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β1-noradrenergic system of the dorsal hippocampus is involved in scopolamine state-dependent memory in rat

Bahareh Pakpour[1*], Morteza Piri[2], Majid Navaeian[3]

[1]*Department of Biology, Faculty of Basic Sciences, Islamic Azad University, Central Tehran Branch, Tehran, Iran*

[2]*Department of Biology, Faculty of Basic Sciences, Islamic Azad University, Ardabil Branch, Ardabil, Iran*

[3]*Department of Biology, Faculty of Basic Sciences, Islamic Azad University, Shahr-e-rey Branch, Tehran, Iran*

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Abstract

In the present study, we evaluated the possible effects of intra-CA1 administrations of β1-receptor agonist and antagonist, isoprenaline (isoproterenol) and atenolol respectively, on scopolamine state-dependent memory. Male Wistar rats were bilaterally implanted with chronic cannulae in the CA1 regions of the dorsal hippocampus, trained in a step-through type inhibitory avoidance task, and tested 24 h after training to measure step-through latency. Pre-training intra-CA1 injection of scopolamine (1.5 and 3 μg/rat) induced amnesia. The response induced by pre-training scopolamine was significantly reversed by pre-test administration of the drug that is due to a state-dependent effect. Although pre-test intra-CA1 administrations of isoprenaline alone had no effect, its administration (0.09 μg/rat) restored scopolamine amnesia. Furthermore, pre-test intra-CA1 injection of isoprenaline (0.01, 0.03 and 0.09 μg/rat) with an ineffective dose of scopolamine (0.25 μg/rat), synergistically improved memory performance impaired by pre-training scopolamine. The results also showed that pre-test intra-CA1 administrations of atenolol at dose of 0.09 μg/rat induced amnesia and disrupted state-dependent memory induced by scopolamine. Noteworthy, the response induced by the pre-test injection of isoprenaline plus scopolamine was antagonized with atenolol. These results suggest that β1-adrenergic receptors of the dorsal hippocampal CA1 regions may play an important role in scopolamine-induced amnesia and scopolamine state-dependent memory.

* **Corresponding Author:** Bahareh pakpour ✉ b_pakpour@yahoo.com

Introduction

The cholinergic input to the hippocampus has important roles in the learning and memory processes (Hasselmo, 1999; Kesner, 1988). The hippocampus receives cholinergic afferents from basal forebrain structures such as the medial septum and diagonal band of Broca (Mesulam *et al.*, 1983). Neurodegeneration of the cholinergic input to the hippocampus can be detected in patients with Alzheimer's disease and aging rodents (Sugaya *et al.*, 1998). Evidence indicates that drugs that support cholinergic function improve performance in several cognitive models in both rodents and humans, whereas anticholinergic drugs impair learning and memory in a variety of tasks (Azami *et al.*, 2010; Fibiger *et al.*, 1991; Gallagher and Colombo, 1995; Power *et al.*, 2003; Zarrindast *et al.*, 2002a). Further evidence also shows that release of acetylcholine (ACh) in the hippocampus increases during performance of a learned memory task (Stancampiano *et al.*, 1999). The increase in ACh is positively correlated with performance improvement during learning (Fadda *et al.*, 2006). Scopolamine, a nonselective muscarinic ACh antagonist, impairs learning and memory performance that has been proposed as an animal model of dementia (Azami *et al.*, 2010; Collerton, 1986; Jensen *et al.*, 1987; Mahmoodi *et al.*, 2010; Pakpour *et al.*, 2010; Quartermain and Leo, 1988). Similarities in the learning deficits between Alzheimer patients and scopolamine treated animals have been reported. Thus, it has been proposed that scopolamine, could serve as a useful pharmacological tool to produce a partial model of the disorder (Bartus, 2000). Furthermore, along with cholinergic atrophy, monoamines are reduced in Alzheimer's disease and the possibility may exist that enhancement of monoaminergic functions may elicit beneficial effects on behavior and cortical activity (Dringenberg, 2000; Hertz, 1989). For example, the Alzheimer's diseased brain undergoes severe noradrenergic deficits evidenced by cell losses in the locus coeruleus and by reduced noradrenaline contents (Hardy *et al.*, 1985; Hertz, 1989).

Monoaminergic systems are crucially involved in the control of behavioral processes related to anxiety, exploration, learning and memory (Graeff, 2002; Izquierdo, 1989; McGaugh, 1983). The various areas of the brain, including the hippocampus and the neocortex are innervated by the ascending noradrenergic system that originates in the locus coeruleus. Noradrenaline acts through two classes of receptors (α and β), both coupled with G-proteins (Sirvio and MacDonald, 1999). Although the expressions of β-adrenergic receptors in the brain are substantially lesser than the α subtype, they are critical for cognitive functions (Stuchlik and Vales, 2008). It has been shown that β-adrenergic receptors exhibit modulatory roles in the regulation of vigilance, learning and memory (Aston-Jones *et al.*, 1991; Cahill *et al.*, 2000; Przybyslawski *et al.*, 1999; Sara *et al.*, 1995). Administrations of norepinephrine (NE) and/or a β-adrenoreceptor agonist, isoprenaline (isoproterenol) improved retention performance in either spatial (Hatfield and McGaugh, 1999; Packard *et al.*, 1994) or emotionally-motivated memory tasks (Ferry and McGaugh, 1999; Introini-Collison *et al.*, 1991; Izquierdo *et al.*, 1992; Liang *et al.*, 1995; Liang *et al.*, 1986). Conversely, administration of β-adrenergic receptor antagonists impaired learning and memory in a variety of tasks (Barros *et al.*, 2001; Ferry *et al.*, 1999a; Gallagher *et al.*, 1977; Ikegaya *et al.*, 1997; Ji *et al.*, 2003b; Li and Mei, 1994; Singh *et al.*, 1990). Previous studies indicated that noradrenergic and cholinergic mechanisms interact in influencing memory (Azami *et al.*, 2010; Decker and Gallagher, 1987; Decker *et al.*, 1990; Decker and McGaugh, 1989). For example, noradrenaline may modulate the response of cortical and hippocampal neurons to ACh. Indeed, it has been shown that noradrenaline increases the response of cortical neurons to ACh and this effect seems to be under the control of fibers arising from the locus coeruleus since the responsiveness of cortical neurons to ACh is reduced after noradrenergic lesions (Waterhouse *et al.*, 1981). In addition, dorsal noradrenergic bundle lesions decrease the efficacy of physostigmine in reversing passive avoidance deficits in rats with basal forebrain lesions (Haroutunian *et al.*, 1990). Others

report that noradrenergic depletion potentiates the effects of cholinergic blockade in mice (Decker and Gallagher, 1987; Decker and McGaugh, 1989).

