg/mouse, intra-CA1) also improved the memory retrieval and mimicked the effects of pre-test muscimol treatment [Kruskal–Wallis non-parametric ANOVA, $H(3) = 27.33$, $P < 0.001$].

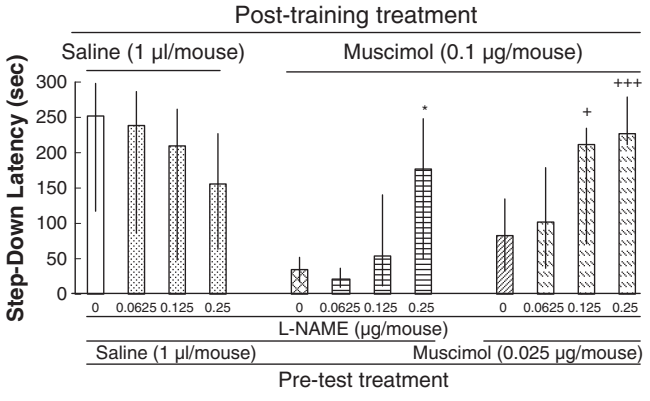

Fig. 4. The effects of pre-test administration of L-NAME following post-training treatment with saline or muscimol. The control group was administered post-training and pre-test saline (1 μl/mouse, intra-CA1). The other animals in each group received saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) immediately after training and L-NAME (0, 0.0625, 0.125 and 0.25 μg/mouse, intra-CA1) in the presence or absence of muscimol (0.025 μg/mouse, intra-CA1) before testing. Each value represents the median and interquartile ranges for 10 mice. *P < 0.05 different from muscimol (0.1 μg/mouse)/saline group. $^{+}P < 0.05$, $^{+++}P < 0.001$ different from post-training muscimol (0.1 μg/mouse)/pre-test muscimol (0.025 μg/mouse) group.

4. Discussion

Considerable evidence suggests that muscimol have impairing effects on learning and memory processes in laboratory animals (Castellano and McGaugh, 1990; Izquierdo et al., 1992; Nagahara and McGaugh, 1992; Nakagawa et al., 1995; Zarrindast et al., 2002). Our previous studies have shown that pre-training microinjection of muscimol-induced memory impairment in the step-down passive avoidance task in mice (Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011; Jafari-Sabet et al., 2013).

In this study muscimol was used after training (post-training) because it has been proposed that with pre-training administration, a drug might alter performance owing to its influences on sensitivity to shock or degree of arousal during the original training, rather than by directly modifying memory storage processes (Castellano et al., 2001; Khavandgar et al., 2003; Zarrindast et al., 2007; Darbandi et al., 2008).

Consistent with our previous studies, the present data showed that post-training intra-dorsal hippocampal (intra-CA1) administration of different doses of the $GABA_A$ receptor agonist, muscimol impaired memory retrieval in a one-trial step-down inhibitory avoidance task when test 24 h later.

Similarly, other investigations have also shown that pre-training administration of muscimol impaired memory formation in different paradigms (Farr et al., 2000; Chapouthier, 2004; Amaral et al., 2007) and in a state-dependent manner (Nabeshima et al., 1998; Nakagawa and Iwasaki, 1995).

Moreover, our results also indicated that pre-test microinjection of muscimol reverse memory impairment induced by post-training muscimol administration in a time- and dose-specific manner. Also, maximum effect occurred with the same dose of muscimol used during post-training. Together, memory retrieval will be better if tested under the influence of the same drug state (Carlezone et al., 1995; Bruins Slot and Colpaert, 1999; Jafari-Sabet et al., 2005; Zarrindast et al., 2006; Jafari-Sabet, 2011).

Present findings support our previous studies and demonstrate that muscimol produces a state of memory in which animals could learn and retrieve a specific response. State-dependent memory is a phenomenon in which the retrieval of newly acquired information is possible only if the subject is in the same sensory context and physiological state as during the encoding phase (Shulz et al., 2000; Jafari-Sabet et al., 2005; Zarrindast et al., 2006; Izquierdo et al., 2006).

