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Involvement of dorsal hippocampal muscarinic cholinergic receptors on muscimol state-dependent memory of passive avoidance in mice

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ABSTRACT

Aims: In the present study, the effects of bilateral intra-dorsal hippocampal (intra-CA1) injections of cholinergic agents on muscimol state-dependent memory were examined in mice.
Main methods: A single-trial step-down passive avoidance task was used for the assessment of memory retention in adult male NMRI mice.
Key findings: Pre-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, intra-CA1) induced state-dependent retrieval of the memory acquired under pre-training muscimol (0.1 μg/mouse, intra-CA1) influence. Pre-test intra-CA1 injection of an acetylcholinesterase inhibitor, physostigmine (0.5 and 1 μg/mouse, intra-CA1) reversed the memory impairment induced by pre-training administration of muscimol (0.1 μg/mouse, intra-CA1). Moreover, pre-test administration of physostigmine (0.5 and 1 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 physostigmine (0.25, 0.5 and 1 μg/mouse) by itself cannot affect memory retention. Pre-test intra-CA1 injection of the muscarinic receptor antagonist, atropine (1 and 2 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 atropine (0.5, 1 and 2 μg/mouse) by itself cannot affect memory retention.
Significance: The results suggest that muscarinic cholinergic mechanism of the CA1 may influence muscimol state-dependent memory.

Introduction

It is a well known fact that γ-aminobutyric acid (GABA)-ergic system affects learning and memory processes (Castellano and McGaugh, 1990; Nakagawa et al., 1999; Reis et al., 2009; Makkar et al., 2010). GABA plays a controlling role on the balance of excitability and inhibitory states in the cortex, hippocampus and the interneurons and is involved in information processing in the hippocampus (Paulsen and Moser, 1998).

The administration of GABAergic receptor agonists impairs memory, while their antagonists facilitate memory storage and retrieval in inhibitory avoidance tasks (Castellano and McGaugh, 1990; Farr et al., 2000; Chapouthier, 2004; Amaral et al., 2007). GABA exerts its action by interaction with GABA-A, GABA-B and GABA-C receptor subtypes. GABA-A and GABA-C are associated with ligand gated chloride channels, whereas GABA-B receptors are linked to G-proteins (Emson, 2007; Olsen and Sieghart, 2009).

Our previous study 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 (Jafari-Sabet and Jannat-Dastjerdi, 2009). 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).

Hippocampal muscarinic cholinergic receptors are critically involved in cognitive functions, including learning and memory (Ikonen et al., 2002; Manns et al., 2003; Varga et al., 2003; Bainbridge et al., 2008; Doralp and Leung, 2008).

It is well documented that administration of muscarinic cholinergic agonists (Castellano et al., 1996) and acetylcholinesterase inhibitors, which enhance the availability of acetylcholine in the synaptic cleft

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(Liang and Tang, 2006), improved memory (Molchan et al., 1992; Degroot and Parent, 2001; Jafari-Sabet, 2006a,b), while anticholinergic drugs impaired of learning and memory in a variety of tasks (Fibiger, 1991; Izquierdo et al. 1992; Jafari-Sabet, 2006a,b).

Extensive evidence indicates that GABA-A receptor activation increases the dose of acetylcholine receptor agonists needed in the hippocampus to reverse memory deficits (Durkin, 1992; Gorman et al., 1994; Farr et al., 2000; Degroot and Parent, 2000; Degroot and Treit, 2003; Krebs and Parent, 2005).

Moreover, neuroanatomical data indicate that GABA-A receptors are present on the cell bodies of both GABAergic and cholinergic septohippocampal neurons (Gao et al., 1995).

Also medial septum is connected to the hippocampus via the fimbria fornix, which is composed primarily of cholinergic and GABAergic projection neurons (Lewis et al., 1967; Freund and Buzsáki, 1996; Krebs-Kraft et al., 2007).

Since the role of CA1 muscarinic cholinergic system on muscimol state-dependent memory has not been shown previously, the aim of the present study was to investigate the effects of bilateral intra-dorsal hippocampal (intra-CA1) injections of an acetylcholinesterase inhibitor and the muscarinic receptor antagonist on muscimol induced state-dependent memory retrieval in a passive avoidance task in mice.

Experimental procedures

Animals

Male albino NMRI mice (Razi Institute, Iran), weighing 25–35 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.

Surgery

Mice were anesthetized with intraperitoneal 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 23-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 1-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.