Our recent data has indicated that pre-training or post-training administration of scopolamine can impair inhibitory avoidance memory in a state-dependent manner, which is reversible by pre-test scopolamine administration (Azami *et al.*, 2010; Jamali-Raeufy *et al.*, 2011). State-dependent learning 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 the encoding phase (Azami *et al.*, 2010; Izquierdo and Dias, 1983; Nasehi *et al.*, 2010; Overton, 1966; Piri and Zarrindast, 2011a). According to research, inhibitory avoidance memory is modulated by the hippocampus through, at least in part, an adrenergic action (Azami *et al.*, 2010; Moshfegh *et al.*, 2010; Piri and Zarrindast, 2011a). Our previous studies also showed that α-adrenoceptors of the dorsal hippocampus play an crucial role on state-dependent memory induced by scopolamine or cannabinoid in adult male rats (Azami *et al.*, 2010; Moshfegh *et al.*, 2010; Piri and Zarrindast, 2011a), but role of β-adrenoceptors of the dorsal hippocampus on scopolamine state-dependent memory cannot be excluded. Therefore, the present study has aimed to investigate the effects of intra-CA1 administration of β1 noradrenergic agonist, isoprenaline and its antagonist, atenolol, on state-dependent memory induced by scopolamine in rat.

Materials and methods

Animals

Adult male Wistar rats (Pasteur institute, Tehran, Iran) weighing 220– 270 g at time of surgery were used. They had free access to food and water, were housed four in a cage, and kept at (22 ± 2) ◦C under a 12/12 h light-dark cycle (light beginning at 7:00 a.m). All experiments were carried out during the light phase between 8:00 and 14:00. Experimental groups consisted of eight animals and each animal was tested once. All procedures were performed in accordance with institutional guidelines for animal care and use.

Surgery

Animals were anaesthetized intraperitoneally with a ketamine/xylazine mixture (100 and 10 mg/kg, respectively) and placed in a stereotaxic frame (David Kopf Instruments, USA) with flat-skull position. A midline incision was made and the skin and underlying periosteum retracted. Stereotaxic coordinates for the CA1 regions of dorsal hippocampi were AP: −3 mm from bregma, L: ±2 mm from midline and V: −2.8 mm from the skull surface (Paxinos, 1997). The cannulae were anchored to the skull with dental cement, and then stainless steel stylets (27 gauge) were inserted into the guide cannulae to maintain patency prior to microinfusions.

Drugs and microinfusions

The drugs included scopolamine hydrobromide (Tocris, UK), atenolol (Daroopakhsh, Tehran, Iran), isoprenaline (isoproterenol) (Sigma, Poole, Dorset, UK). All drugs were dissolved in sterile saline and were injected into CA1 of dorsal hippocampus.

Intra- CA1 injections

For bilateral drug infusion, the animals were gently restrained by hand; the stylets were removed from the guide cannulae and replaced by 27-gauge injection needles (1mm below the tip of the guide cannula). The injection solutions were administered in a total volume of 1 µl/rat (0.5 µl in each side) over a 60 s period. Injection needles were left in place for an additional 60 s to facilitate the diffusion of the drugs.

Inhibitory avoidance apparatus.

A step-through inhibitory avoidance apparatus consisted of two compartments of the same size (20 × 20 × 30 cm3). In the middle of a dividing wall, a guillotine door (7.9 cm^2) could be lifted manually. The walls and floor of one compartment consisted of white opaque resin, the walls of the other compartment were dark. Stainless steel bars (3 mm in diameter and 1 cm intervals) constituted the floor of the dark compartment. Intermittent electric shocks (50 Hz, 3 s, 1 mA intensity) were delivered to the grid floor of the dark compartment by an isolated stimulator.

Behavioral procedures

Training was based on our previous studies (Zarrindast *et al.*, 2002b; Zarrindast *et al.*, 2005a). All animals were allowed to habituate in the experimental room (with light and sound attenuated) for at least 30 min prior to the experiments. Then, each animal was 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 with which the animal crossed into the dark compartment was recorded. Animals that waited more than 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 immediately withdrawn from the compartment. The trial was repeated after 30 min as in the acquisition trial where after 5 s the guillotine door was opened and as soon as the animal crossed to the dark (shock) compartment the door was closed and a foot shock (50 Hz, 1 mA and 3 s) was immediately delivered to the grid floor of the dark room. After 20 s, the rat was removed from the apparatus and placed temporarily into its home cage. Two minutes later, the animal was retested in the same way as in the previous trials; if the rat did not enter the dark compartment during 120 s a successful acquisition of IA response was recorded. Otherwise, when the rat entered the dark compartment (before 120 s) a second time, the door was closed and the animal received the shock again. Intra-CA1 infusions were performed 5 min prior to the train and/or test. For the study of memory 24 h after training, each animal was gently placed in the light compartment and after 5 seconds (sec) the door was opened, and Step-through latency (sec) was measured in absence of electric foot shocks, as indicators of inhibitory avoidance behavior. An upper cut-off of 300 sec was set. The retention test was also carried out between 8:00 a.m. and 2:00 p.m.

Data analysis

The data are expressed as mean ± S.E.M. The statistical analysis was performed using one- and two-way analysis of variance (ANOVA). Post-hoc comparison of means was carried out with the Tukey 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.

Histology

After the testing sessions each rat was deeply anesthetized and 1 ml of a 4% methylene-blue solution was bilaterally infused into the CA1 (0.5 ml/ side), as described in the drug section, then decapitated and its brain removed and placed in formaldehyde (10%). After several days, the brains were sliced and the sites of injections were verified according to Paxinos & Watson, 2007. Only data from animals with correct cannulae implants.

Experimental design

Eight animals were used in each experimental group. In experiments where animals received one or two injections, the control groups also received one or two saline injections. The intervals of drug administration were based on previous studies in order to obtain a maximum response.

Experiment 1: effect of scopolamine on memory retrieval

In this experiment, the effect of pre-training and pre-test administration of scopolamine on inhibitory avoidance response was examined. Five groups of animals received saline or different doses of scopolamine (0.25, 0.75, 1.5 and 3 µg/ rat, intra-CA1), 5 min before the training phase (pre-training). On the test day, the animals received saline (1 µl/rat, intra-CA1) 5 min before the test. The other eight groups of animals received saline (1 µl/rat, intra-CA1) or scopolamine (3 µg/ rat, intra-CA1), 5 min before the training and pre-test (5 min before the test) injections of different doses of scopolamine (0.25, 0.75, 1.5 and 3 µg/ rat, intra-CA1).