Previously, we have shown that opioidergic (Jafari-Sabet and Jannat-Dastjerdi, 2009), muscarinic cholinergic (Jafari-Sabet, 2011) and α_2-adrenergic (Jafari-Sabet et al., 2013) systems in the CA1 region of the dorsal hippocampus are essential for producing muscimol-induced state dependent memory.

Considering that in hippocampal pyramidal cells, nNOS is associated with the postsynaptic active zone of different GABAergic synapses and also NO can directly modify GABAergic synapses on hippocampal pyramidal cells in an activity-dependent manner in animals (Szabadits et al., 2007) and cultured hippocampal neurons (Zanelli et al., 2009), the aim of the present study was to investigate the possible role of dorsal hippocampal NO system in muscimol state-dependent memory.

The present data show that pre-test intra-dorsal hippocampal (intra-CA1) administration of lower doses of a NO precursor, L-arginine had no significant effect on memory retrieval, while the higher doses of L-arginine significantly improved the memory retrieval in the step-down passive avoidance task.

Also, pre-test intra-dorsal hippocampal (intra-CA1) administration of lower doses of an inhibitor of NO-synthase, L-NAME had no significant effect on memory retrieval, while the higher doses of L-NAME significantly impaired the memory retrieval in the step-down passive avoidance task.

The results of the present experiments show that pre-test intra-dorsal hippocampal (intra-CA1) administration of lower doses of L-arginine do not affect the retrieval of memory by itself, while pre-test intra-dorsal hippocampal (intra-CA1) administration of the same doses of the drug with muscimol (0.1 μg/mouse) significantly and dose-dependently inhibited the muscimol-induced memory retrieval improvement.

Inhibition of the muscimol-induced improvement of memory recall by L-arginine, may suggest the involvement of the hippocampal NO system the processes. On the other hand, the effect of L-arginine may be produced through a dorsal hippocampal NO-dependent pathway.

It has been shown that the microinjection of L-arginine to the hippocampus dose-dependently increased the extracellular levels of the oxidative NO products by nNOS (Wu and Morris, 1998; Esplugues, 2002; Hara et al., 2004; Guimaraes et al., 2005). Furthermore, the synthesis of NO in the dorsal hippocampus is important in the acquisition of inhibitory avoidance in the step-down test (Bernabeu et al., 1995; Fin et al., 1995; Naassila et al., 2002).

Moreover, recent evidence suggest that nNOS is present in hippocampal GABAergic synapses in adult rodents (Szabadits et al., 2007).

It has been suggested that administration of high concentrations of NO donors enhance GABA release, while their low concentrations (range around basal NO levels) decrease GABA release in the hippocampus (Getting et al., 1996; Piri and Zarrindast, 2011) and in a cultured hippocampal neuron model (Zanelli et al., 2009).

Other investigations have also shown that NO through cGMP synthesis reduces the function of $GABA_A$ receptors in the cerebellum (Zarri et al., 1994; Robello et al., 1996; Prast and Philippu, 2001).

Our results also indicate that pre-test intra-CA1 administration of L-NAME alone, in the doses used, cannot affect memory formation. However, pre-test intra-CA1 administration of L-NAME (0.25 μg/mouse) reversed the memory impairment induced by post-training administration of muscimol (0.1 μg/mouse). In addition, L-NAME when co-administered with the lower dose of muscimol (0.025 μg/mouse) which did not induce state-dependent memory on the test day by itself, potentiated pre-test muscimol induced memory improvement. On the other hand, pre-test co-administration of L-NAME with an ineffective dose of muscimol (0.025 μg/mouse) restored muscimol-induced memory impairment and mimicked the effects of pre-test administration of a 0.1 μg/mouse of muscimol. These results also indicate an association between decrease in the NO release and the physiological state under which muscimol facilitates memory retrieval. These results may indicate that NO system in the dorsal hippocampus is involved in the muscimol state-dependent retrieval.