Drugs

The drugs used in the present study were muscimol (Tocris Cookson Ltd., UK), physostigmine (Sigma, St. Louis, CA, USA), atropine (Sigma, St. Louis, CA, USA). All drugs were dissolved in sterile 0.9% saline and were injected into the dorsal hippocampal CA1 regions (intra-CA1) 1 μl/mouse. Control animals received saline.

Apparatus

The passive avoidance apparatus consisted of a wooden box (30 cm × 30 cm × 40 cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter, set 1 cm apart). A wooden platform (4 cm × 4 cm × 4 cm) was set in the center of the grid floor. Intermittent electric shocks (1 Hz, 0.5 s, 45 V DC) were delivered to the grid floor by an insulated stimulator (Harvard Stimulator 6002, England).

Behavioural training

A single-trial step-down passive avoidance task was used. Animals were submitted to the behavioral procedure 7 days after surgery. Each mouse was gently placed on the wooden platform. When the mouse stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s. This training procedure was carried out between 9:00 and 15:00 h. Each mouse was placed on the platform again at 24-h after training and the step-down latency was measured with a stopwatch as passive avoidance behavior. An upper cut-off time of 300 s was set. The retention test was also carried out between 9:00 and 15:00 h.

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.

Experiment 1. The effects of muscimol on memory retrieval

In this experiment, seven groups of animals were used. The control group received saline (1 μl/mouse, intra-CA1) 15 min before training (pre-training) and 15 min before testing (pre-test). Three groups of animals received pre-training muscimol (0.025, 0.05 and 0.1 μg/mouse, intra-CA1) 15 min before training, followed by pre-test saline (1 μl/mouse, intra-CA1) 15 min before testing. Another three groups of animals received pre-training muscimol (0.1 μg/mouse, intra-CA1) 15 min before 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.

Experiment 2. Effects of pre-test administration of physostigmine in mice trained under saline or muscimol (0.1 μg/mouse)

In this experiment, four groups received saline (1 μl/mouse, intra-CA1) 15 min before training and also different doses of an acetylcholinesterase inhibitor, physostigmine (0, 0.25, 0.5 and 1 μg/mouse, intra-CA1) plus saline (1 μl/mouse) 15 min before testing. Another four groups were trained 15 min after muscimol administration (0.1 μg/mouse, intra-CA1), and were tested 24 h later, 15 min after pre-test administration of physostigmine (0, 0.25, 0.5 and 1 μg/mouse, intra-CA1) plus saline (1 μl/mouse, intra-CA1). Further four groups were trained 15 min after muscimol administration (0.1 μg/mouse, intra-CA1) and were tested 24 h later, 15 min after pre-test administration of physostigmine (0, 0.25, 0.5 and 1 μg/mouse, intra-CA1) plus muscimol (0.025 μg/mouse, intra-CA1).

Experiment 3. Effects of pre-test administration of atropine in mice trained under saline or muscimol (0.1 μg/mouse)

In this experiment, eight groups of animals were used. The animals received pre-training saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) 15 min before training. On the testing day,

they received different doses of a muscarinic receptor antagonist, atropine (0, 0.5, 1 and 2 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.

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.

Fig. 1 shows the approximate point of the drug injections in the CA1 regions of the dorsal hippocampus. The histological results were plotted on representative sections taken from the mouse brain atlas of Paxinos and Franklin (2001). Data from animals with injection sites located outside the CA1 regions were not used in the analysis.