Experiment 2: effects of pre-test administration of isoprenaline on inhibitory avoidance memory in the presence or absence of scopolamine In this experiment, four groups of animals received

saline (1 µl/rat, intra-CA1) 5 min before the training and different doses of isoprenaline (0, 0.01, 0.03 and 0.09 µg/rat, intra-CA1) 2 min before saline (1 µl/rat, intra - CA1). Another four groups received pre-training administration of scopolamine (3 µg/ rat, intra-CA1). , The animals received the isoprenaline (0, 0.01, 0.03 and 0.09 µg/rat, intra-CA1) 2 min before saline (1 µl/rat, intra - CA1). A further four groups of animals received scopolamine (3 µg/ rat, intra - CA1) 5 min prior to training. The animals received the same doses of isoprenaline 2 min before scopolamine (0.25 µg/ rat, intra - CA1). The step-through latency was measured 5 min after the last injection.

Experiment 3: effects of pre-test administration of atenolol on inhibitory avoidance memory in the presence or absence of scopolamine.

On the training day, all animals received pre-training administration of saline (1 µl/rat, intra-CA1) or scopolamine (3 µg/ rat, intra-CA1). On the test day, the animals received pre-test intra-CA1 administration of atenolol (0, 0.01, 0.03 and 0.09 µg/rat, intra -CA1) 2 min before saline (Fig. 3, left panel) or scopolamine (3 µg/ rat) (Fig. 3, right panel). The step-through latency was measured 5 min after the last injection.

Experiment 4: effect of atenolol on the isoprenaline-induced potentiation of the scopolamine response. In this experiment, on the training day, all animals received pre-training administration of scopolamine (3 µg/ rat, intra-CA1). On the testing day, four groups of the animals received a pre-test intra-CA1 injection of atenolol (0, 0.01, 0.03 and 0.09 µg/rat, intra -CA1). After 2 min, they were injected with isoprenaline (0.01 µg/rat, intra -CA1) and 2 min later, they received scopolamine (0.25 µg/ rat). Two control groups were also used in this experiment. The first group received three pre-test intra-CA1 injections of saline (1 µl/rat) with 2 min interval. The second group received two pretest intra-CA1 microinjections of saline (1 µl/rat) with 2 min interval, and after 2 min they were injected with scopolamine (0.25 µg/ rat). The step-through latency was measured 5 min after the last injection.

Results

Effects of Scopolamine on inhibitory avoidance memory

Fig. 1 shows the effects of pre-training (left panel) or pre-test (middle panel) intra-CA1 administration of scopolamine on step-through latency. One-way ANOVA revealed that pre-training [F (4,35) = 16.49, P<0.001] or pre-test [F(4,35)= 14.96, P<0.001] scopolamine (1.5 and 3 µg/rat, intra-CA1) dose-dependently reduced the step-through latency in the inhibitory avoidance task, showing scopolamine-induced amnesia. Fig. 1 (right panel) indicates that animals in which memory was impaired due to pre-training administration of scopolamine (scopolamine-induced amnesia), pre-test scopolamine (0.75, 1.5 and 3 µg/rat, intra-CA1) restored the memory to the control level (scopolamine state of memory) [F(4,35)= 24.83, P<0.001].

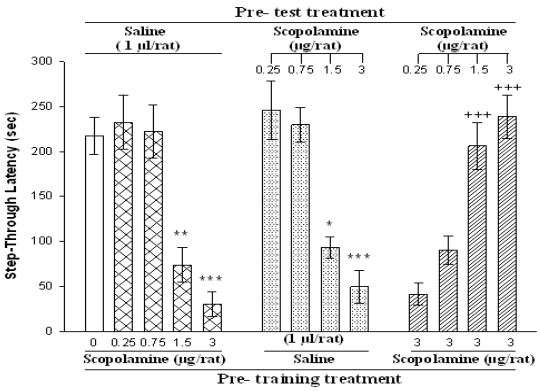

Fig. 1. The effects of pre-training and pre-test administration of scopolamine on inhibitory avoidance memory. Five groups of animals received saline or different doses of scopolamine (0.25, 0.75, 1.5 and 3 µg/ rat, intra-CA1), 5 min before the training phase (pre-training). On the test day, animals received saline (1µl/rat, intra-CA1) 5 min before the test (pretest). Other four groups of animals received pre-training injection of saline (1 µl/rat) and pretesting injections of different doses of scopolamine (0.25, 0.75, 1.5 and 3 µg/rat, intra-CA1). In another four groups, the animals received pre-training administration of a high dose of scopolamine (3 µg/rat, intra-CA1) and pretesting injections of different doses of scopolamine (0.25, 0.75, 1.5 and 3 µg/rat, intra-CA1). Data are expressed as mean ±

S.E.M. of eight animals per group. *P< 0.05, ***P< 0.01, ***P< 0.001different from pre-training saline/pre-test saline group. +++P< 0.001different from pre-training scopolamine (3 µg/rat)/pre-test saline group.

Effects of pre-test administration of isoprenaline on memory retrieval in the presence or absence of Scopolamine Fig. 2 indicates the effects of pre-test intra-CA1 injection of isoprenaline in the presence or absence of scopolamine on memory retrieval. Two-way ANOVA indicated an interaction between the groups of animals which received pre-training saline (1 µl/rat) and pre-test isoprenaline (0 ,0.01, 0.03 and 0.09 µg/rat, intra-CA1) and those which received pre -training scopolamine (3 µg/rat, intra-CA1) and pre-test isoprenaline [for Treatment, $F(1,56)= 62.97$ $P<0.001$; Dose, $F(3,56)= 9.68$, $P<0.001$; and Treatment × Dose interaction, $F(3,56)= 5.45$, $P<0.01$] on memory retrieval. Two-way ANOVA also revealed a significant difference between the groups of animals which received pre-training saline (1 µl/rat) and pre-test isoprenaline and those which received pre-training scopolamine (3 µg/rat, intra-CA1), followed by pre-test isoprenaline plus a lower dose of scopolamine (0.25 µg/rat, intra-CA1) [for Treatment, $F(1,56)= 6.01$, $P<0.05$; Dose, $F(3,56)= 5.04$, $P<0.01$; and Treatment ×Dose interaction, $F(3,56)= 6.18$, $P<0.001$] on memory retrieval. Furthermore, two-way ANOVA revealed a significant difference between the groups of animals which received pre-training scopolamine (3 µg/rat, intra-CA1) and pre-test isoprenaline and those which received pre-training scopolamine (3 µg/rat, intra-CA1), followed by pre-test isoprenaline plus a lower dose of scopolamine (0.25 µg/rat, intra-CA1) [for Treatment, $F(1,56)= 35.47$, $P<0.001$; Dose, $F(3,56)= 28.76$, $P<0.001$; and Treatment ×Dose interaction, $F(3,56)= 7.56$, $P<0.001$] on memory retrieval. In addition, post hoc analysis revealed that in the animals that received saline before training and tested following intra-CA1 administration of isoprenaline (Fig. 2, left panel), no significant change was observed in the retrieval latencies [$F(3,28)= 0.63$, $P>0.05$] as compared with the saline/saline control group. Furthermore, in the animals that pre-training administration of scopolamine (3 µg/rat, intra-CA1) impaired inhibitory avoidance memory, administration of isoprenaline (0.09 µg/rat), on the test day, significantly [$F(3,28)= 28.99$, $P<0.001$] reversed memory impairment (Fig. 2, middle panel). Moreover, the lower dose of pre-test scopolamine (0.25 µg/rat, intra-CA1) alone did not induce a significant scopolamine state-dependent memory. However, co-administration of the different doses of isoprenaline (0.01, 0.03 and 0.09 µg/rat, intra-CA1) with 0.25 µg/rat of scopolamine significantly improved the memory retrieval and mimicked the effects of pre-test administration of a higher dose of scopolamine treatment [$F(3,28)= 12.97$, $P<0.001$] (Fig. 2, right panel).