The data are in agreement with previous investigations, indicating an interaction between GABAergic and NO systems in the laboratory animals, concerning memory consolidation (Segovia et al., 1994; Guevara-Guzman et al., 1994; Casamenti et al., 1999; Prast and Philippu, 2001; Zanelli et al., 2009; Szabadits et al., 2011).

Ample evidence indicates that NOS are localized in the somata and dendrites of GABAergic medium spiny neurons where a high density of NMDA receptors is found (Gracy and Pickel, 1997; Afanas'ev et al., 2000).

Moreover, it has been suggested that molecular mechanism for NO signaling is present in the majority of hippocampal GABAergic synapses, and it is different from that found in glutamatergic synapses (Szabadits et al., 2007).

Furthermore, Szabadits et al. (2011) have shown that the retrograde NO–cGMP cascade triggered by NMDA receptor activation plays a role in the control of hippocampal GABAergic transmission in mice. On the other hand, NMDA receptors can modulate hippocampal GABAergic inhibition via NO–cGMP signaling in an activity-dependent manner and that this effect is subregion specific in the mouse hippocampus.

It has been shown that low concentrations of L-NAME and also high concentrations of a NO donor, SNAP (*S*-nitroso-*N*-acetylpenicillamine) enhance GABA release in the hippocampus (Getting et al., 1996; Prast and Philippu, 2001). Furthermore, previous studies have reported that low concentrations of the NO in the hippocampus inhibits, while elevated NO levels increase activity of excitatory and inhibitory amino acid utilizing neurons (Prast and Philippu, 2001).

Taken together, these findings support the idea that NO may have biphasic influences (i.e., both excitatory and inhibitory), based on the NO concentration and also a complex interaction between glutamatergic, GABAergic and other neuronal systems in the brain (Getting et al., 1996; Lin et al., 2000; Prast and Philippu, 2001; Edwards and Rickard, 2007; Piri et al., 2012; Zarrindast et al., 2012).

Moreover, it should be noted that the increases of GABA release may not be the only pathway responsible for NO effect on inhibitory avoidance memory and other neurotransmitters (dopamine, serotonin, glutamate, acetylcholine etc.) may also be involved therein (Myhrer, 2003).

Recent findings indicating the major molecular steps involved in memory retrieval in selected brain regions of the mammalian brain. Together the findings strongly suggest that memory formation and retrieval may share some molecular mechanisms in the hippocampus and that retrieval initiates extinction requiring activation of several signaling cascades and protein synthesis (Szapiro et al., 2002; Izquierdo et al., 2006). Furthermore, retrieval of one-trial avoidance require protein kinases such as protein kinase A (PKA), MAPKs, protein kinase C (PKC) activity and are modulated by $GABA_A$ receptors, α_2-adrenoceptors, dopamine D_1 receptors, β-adrenoceptors, $5HT_{1A}$ receptors, muscarinic cholinergic receptors and μ-opioid receptors in the hippocampus, the entorrhinal, parietal and cingulated cortex and the basolateral amygdala (Holt and Maren, 1999; Barros et al., 2001; Szapiro et al.,2002; Rossato et al., 2004; Phelps, 2004; Izquierdo et al., 2006; Jafari-Sabet, 2006a, b; Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011; Jafari-Sabet et al., 2013).

In addition, peripheral hormones and brain opioids are important in modulating retrieval and might be involved in endogenous state dependency (Izquierdo et al., 2006).

In conclusion, considering the effects of intra-CA1 administration of L-arginine (prevention of memory recall), and the effects of intra-CA1 administration of L-NAME (enhancement of memory recall) when co-administered with muscimol, it is possible that muscimol-induced memory recall is related to activation of the dorsal hippocampal nitrergic system. In addition, it must not be forgotten that, as is true in the CA1, all other connections among the hippocampus, amygdala and neocortex are bidirectional and involves a complex network of brain systems and serial and parallel molecular events, even for a task as deceptively simple as one-trial avoidance.

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