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## **Muscarinic Receptors in the Basolateral Amygdala involve in the effect of Pre-test administration of Dexamethasone on Memory Retrieval in Rats**

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### **ABSTRACT**

The effects of glucocorticoids on brain functions such as modulation of learning and memory are well documented. This study was conducted to examine the involvement of acetylcholine muscarinic receptors (mAChRs) of the baso-lateral amygdala (BLA) in the impairment effect of dexamethasone on memory retrieval. Adult male Wistar rats (220-250 g) were bilaterally cannulated in the BLA by stereotaxic surgery. The animal were trained and tested in the step-through apparatus, that consisted of two compartments which were connected via a small door, after one week. The rats were trained by induction of electric shock (1 mA, 3 sec) and then they were tested for memory retrieval 24 h later (without receive shock). The time of latency (Step-through latencies) for entering the place of receiving the shock, the dark compartment of the instrument and the time spent by rats in this chamber (Time spent in dark chamber) were recorded for evaluation of the passive avoidance memory retrieval. Administration of the dexamethasone (2 mg kg<sup>-1</sup>, s.c.) before testing impaired memory retrieval. This effect of dexamethasone was reversed by pre-test administration of different doses of pilocarpine (1, 2 µg/rat, intra-BLA), a muscarinic receptor agonist. While, Pre-test co-administration of low doses of scopolamine (0.3 and 0.5 µg/rat, intra-BLA), a muscarinic receptor antagonist, with the ineffective dose of the dexamethasone (0.5 mg kg<sup>-1</sup>, s.c.) impaired memory retrieval. However, the same doses of pilocarpine and scopolamine without dexamethasone did not affect memory processes. Our findings indicate that mechanisms of the mAChRs of the BLA may be mediate the impairment effect of dexamethasone on memory retrieval.

**Key words:** Baso-lateral amygdala, dexamethasone, muscarinic receptors, passive avoidance task, memory retrieval

### **INTRODUCTION**

Glucocorticoids are important adrenal hormones which different stressors affect their secretion, via the hypothalamus-pituitary system. The last decades studies have shown that these hormones are involved in cognitive functions such as, the learning and memory processes (Power and McGaugh, 2002; Rashidy-Pour *et al.*, 2004; Tehranipour and Kafaei, 2010). Glucocorticoids have different effects on the memory stages. They have enhancing effect on the consolidation of memory

and induce memory retrieval impairments in certain memory types. For example, pre or post training systemic administration of the agonists of glucocorticoids enhances memory consolidation. While, these drugs impair memory retrieval when given before retention testing (Rashidy-Pour *et al.*, 2004). Glucocorticoids act via intracellular receptors (genomic effect) and a nongenomic pathway by interaction with the membrane receptors (Mikics *et al.*, 2004; Koyano *et al.*, 2005). The effects of glucocorticoids in the brain can be mediated via these two receptor mechanisms by interaction with several neurotransmitter systems in the brain including noradrenergic (Roozendaal, 2000), cholinergic (Power and McGaugh, 2002), dopaminergic (Pakdel and Rashidy-Pour, 2006) and opiodergic systems (Sajadi *et al.*, 2007).

It is well known that the baso-lateral amygdale (BLA) require for modulation of learning and memory. BLA also mediate the effects of some hormones and neurotransmitters on the memory formation. On the other hand, it send widespread projections to the hippocampus and the prefrontal cortex. These structures have an important role in memory processing (Pare, 2003; Tehranipour and Khakzad, 2008; Rahim *et al.*, 2010). The BLA has a high accumulation of glucocorticoids receptors (Grs) and it is an important brain region for the cognitive effects of glucocorticoids (Roozendaal, 2000; McReynolds *et al.*, 2010). As the enhancement of memory consolidation by the systemic injection of glucocorticoids drugs, in passive avoidance tasks, is blocked by lesion of the BLA (Roozendaal *et al.*, 1996). There are also an extensive neuronal networks of cholinergic (McGaugh and Roozendaal, 2008; Carballo-Marquez *et al.*, 2009), noradrenergic, GABAergic and glutamatergic in the BLA. It has suggested that some of these neuronal pathways mediate the glucocorticoids functions in BLA (Pare, 2003; McGaugh and Roozendaal, 2008).

Extensive studies show that the central cholinergic neurotransmission is essential for cognitive function and underlying memory processes. The findings of these researches indicate that increase of the brain cholinergic activity is accompanied with enhancement of memory. It has been proposed that dysfunction of central cholinergic system is involved in the memory deficiency diseases including, Alzheimer (Lee *et al.*, 2008; Power *et al.*, 2003).