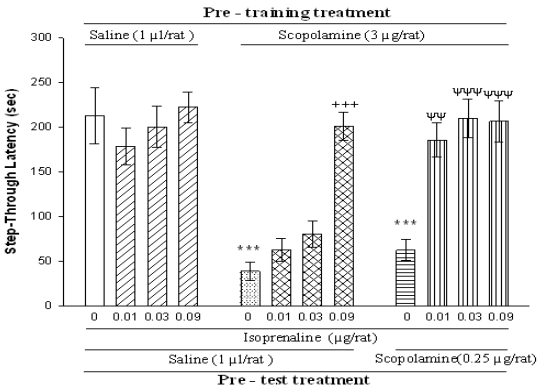

Fig. 2. The effects of pre-test administration of isoprenaline on inhibitory avoidance memory in the presence or absence of scopolamine. In one series, all animals received pre-training administration of saline (1 µl/rat, intra CA1), and pre-testing, administration of isoprenaline (0, 0.01, 0.03 and 0.09 µg/rat, intra-CA1) 2 min before saline (1 µl/rat, intra CA1). In another groups, the animals received pre-training administration of scopolamine (3 µg/rat, intra-CA1) and pre-test injection of isoprenaline (0, 0.01, 0.03 and 0.09 µg/rat, intra-CA1) 2 min before the administration of saline (1 µl/rat, intra CA1) or scopolamine (0.25 µg/rat, intra-CA1). The step-through latency was measured 5 min after the last injection in all animals. Data are expressed as mean ± S.E.M. of eight animals per group. ***P< 0.001 different from saline/saline group. +++ P<0.001different from scopolamine (3 µg/rat)/saline group. ψψ P< 0.01, ψψψ P< 0.001 different from scopolamine (3 µg/rat)/scopolamine (0.25 µg/rat) group.

Effects of pre-test administration of atenolol on memory retrieval in the presence or absence of Scopolamine Two-way ANOVA indicated no significant difference between the effects of atenolol (0, 0.01, 0.03 and 0.09 µg/rat, intra -CA1) in the absence or presence of effective dose of scopolamine (3 µg/rat, intra-CA1) [for Treatment, $F(1,56)= 0.03$, $P>0.05$; Dose, $F(3,56)= 16.59$, $P <0.001$; and Treatment × Dose interaction, $F(3,56) = 0.46$, $P>0.05$]. In addition, post hoc analysis revealed that pre-test injection of atenolol reduced the step-through latency in the inhibitory avoidance task [$F(3,28) = 12.62$, $P<0.001$]. Furthermore, in the animals which received pre-training and pre-test administration of scopolamine (3 µg/rat, intra-CA1), pre-test intra-CA1 administration of atenolol decreased the improvement of memory retrieval by pre-test scopolamine (3 µg/rat, intra-CA1) treatment [$F(3,28) = 5.35$, $P<0.01$].

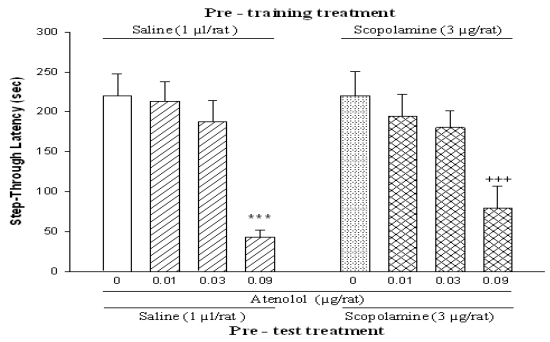

Fig. 3. The effects of pre-test administration of atenolol on inhibitory avoidance memory in the presence or absence of scopolamine. All animals received pre-training administration of saline (1 µl/rat, intra CA1) or scopolamine (3 µg/rat, intra-CA1) and pre-test administration of different doses of atenolol (0, 0.01, 0.03 and 0.09 µg/rat, intra -CA1) 2 min before saline (1 µl/rat, intra CA1) or scopolamine (3 µg/rat, intra-CA1). The step- through latency was measured 5 min after the last injection in all animals. Data are expressed as mean ± S.E.M. of eight animals per group. ***P< 0.001different from saline/saline group. +++ P<0.001different from scopolamine (3 µg/rat)/scopolamine (3 µg/rat) group.

Effects of intra-CA1 administration of atenolol on the isoprenaline-induced potentiation of the scopolamine response Figure 4 shows the effect of intra-CA1 microinjections of atenolol on the response induced by isoprenaline plus scopolamine. One-way ANOVA revealed that intra-CA1 microinjection of different doses of atenolol altered the response induced by co-administration of isoprenaline (0.01 µg/rat, intra-CA1) plus scopolamine (0.25 µg/rat, intra-CA1) [$F(5,42)= 23.01$, $P<0.001$]. Post-hoc analysis showed that different doses of atenolol (0.01, 0.03 and 0.09 µg/rat) reversed the isoprenaline-induced potentiating of the scopolamine response.