Statistical analysis

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

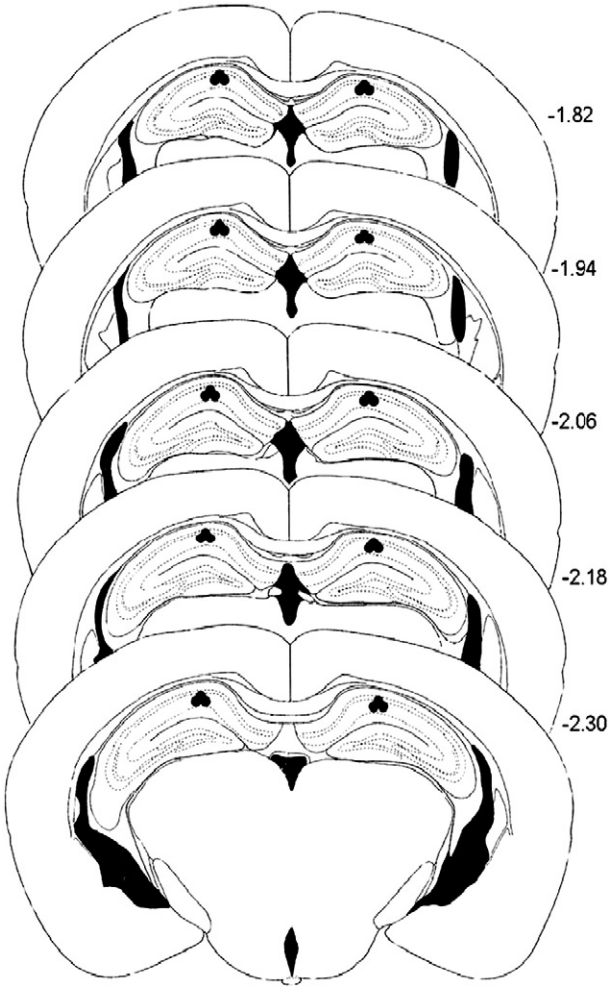

Fig. 1. Schematic illustrations of coronal sections of the mouse brain showing the approximate location of dorsal hippocampus sites in the experiments. The numbers indicate AP coordinates relative to bregma. Atlas plates adapted from Paxinos and Franklin (2001).

Results

The effects of muscimol on memory retrieval

As shown in Fig. 2, pre-training administration of different doses of GABA-A receptor agonist, muscimol (0.05 and 0.1 μg/mouse, intra-CA1) altered the memory retrieval on the test day, compared with saline-treated animals. Lower doses of muscimol (0.025 μg/mouse) had no significant effect on memory retrieval, while the higher doses of muscimol (0.05 and 0.1 μg/mouse) significantly impaired the memory retrieval on the test day (Kruskal–Wallis non-parametric ANOVA, $H(3)=19.62$, $p<0.001$). The greatest response was obtained with 0.1 μg/mouse of drug. In the other group, pre-training administration of muscimol (0.1 μg/mouse, intra-CA1) impaired memory retrieval 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, $H(3)=21.54$, $p<0.001$). The greatest response was obtained with 0.1 μg/mouse of drug. The results indicate that pre-training injection of muscimol induced memory impairment which was restored when the same dose of the drug was administered 24 h later in a pre-test session.

Effects of pre-test administration of physostigmine in mice trained under saline or muscimol (0.1 μg/mouse)

As shown in Fig. 3, in animals trained after saline treatment and tested following administration of three different doses of physostigmine (0.25, 0.5 and 1 μg/mouse), no significant change was observed in the retention latencies as compared with saline/saline control group [Kruskal–Wallis non-parametric ANOVA, $H(3)=8.6$, $p>0.05$]. In the animals that pre-training administration of muscimol (0.1 μg/mouse, intra-CA1) impaired memory retrieval, administration of physostigmine

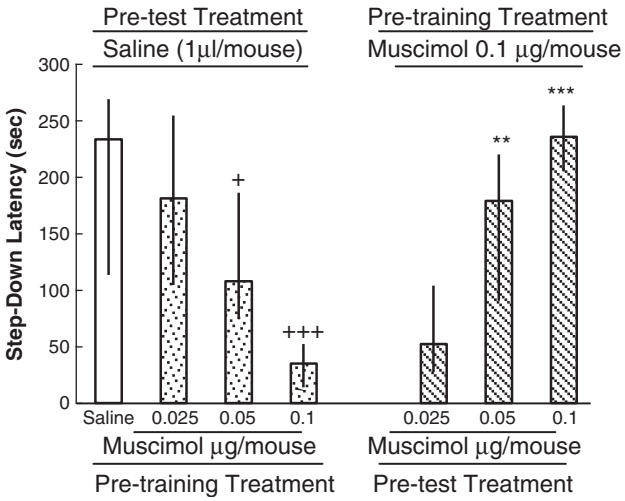

Fig. 2. The effects of pre-training and pre-test administration of muscimol or saline on step-down latencies in mice. The control group was administered pre-training and pre-test saline (1 μl/mouse, intra-CA1). Three groups of animals were trained 15 min after muscimol administration (0.025, 0.05 and 0.1 μg/mouse, intra-CA1) and were tested 15 min after receiving saline. Another three groups of animals were trained 15 min after 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 pre-training saline/pre-test saline group. ** $p<0.01$, *** $p<0.001$ different from pre-training muscimol (0.1 μg/mouse)/pre-test saline group.