Generally, it should be considered that the administration of cholinergic receptor agonists improve, while cholinergic receptor antagonists impair memory retrieval, respectively (Power *et al.*, 2003; Rezayof *et al.*, 2009). It is important to note that the cholinergic receptors of the BLA modulates processes of memory. Some experimental models, including inhibitory avoidance or contextual fear conditioning, were used for evaluation of the effect of cholinergic drugs on memory (Boccia *et al.*, 2009). Furthermore, there is evidence that the BLA Muscarinic acetylcholine receptors (mAChRs) are important for memory storage. Intra BLA injections of mAChRs agonists enhance the memory formation. On the other hand, microinjections of the antagonists of these receptors impair memory retrieval (Boccia *et al.*, 2009; Carballo-Marquez *et al.*, 2009).

Prior studies showed that the BLA has a high distribution of mAChRs and GRs, however interaction of these receptors on the retrieval in the passive avoidance memory task have not been studied. Therefore, the present study was investigated whether mAChRs of the BLA interact with the impairment effect of dexamethasone on memory retrieval in rats.

## **MATERIALS AND METHODS**

This study was carried out in years of 2010-2011 and lasted 9 month for experiments and data analysis in our laboratory of animal behavioral research.

**Animals:** In this study, 132 adult male Wistar rats (200-250 g) were used were housed four per cage and given free access to food and water. The experiments were carried out 09:00 a.m. - 14: 00

p.m. Procedures used in this research were performed in compliance with the National Academy's Guide for the care and use of animals in research.

**Drugs:** The drugs used in the present study were dexamethasone (Synopharm, Italy), a glucocorticoids agonist, was dissolved in a vehicle (saline containing 2% ethanol). Pilocarpine (Sina-daru, Iran) and Scopolamine hydrochloride (Sigma, St. Louis, CA, USA) were dissolved in sterile 0.9% saline.

**Surgery and microinjections:** One week before the experiments, the animals were anesthetized by intraperitoneal injection of ketamine hydrochloride ( $50 \text{ mg kg}^{-1}$ ) plus xylazine ( $4 \text{ mg kg}^{-1}$ ) and then they cannulated for BLA by the stereotaxic surgery, according to the atlas of Paxinos and Watson (2007): anterior to bregma (AP) = -2.8 mm, lateral to the sagittal suture (L) = 5 mm and ventral from the surface of the skull (V) = 6.6 mm. Two sterile guide cannulas made from stainless steel were placed bilaterally 1 mm above the BLA. A Hamilton syringe ( $2 \mu\text{L}$ ) and a needle joined together by a polyethylene tube were used for the intra BLA microinjections of  $0.5 \mu\text{L}$  lution (saline or pilocarpine or scopolamine) per side ( $1 \mu\text{L/rat}$ ) within a period of 120 sec.

**Apparatus:** The passive avoidance model have been used for evaluation of memory stages in several studies (Introini-Collison *et al.*, 1996; Power and McGaugh, 2002; Power *et al.*, 2003; Moazedi *et al.*, 2007; Ali *et al.*, 2010; Rezayof *et al.*, 2009, 2011). The step-through apparatus, like our pervious study (Khajepour *et al.*, 2008), used for training and testing of the animals as model of passive avoidance memory. This instrument, consisted of two compartments one light (white) and another dark (black) which were connected via a small door. Rods of stainless steel were placed in the floor of the dark chamber. A stimulator delivered electric shocks (50 Hz, 1 mA for 3 sec duration) to the floor of the dark chamber via the rods.

**Training session:** Each animal was placed in the light chamber and the door was opened after 10 sec and immediately after the animal entered the dark compartment, the door was closed and the rat was transferred to the home cage. The time of latency for entering the dark compartment was recorded. Animals with a latency of more than 100 sec were omitted from this research. The acquisition trial was carried out 30 min later. Each animal was placed in the light compartment and after 10 sec the door was opened. As soon as the animal entered the dark compartment and all four paws had been placed on the grid floor, the door was closed and an electric shock was immediately delivered to this chamber. The rat was transferred to outside of the apparatus about 20 sec after receiving the shock.

**Testing session:** Retrieval testing was performed 24 h after training. The animals were placed in the light chamber and after 10 sec the door was opened. Without using the electrical shock during this phase, the latency of entering the dark compartment (Step-through latency) and the time spent by rats in this chamber (Time spent in dark chamber) were recorded for evaluation of the passive avoidance memory retrieval (within a period of 300 sec). Increase of the step-through latency and decrease the time spent in dark chamber indicate memory potentiation.