Discussion

Step-through is a model of inhibitory avoidance task which is extensively used in pharmacological studies of long-term memory in rodents (Izquierdo *et al.*, 2006; Izquierdo and McGaugh, 2000). In the present study, effects of local injections of β1 noradrenergic receptor agents in the dorsal hippocampus on scopolamine-induced amnesia and scopolamine state-dependent memory were investigated. In agreement with other investigations, our data showed that pre-training or pre-test intra-CA1 administration of scopolamine by itself impaired inhibitory avoidance memory on the test day (Azami *et al.*, 2010; Ghorbanalizadeh-Khalifeh-Mahaleh *et al.*, 2008; Mahmoodi *et al.*, 2010; Pakpour *et al.*, 2010). Ample evidence showed that hippocampal dependent learning is associated with an increase in hippocampal ACh levels (Micheau and Marighetto, 2011). There are reports indicating that anticholinergic drugs such as scopolamine impair learning and memory in different tasks, which is directly related to a decrease in central cholinergic functions (Fibiger, 1991; Gallagher and Colombo, 1995). In many behavioral paradigms, the deficits produced by muscarinic cholinergic antagonism are similar to the effects produced by hippocampal lesions (Watts *et al.*, 1981). Data obtained by some investigators indicate that the degeneration and dysfunction of cholinergic neurons is also closely associated with the cognitive deficits of Alzheimer's disease and aging (Bartus *et al.*, 1982; Coyle *et al.*, 1983; Kesner, 1988; Sugaya *et al.*, 1998). The present results also showed that pre-test intra-CA1 administration of the same dose of scopolamine

reversed scopolamine-induced amnesia. A similar response has been shown for morphine (Piri and Zarrindast, 2011b; Zarrindast *et al.*, 2006; Zarrindast *et al.*, 2012b), lithium (Zarrindast *et al.*, 2005b), histamine (Zarrindast *et al.*, 2005b) and cannabinoids (Nasehi *et al.*, 2010; Piri and Zarrindast, 2011a) which have been considered as state-dependent memory. This phenomenon is related to the dose of drug and the time of its administration (Izquierdo and Dias, 1983; Overton, 1966; Piri and Zarrindast, 2011a; b; Zarrindast *et al.*, 2012b). It has been shown that acquisition, consolidation and retrieval of operant and inhibitory avoidance memory is accompanied and regulated by different molecules and neuromodulatory states (Azami *et al.*, 2010; Kim and Baxter, 2001), but the exact mechanism involved in scopolamine state-dependency is not clear.

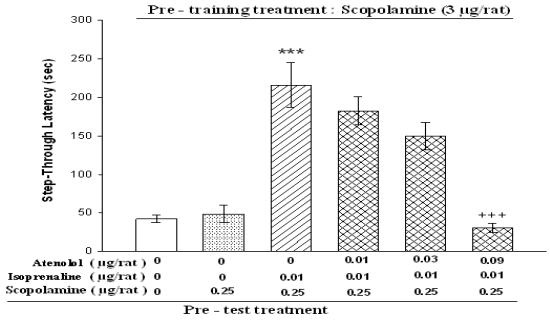

Fig. 4. The effect of atenolol on the isoprenaline-induced potentiation of the scopolamine response.

Six groups of animals were used. All animals received pre-training administration of (3 µg/ rat, intra-CA1). On the test day, one groups received three intra-CA1 injections of saline (1 µl/rat, intra-CA1) with 2 min interval. Another group received two intra-CA1 injections of saline (1 µl/rat, intra-CA1) with 2 min interval, and after 2 min they were injected with scopolamine (0.25 µg/ rat, intra-CA1). Four groups of animals received intra-CA1 microinjections of different doses of atenolol (0, 0.01, 0.03 and 0.09 µg/rat, intra -CA1) and after 2 min, were injected with isoprenaline (0.01 µg/rat, intra-CA1) and 2 min later, they received scopolamine (0.25 µg/ rat). The step-through latency was measured 5 min after the last injection in all animals. Data are expressed as mean ± S.E.M. of eight animals per group. ***p<0.001 different from scopolamine (3 µg/ rat)/saline. +++p<0.001 different from scopolamine (3 µg/ rat)/isoprenaline (0.01 µg/rat) plus scopolamine (0.25 µg/ rat).

In the next part of the study, the effects of β1-noradrenergic receptors of dorsal hippocampus on inhibitory avoidance memory and scopolamine amnesia have been investigated. Our results, it has been shown that pre-test microinjection of β1-noradrenergic agonist, isoprenaline into the CA1 region of dorsal hippocampus by itself does not significantly alter inhibitory avoidance memory, but can reverse memory impairment induced by pre-training administration of scopolamine. Furthermore, pre-test co-administration of non-effective doses of the isoprenaline with a dose of scopolamine (0.25 µg/rat), which by itself did not induce a response, reversed memory impairment due to pre-training scopolamine injection. The data obtained in the study indicate that activation of dorsal hippocampal β1-noradrenergic receptors could reverse scopolamine amnesia. In agreement with our present data, other investigators have shown that adrenergic agonists such as amphetamine (Martinez *et al.*, 1980), phenylephrine (Ferry *et al.*, 1999a; b) and isoprenaline (Ghiasvand *et al.*, 2011; Zarrindast *et al.*, 2012a) have enhancing effects on memory, primarily in memory-deficit models. The data may be supported by previous investigations showing that systemic administration of subeffective doses of epinephrine potentiates the memory-enhancing effects of low doses of physostigmine in inhibitory avoidance and a Y-maze discrimination tasks (Introini-Collison and McGaugh, 1988). Our previous studies indicated that the activation of α-adrenergic receptors of dorsal hippocampus restored scopolamine amnesia. There is also evidence that some behavioral effect of α-adrenergic receptors potentiated or mediated by β-noradrenergic receptors. For example, evidence indicated that α1-adrenoceptors are implicated in mediation of the effects of norepinephrine on memory and their action depends on concurrent β-adrenoceptor activation (Ferry *et al.*, 1999a). There are also some reports indicating activation of α1-adrenoceptors potentiates

β-adrenoceptor mediated activation of cAMP formation (Ferry *et al.*, 1999a; b). The data obtained by isoprenaline in this study are similar to those obtained by α-noradrenergic receptor agonist in our previous work and proposed that activation of noradrenergic receptors of dorsal hippocampus can influence scopolamine amnesia. Since cAMP/PKA signaling has important role in learning and memory (Drain *et al.*, 1991), one may expect that intra-CA1 injections of isoprenaline may influence inhibitory avoidance memory via activation of cAMP/PKA pathway. On the other hand, there is also a report showing that the ascending noradrenergic system can regulate the activity of cholinergic neurons in the brain. For example, systemic or intracerebroventricular injection of NE reduces release of ACh from cortical slices (Moroni *et al.*, 1983; Vizi, 1980). Conversely, lesions of the LC have been reported to increase release of ACh from cortical slices, suggesting that NE control of ACh release is tonically engaged (Vizi, 1980). On the contrary, some investigations have suggested that NE have a different effect on the septohippocampal cholinergic system: NE release in the septal region increases ACh turnover in hippocampus (Costa *et al.*, 1983). Given that we found a β1-noradrenergic receptors agonist potentiated reversal effect of scopolamine on scopolamine amnesia, these interactions in which the effects of β1-noradrenergic receptors agonist on cholinergic function are inhibitory would appear to provide a basis for our results.