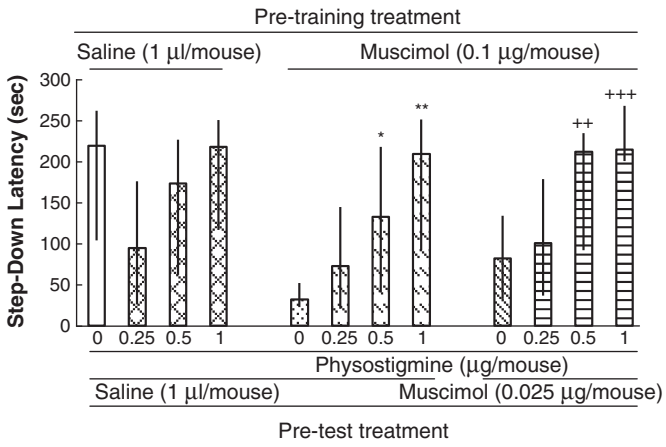

Fig. 3. The effects of pre-test administration of physostigmine following pre-training treatment with saline or muscimol. The control group was trained and tested 15 min after saline administration (1 μl/mouse, intra-CA1). The other animals in each group received saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) 15 min before training and physostigmine (0, 0.25, 0.5 and 1 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,**p<0.01 different from muscimol (0.1 μg/mouse)/saline group.++p<0.01, +++p<0.001 different from pre-training muscimol (0.1 μg/mouse)/pre-test muscimol (0.025 μg/mouse) group.

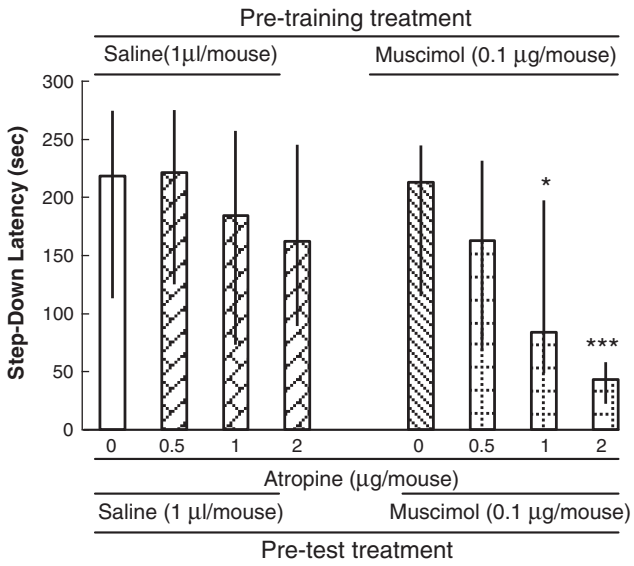

Fig. 4. The effects of pre–test administration of atropine following pretraining treatment with saline or muscimol. All animals received saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra–CA1) 15 min before training. On the testing day, they received atropine (0, 0.5, 1 and 2 μg/mouse, intra–CA1) 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 pre–training muscimol/pre–test muscimol group.

(0.5 and 1 μg/mouse; intra-CA1), on the test day, improved the memory retrieval significantly [Kruskal–Wallis, non-parametric ANOVA, $H(3) = 27.18$, $p<0.01$]. Pre-test administration of physostigmine (0.5 and 1 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, $H(3) = 21.99$, $p<0.001$].

Effects of pre-test administration of atropine in mice trained under saline or muscimol (0.1 μg/mouse)

Fig. 4, indicates that in animals trained after saline treatment and tested following the administration of three different doses of atropine (0.5, 1 and 2 μg/mouse), no significant change was observed in the retention latencies compared to the saline/saline control group [Kruskal–Wallis non-parametric ANOVA, $H(3) = 0.68$, $p>0.05$].

However, in the animals which received pre-training and pre-test administration of muscimol (0.1 μg/mouse, intra-CA1), pre-test administration of atropine (1 and 2 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, $H(3) = 19.88$, $p<0.001$].

Discussion

The CA1 region of the hippocampus is essential for memory formation of one-trial avoidance (Izquierdo and Medina, 1997; Riedel et al., 1999; Jafari-Sabet, 2006b).

One-trial step-down passive avoidance in rodents has long been a favorite model for biochemical and pharmacological studies of memory (Izquierdo et al., 2006) and induces LTP in CA1 (Whitlock et al., 2006).