In addition, the present study investigated the effects of pre-test microinjection of β1-adrenergic receptor antagonist, atenolol on inhibitory avoidance memory. Our results reveal impairment in inhibitory avoidance performance after pre-test intra-CA1 administration of atenolol. Other studies have shown that blockade of β1-noradrenergic receptors impairs memory. In agreement with our present studies, several lines of evidence have been reported that β- noradrenergic receptor is a crucial for learning and memory (Gibbs *et al.*, 2008; Ji *et al.*, 2003a; Ji *et al.*, 2003b). β1-adrenoceptors also appears to be involved in the modulation of memory by the dorsal hippocampus (Gibbs *et al.*, 2008; Ji *et al.*, 2003a; Ji *et al.*, 2003b). Blockade of beta-adrenoceptors in the CA1 region of dorsal hippocampus impairs spatial memory and long-term contextual fear memory (Ji *et al.*, 2003a; Ji *et al.*, 2003b). Furthermore, it has been shown that noradrenergic receptors play a role in state-dependent learning (Azami *et al.*, 2010; Berridge and Waterhouse, 2003; Homayoun *et al.*, 2003; Piri and Zarrindast, 2011a). We have already shown that α-adrenergic receptors of dorsal hippocampus are involved in scopolamine state-dependent memory (Azami *et al.*, 2010). To support the involvement of β1-noradrenergic receptor mechanism of the dorsal hippocampus in the scopolamine state-dependent memory, more experiments were done with the blockade of β1-noradrenergic receptors in the dorsal hippocampus. The results revealed that pre-test intra-CA1 administrations of β1- noradrenergic receptor antagonist, atenolol, disrupted state-dependent memory induced by scopolamine. For further support of the hypothesis, we examined the effect of pre-test intra-CA1 administration of atenolol on memory restoration by co-administration of isoprenaline plus scopolamine. The present results indicated that atenolol prevented reversal effect of pre-test intra-CA1 administrations of isoprenaline along with a low dose of scopolamine on scopolamine amnesia. The decrease in retrieval now induced by atenolol may agree with findings of others indicating that β-noradrenergic receptor antagonist exerts amnesic effects in different models of memory (Gibbs *et al.*, 2008; Ji *et al.*, 2003a; Ji *et al.*, 2003b) such as inhibitory avoidance memory (Liang *et al.*, 1986), spatial memory (Ji *et al.*, 2003b), contextual fear memory (Ji *et al.*, 2003a), and auditory fear memory (Ghorbanalizadeh-Khalifeh-Mahaleh *et al.*, 2008). The results obtained in the study are in agreement with others who found that pre-test injection of the β1- noradrenergic receptor antagonist inhibited cannabinoid state-dependent memory (Ghiasvand *et al.*, 2011). The idea may be supported by previous investigations showing that Blockade of dorsal hippocampal α-noradrenergic receptors inhibits scopolamine-state-dependent memory (Azami *et al.*, 2010). The data also may be supported by previous

investigations showing that systemic pre-training administration of scopolamine and propranolol (a nonselective β-adrenoceptor antagonist), in subeffective doses, impairs inhibitory avoidance and spatial memory when the drugs are administered together prior to training (Decker *et al.*, 1990).

In conclusion, considering that pre-training scopolamine-induced amnesia can be decreased by pre-test injection of β1-adrenergic agonists and inhibition of memory retrieval in the animals which received both pre-training and pre-test administration of scopolamine by the β1-adrenergic antagonists, it is possible that scopolamine state-dependent memory may be related to activation of the CA1 β1-adrenergic receptors. However, more experiments are required to clarify the exact mechanism(s) involved in the interaction between scopolamine and β1-adrenoceptors.

Conclusion

This paper is extracted from the research project entitled"β1-noradrenergic system of the dorsal hippocampus is involved in scopolamine state-dependent memory in rat "which has been operated in Islamic Azad university, central Tehran branch.

References

Aston-Jones G, Chiang C, Alexinsky T. 1991. Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. Brain Research **88,** 501-520.

Azami NS, Piri M, Oryan S, Jahanshahi M, Babapour V, Zarrindast MR. 2010. Involvement of dorsal hippocampal alpha-adrenergic receptors in the effect of scopolamine on memory retrieval in inhibitory avoidance task. Neurobiology of Learning and Memory **93,** 455-462.

Barros DM. 2001. Simultaneous modulation of retrieval by dopaminergic D(1), beta-noradrenergic, serotonergic-1A and cholinergic muscarinic receptors in cortical structures of the rat. Behavioral Brain Research **124,** 1-7.

Bartus RT. 2000. On neurodegenerative diseases, models, and treatment strategies: lessons learned and lessons forgotten a generation following the cholinergic hypothesis. Experimental Neurology **163,** 495-529.

Bartus RT, Dean RL, 3rd, Beer B, Lippa AS. 1982. The cholinergic hypothesis of geriatric memory dysfunction. Science **217,** 408-414.

Berridge CW,Waterhouse BD. 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Research Brain Reserch Review **42,** 33-84.

Cahill L, Pham CA, Setlow B. 2000. Impaired memory consolidation in rats produced with beta-adrenergic blockade. Neurobiology of Learning and Memory **74,** 259-266.

Collerton D. 1986. Cholinergic function and intellectual decline in Alzheimer's disease. Neuroscience **19,** 1-28.

Costa E, Panula P, Thompson HK, Cheney DL. 1983. The transsynaptic regulation of the septal-hippocampal cholinergic neurons. Life Science **32,** 165-179.

Coyle JT, Price DL, DeLong MR. 1983. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science **219,** 1184-1190.

Decker MW, Gallagher M. 1987. Scopolamine-disruption of radial arm maze performance: modification by noradrenergic depletion. Brain Research **417,** 59-69.

Decker MW, Gill TM, McGaugh JL. 1990. Concurrent muscarinic and beta-adrenergic blockade in rats impairs place-learning in a water maze and retention of inhibitory avoidance. Brain Research, **513,** 81-85.

Decker MW, McGaugh JL. 1989. Effects of concurrent manipulations of cholinergic and noradrenergic function on learning and retention in mice. Brain Research, **477,** 29-37.

Drain P, Folkers E, Quinn WG. 1991. cAMP-dependent protein kinase and the disruption of learning in transgenic flies. Neuron-cell, **6,** 71-82.

Dringenberg HC. (2000). Alzheimer's disease: more than a 'cholinergic disorder' - evidence that cholinergic-monoaminergic interactions contribute to EEG slowing and dementia. Behavioral Brain Research **115,** 235-249.

Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. 2006. Scopolamine and MK801-induced working memory deficits in rats are not reversed by CBD-rich cannabis extracts. Behavioral Brain Research **168,** 307-311.

Ferry B, McGaugh JL. 1999. Clenbuterol administration into the basolateral amygdala post-training enhances retention in an inhibitory avoidance task. Neurobiology of Learning and Memory **72,** 8-12.

Ferry B, Roozendaal B, McGaugh JL. 1999a. Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between beta- and alpha1-adrenoceptors.The Jornal of Neuroscience **19,** 5119-5123.

Ferry B, Roozendaal B, McGaugh JL. 1999b. Involvement of alpha1-adrenoceptors in the basolateral amygdala in modulation of memory storage. Europian Jornal of Pharmacology **372,** 9-16.

Fibiger HC. 1991. Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. Trends in Neuroscience **14,** 220-223.

Fibiger HC, Damsma G, Day JC. 1991. Behavioral pharmacology and biochemistry of central cholinergic neurotransmission. Advance in Experimental Medicine & Biology **295,** 399-414.

Gallagher M, Colombo PJ. 1995. Ageing: the cholinergic hypothesis of cognitive decline. Current Opinion in Neurobiology, **5**, 161-168.

Gallagher M, Kapp BS, Musty RE, Driscoll PA. 1977. Memory formation: evidence for a specific neurochemical system in the amygdala. Science **198**, 423-425.

Ghiasvand M, Rezayof A, Ahmadi S, Zarrindast MR. 2011. beta1-noradrenergic system of the central amygdala is involved in state-dependent memory induced by a cannabinoid agonist, WIN55,212-2, in rat. Behavioral Brain Research **225**, 1-6.

Ghorbanalizadeh Khalifeh Mahaleh B, Taheri S, Sahebgharani M, Rezayof A. Haeri-Rohani A, Zarrindast MR. 2008. Intra-dorsal hippocampal microinjections of lithium and scopolamine induce a cross state-dependent learning in mice. Archives of Iranian Medicine, **11,** 629-638.

Gibbs ME, Bowser DN, Hutchinson DS, Loiacono RE, Summers RJ. 2008. Memory processing in the avian hippocampus involves interactions between beta-adrenoceptors, glutamate receptors, and metabolism. Neuropsychopharmacology **33,** 2831-2846.

Graeff FG. 2002. On serotonin and experimental anxiety. Psychopharmacology (Berl) **163,** 467-476.

Hardy J. 1985. Transmitter deficits in Alzheimer's disease. Neurochemistry International, **7**, 545-563.

Haroutunian V, Kanof PD, Tsuboyama G, Davis KL. 1990. Restoration of cholinomimetic activity by clonidine in cholinergic plus noradrenergic lesioned rats. Brain Research **507,** 261-266.

Hasselmo ME. 1999. Neuromodulation: acetylcholine and memory consolidation. Trends in Cognitive Sciences **3,** 351-359.

Hatfield T, McGaugh JL. 1999. Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. Neurobiology Learn and Memory **71,** 232-239.

Hertz L. 1989. Is Alzheimer's disease an anterograde degeneration, originating in the brainstem, and disrupting metabolic and functional interactions between neurons and glial cells? Brain Research Review **14,** 335-353.

Homayoun H, Khavandgar S, Zarrindast MR. 2003. Morphine state-dependent learning: interactions with alpha2-adrenoceptors and acute stress. Behavioral of Pharmacology **14,** 41-48.

Ikegaya Y, Nakanishi K, Saito H, Abe K. 1997. Amygdala beta-noradrenergic influence on hippocampal long-term potentiation in vivo. Neuroreport **8,** 3143-3146.

Introini-Collison IB, McGaugh JL. 1988. Modulation of memory by post-training epinephrine: involvement of cholinergic mechanisms. Psychopharmacology (Berl), **94,** 379-385.

Introini-Collison IB, Miyazaki B, McGaugh JL. 1991. Involvement of the amygdala in the memory-enhancing effects of clenbuterol. Psychopharmacology (Berl), **104,** 541-544.

Izquierdo I. 1989. Different forms of post-training memory processing. Behavioral Neural of Biology **51**, 171-202.

Izquierdo I, Bevilaqua LR, Rossato JI, Bonini JS, Medina JH, Cammarota M. 2006. Different molecular cascades in different sites of the brain control memory consolidation. Trends in Neurosciences **29,** 496-505.

Izquierdo I, da Cunha C, Rosat R, Jerusalinsky D, Ferreira MB, Medina JH. 1992. Neurotransmitter receptors involved in post-training memory processing by the amygdala, medial septum, and hippocampus of the rat. Behavioral Neural Biology **58,** 16-26.

Izquierdo I, Dias RD. 1983. Endogenous state-dependency:memory regulation by post-training and pre-testing administration of ACTH, beta -endorphin, adrenaline and tyramine. Brazilian Jornal of Medical and Biology Research **16,** 55-64.

Izquierdo I, McGaugh JL. 2000. Behavioural pharmacology and its contribution to the molecular basis of memory consolidation. Behavioral of Pharmacology **11,** 517-534.

Jamali-Raeufy N, Nasehi M, Ebrahimi-Ghiri M, Zarrindast MR. 2011. Cross state-dependency of learning between WIN55, 212-2 and scopolamine in rat dorsal hippocampus. Neuroscience Letter **491**, 227-231.

Jensen LH, Stephens DN, Sarter M, Petersen EN. 1987. Bidirectional effects of beta-carbolines and benzodiazepines on cognitive processes. Brain Reserch Bulletin **19,** 359-364.

Ji JZ, Wang XM, Li BM. 2003a. Deficit in long-term contextual fear memory induced by blockade of beta-adrenoceptors in hippocampal CA1 region. Europian Jornal of Neuroscience **17,** 1947-1952.

Ji JZ, Zhang XH, Li BM. 2003b. Deficient spatial memory induced by blockade of beta-adrenoceptors in the hippocampal CA1 region. Behavioral of Neuroscience, **117,** 1378-1384.

Kesner RP. 1988. Reevaluation of the contribution of the basal forebrain cholinergic system to memory. Neurobiology of Aging, **9,** 609-616.

Kim JJ, Baxter MG. 2001. Multiple brain-memory systems: the whole does not equal the sum of its parts. Trends in Neurosciences **24,** 324-330. 7

Li BM, Mei ZT. 1994. Delayed-response deficit induced by local injection of the alpha 2-adrenergic antagonist yohimbine into the dorsolateral prefrontal cortex in young adult monkeys. Behavioral Neural Biology **62,** 134-139.

Liang KC, Chen LL, Huang TE. 1995. The role of amygdala norepinephrine in memory formation: involvement in the memory enhancing effect of peripheral epinephrine. The Chinese Jornal of Physiology **38,** 81-91.

Liang KC, Juler RG, McGaugh JL. 1986. Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. *Brain Res*erch **368,** 125-133.

Mahmoodi G, Ahmadi S, Pourmotabbed A, Oryan S, Zarrindast MR. 2010. Inhibitory avoidance memory deficit induced by scopolamine: Interaction of cholinergic and glutamatergic systems in the ventral tegmental area. Neurobioogyl of Learn and Memory **94,** 83-90.