The present data show that pre-training intra-dorsal hippocampal (intra-CA1) administration of different doses of the GABA-A receptor agonist, muscimol impaired memory retrieval in the step-down passive avoidance task. These results are in agreement with our previous study (Jafari-Sabet and Jannat-Dastjerdi, 2009) and other investigators who found that muscimol impaired memory formation (Jerusalinsky et al., 1994; Castellano et al., 1996; Farr et al., 2000; Chapouthier, 2004; Amaral et al., 2007), indicating the possible existence of an inhibitory influence of the brain GABA-A system on memory.

Furthermore, our results also indicate that impairment of memory formation induced by acute pre-training muscimol injection can be reversed by pre-test muscimol in a time- and dose-specific manner. Maximum effect occurring with the same dose of muscimol used during training and administered with the same time interval before testing. Present findings support our previous study and demonstrate that muscimol produces a state of memory in which animals could learn and retrieve a specific response (Jafari-Sabet and Jannat-Dastjerdi, 2009).

Our previous studies (Jafari-Sabet, 2006a,b) have shown that intrahippocampal administration of higher doses of physostigmine increased retention latencies, although lower doses of the drug did not affect retention latencies. Also, intrahippocampal administration of higher doses of atropine decreased retention latencies, although lower doses of the drug did not affect retention latencies. In these experiments, we used lower doses of physostigmine or atropine that alone cannot affect memory retention.

The results of the present experiments show that pre-test intra-CA1 administration of certain doses of an acetylcholinesterase inhibitor, physostigmine by itself cannot affect memory formation. However, pre-test intra-CA1 administration of the same doses of the physostigmine reversed the memory impairment induced by pre-training administration of muscimol. In addition, physostigmine 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.

Zhong et al. (2003) have shown that muscarinic acetylcholine receptors could enhance GABAergic synaptic transmission through a presynaptic and a postsynaptic mechanism. Also Degroot and Parent (2000, 2001) as well as Krebs and Parent (2005) have shown that increase hippocampal acetylcholine levels reverse the memory deficits produced by medial septum GABA-A receptor activation.

Furthermore, medial septum GABA-A receptor activation increases the dose of acetylcholine receptor agonists needed in the hippocampus to reverse memory deficits (Farr et al., 1999).

These results are in agreement with our study and also may indicate that the muscarinic cholinergic receptor stimulation in the dorsal hippocampus is involved in the muscimol state-dependent retrieval.

Our results also indicate that pre-test intra-CA1 administration of certain doses of the muscarinic receptors antagonist, atropine do not affect the retrieval of memory by itself, while pre-test intra-CA1 administration of the same doses of the drugs 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 atropine, may suggest the involvement of the hippocampal muscarinic cholinergic systems in these processes.

These results are in agreement with our previous studies (Jafari-Sabet, 2006a,b) and other investigators who found that muscarinic cholinergic receptors antagonists impair memory formation (Givens and Olton, 1995; Alreja et al., 2000; Elvander et al., 2004).

Many studies have shown that memory consolidation and retrieval are accompanied and regulated by different neuromodulatory and molecular 'states' (McGaugh, 2000; Phelps, 2004). Memories, particularly those of an emotional type, have been suggested to rely on an endogenous state-dependent process (Izquierdo, 1984; Barros et al. 2000).

Both consolidation and retrieval of one-trial avoidance require PKA and ERK activity in the hippocampus, the entorhinal, parietal and cingulate cortex and the basolateral amygdala, and both are modulated by D1 receptors, β-adrenoceptors, 5HT1A receptors and muscarinic cholinergic receptors in all these structures (Izquierdo et al. 1992; Phelps, 2004; Izquierdo et al., 2006; Jafari-Sabet, 2006a). The monoamines dopamine, noradrenaline, 5-hydroytryptamine (5-HT) and acetylcholine all affect cAMP synthesis and thus regulate PKA (Izquierdo and Medina, 1997; Izquierdo and McGaugh, 2000; Rossato et al., 2004).

In conclusion, considering the effects of intra-dorsal hippocampal (intra-CA1) injection of physostigmine (enhancement of memory recall), and the effects of intra-dorsal hippocampal (intra-CA1) injection of atropine (prevention of memory recall) when co-administered with muscimol, it is possible that muscimol-induced memory recall is related to activation of dorsal hippocampal cholinergic 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.

Conflict of interest statement

There is no conflict of interest.

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