Martinez JL, JR. 1980. Attenuation of amphetamine-induced enhancement of learning by adrenal demedullation. Brain Research **195,** 433-443.

McGaugh JL. 1983. Hormonal influences on memory. Annual Review of Psychology **34,** 297-323.

Mesulam MM, Mufson EJ, Levey AI, Wainer BH. 1983. Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. Jornal of Comparative Neurology **214,** 170-197.

Micheau J, Marighetto A. 2011. Acetylcholine and memory: a long, complex and chaotic but still living relationship. Behavioral Brain Research **221,** 424-429.

Moroni F, Tanganelli S, Antonelli T, Carla V, Bianchi C, Beani L. 1983. Modulation of cortical acetylcholine and gamma-aminobutyric acid release in freely moving guinea pigs: effects of clonidine and other adrenergic drugs. Jornal of Pharmacology and Experimental Therapeutics **227,** 435-440.

Moshfegh A, Babaei P, Oryan S, Soltani B. and Zarrindast MR. 2010. Involvement of dorsal hippocampal alpha1-adrenergic receptors in the effect of WIN55,212-2 on memory retrieval in inhibitory avoidance task. Neuroscience Letter **489,** 69-73.

Nasehi M, Piri M, Jamali-Raeufy N, Zarrindast MR. 2010. Influence of intracerebral administration of NO agents in dorsal hippocampus (CA1) on cannabinoid state-dependent memory in the step-down passive avoidance test. Physiology of Behavioral **100,** 297-304.

Overton DA. 1966. State-dependent learning produced by depressant and atropine-like drugs. Psychopharmacologia **10,** 6-31.

Packard MG, Cahill L, McGaugh JL. 1994. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. Proceeding of the National Academy of Sciences of the United States of America **91,** 8477-8481.

Pakpour B, Ahmadi S, Nayer-Nouri T, Oryan S, Zarrindast MR. 2010. Inhibitory avoidance memory deficit induced by scopolamine: interaction with glutamatergic system in the nucleus accumbens. Behavioral of Pharmacology.

Paxinos G, Watson C. 1997. The rat brain in stereotaxic coordinates San Diego: Academic Press.

Piri M, Zarrindast MR. 2011a. Modulation of WIN55,212-2 state-dependent memory by alpha2-adrenergic receptors of the dorsal hippocampus. Archive of Iranian Medicin **14,** 389-395.

Piri M, Zarrindast MR. 2011b. Nitric oxide in the ventral tegmental area is involved in retrieval of inhibitory avoidance memory by nicotine. Neuroscience **175,** 154-161.

Power AE, Vazdarjanova A, McGaugh JL. 2003. Muscarinic cholinergic influences in memory consolidation. Neurobiology of Learning and Memory **80,** 178-193.

Przybyslawski J, Roullet P, Sara SJ. 1999. Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. Jornal Neuroscience **19,** 6623-6628.

Quartermain D, Leo P. 1988. Alleviation of scopolamine amnesia by different retrieval enhancing treatments. Pharmacology Biochemistry and Behavior **30,** 1093-1096.

Sara SJ, Dyon-Laurent C, Herve A. 1995. Novelty seeking behavior in the rat is dependent upon the integrity of the noradrenergic system. Brain Research Cognetive Brain Research **2,** 181-187.

Singh PP, Junnarkar AY, Varma RK., Thomas GP, Tripathi RM. 1990. Effect of various hypotensive agents on locomotor activity and blood pressure of rats. Mater Med Pol- Bilboteca Medical nacional- infomed **22**, 176-178.

Sirvio J, MacDonald E. 1999. Central alpha1-adrenoceptors: their role in the modulation of attention and memory formation. Pharmacology & Therapeutics **83**, 49-65.

Stancampiano R, Cocco S, Cugusi C, Sarais L, Fadda F. 1999. Serotonin and acetylcholine release response in the rat hippocampus during a spatial memory task. Neuroscience **89,** 1135-1143.

Stuchlik A, Vales K. 2008. Role of alpha1- and alpha2-adrenoceptors in the regulation of locomotion and spatial behavior in the active place avoidance task: a dose-response study. Neuroscience Letter, **433,** 235-240.

Sugaya K. 1998. Septo-hippocampal cholinergic and neurotrophin markers in age-induced cognitive decline. Neurobiology of Aging, **19**, 351-361. http://www.sciencedirect.com/science/article/pii/S0197458098000724

Vizi ES. 1980. Modulation of cortical release of acetylcholine by noradrenaline released from nerves arising from the rat locus coeruleus. Neuroscience **5,** 2139-2144.

Waterhouse BD, Moises HC, Woodward DJ. 1981. Alpha-receptor-mediated facilitation of somatosensory cortical neuronal responses to excitatory synaptic inputs and iontophoretically applied acetylcholine. Neuropharmacology **20,** 907-920.

Watts J, Stevens R, Robinson C. 1981. Effects of scopolamine on radial maze performance in rats. Physiology of Behavioral **26,** 845-851.

Zarrindast MR, Bakhsha A, Rostami P, Shafaghi B. 2002a. Effects of intrahippocampal injection of GABAergic drugs on memory retention of passive avoidance learning in rats. Jornal of Psychopharmacol **16,** 313-319.

Zarrindast MR, Bananej M, Khalilzadeh A, Fazli-Tabaei S, Haeri-Rohani A, Rezayof A. 2006. Influence of intracerebroventricular administration of dopaminergic drugs on morphine state-dependent memory in the step-down passive avoidance test. Neurobiology of Learn and Memory, **86,** 286-292.

Zarrindast MR, Eidi M, Eidi A, Oryan S. 2002b. Effects of histamine and opioid systems on memory retention of passive avoidance learning in rats. Europian Jornal of Pharmacology **452,** 193-197.

Zarrindast MR, Farajzadeh Z, Rostami P, Rezayof A, Nourjah P. 2005a. Involvement of the ventral tegmental area (VTA) in morphine-induced memory retention in morphine-sensitized rats. Behavioral Brain Research **163,** 100-106.

Zarrindast MR, Fazli-Tabaei S, Khalilzadeh A, Farahmanfar M, Yahyavi SH. 2005b. Cross state-dependent retrieval between histamine and lithium. Physiology of Behavioral **86,** 154-163.

Zarrindast MR, Ghiasvand M, Rezayof A, Ahmadi S. 2012a. The amnesic effect of intra-central amygdala administration of a cannabinoid CB1 receptor agonist, WIN55,212-2, is mediated by a beta-1 noradrenergic system in rat. Neuroscience **212,** 77-85.

Zarrindast MR, Piri M, Nasehi M, Ebrahimi-Ghiri M. 2012b. Nitric oxide in the nucleus accumbens is involved in retrieval of inhibitory avoidance memory by nicotine. Pharmacology Biochemistry and Behavior **101,** 166-173.