**Experiments groups:** The animals were divided into 16 groups ( $n = 8$  each group). Each group received pre-test of intra BLA microinjections of one of these solution: Saline, pilocarpine and scopolamine (35 min before the testing) and subcutaneously (s.c.) of the vehicle or dexamethasone (5 min after intra-BLA microinjection). The first group (control) received of the saline ( $1 \mu\text{L rat}^{-1}$ ,

intra-BLA) plus of the vehicle (1 ml kg<sup>-1</sup>, s.c.). The three groups of animals first received microinjections of saline (1 µL/rat, intraBLA) plus different doses of dexamethasone (0.5, 1 and 2 mg kg<sup>-1</sup>, s.c.). The other three groups received pilocarpine (0.5, 1 and 2 µg/rat, intraBLA) plus the vehicle (1 mL kg<sup>-1</sup>, s.c.). The three groups received pilocarpine (0.5, 1 and 2 µg/rat, intra BLA) plus the dexamethasone (2 mg kg<sup>-1</sup>, s.c.). The other three groups received scopolamine (0.1, 0.3 and 0.5 µg/rat, intraBLA) plus the vehicle (1 mL kg<sup>-1</sup>, s.c.). The last three groups received scopolamine (0.1, 0.3 and 0.5 µg/rat, intraBLA) plus the dexamethasone (0.5 mg kg<sup>-1</sup>, s.c.).

**Confirmation of sites of injection:** After the experiments, the rats were killed and received methylene blue (0.5 µL side, intra-BLA). They were decapitated and their brains placed in a 10% formalin solution for 10 days. For the determination of the cannula locations and sites of injections, brain sections were examined for the BLA on the basis of the rat brain atlas (Paxinos and Watson, 2007). The data from rats that received drugs outside of the BLA were omitted.

**Analysis of data:** The data were analyzed by one or two-way analysis of variance (ANOVA) and Tukey = s test using SPSS statistical software and the results expressed as mean standard error of the mean (SEM). The statistical significance level was set at p<0.05.

## RESULTS

**Effect of the dexamethasone on memory retrieval:** Figure 1 shows the effects of pretest administration of the dexamethasone on step-through latencies (Fig. 1a) and time spent in the dark chamber (Fig. 1b). One-way ANOVA revealed that pre-testing administration of the dexamethasone (0.5, 1, 2 mg kg<sup>-1</sup>, s.c.) decrease the step-through latencies ( $F(3, 28) = 7.95$ ,  $p < 0.01$ ) and increase the time spent in the dark chamber ( $F(3, 28) = 5.87$ ,  $p < 0.01$ ) compared to control group. This data shows that dexamethasone has impairment effect on memory retrieval.

**Effect of pilocarpine on the effect of dexamethasone on memory retrieval:** Figure 2a indicates the effect of pilocarpine on the effect of dexamethasone on step- through latencies. Statistical analysis by two-way ANOVA showed that there was a significant difference between the groups that received the pilocarpine (0.5, 1, 2 µg/rat, intra BLA) plus the vehicle (1 mL kg<sup>-1</sup>, s.c.)

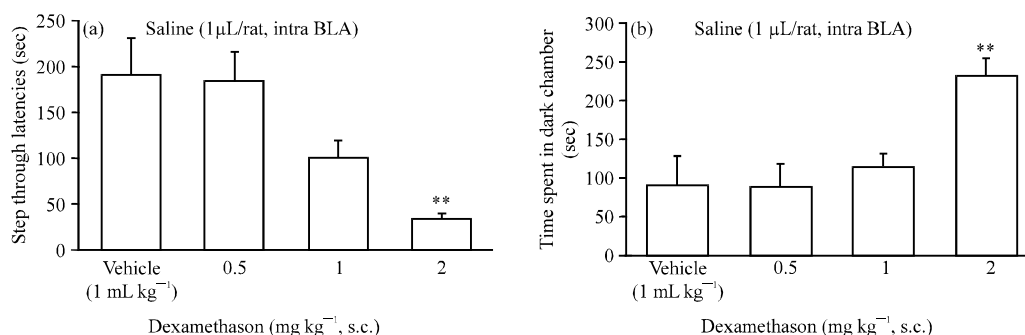


Fig. 1: The effect of pre-testing administration of dexamethasone on memory retrieval: Step through latencies (a) and Time spent in dark chamber. The animals trained in step through passive avoidance task and were tested one day later. They received pre-testing of the vehicle (1 mL kg<sup>-1</sup>, s.c.) or dexamethasone (0.5, 1 or 2 mg kg<sup>-1</sup>, s.c.) plus saline (1 µL/rat, intraBLA), 35 and 30 min before testing, respectively. The columns show the mean SEM (n = 8). \*\*p>0.01, compared to the control group (saline/vehicle)

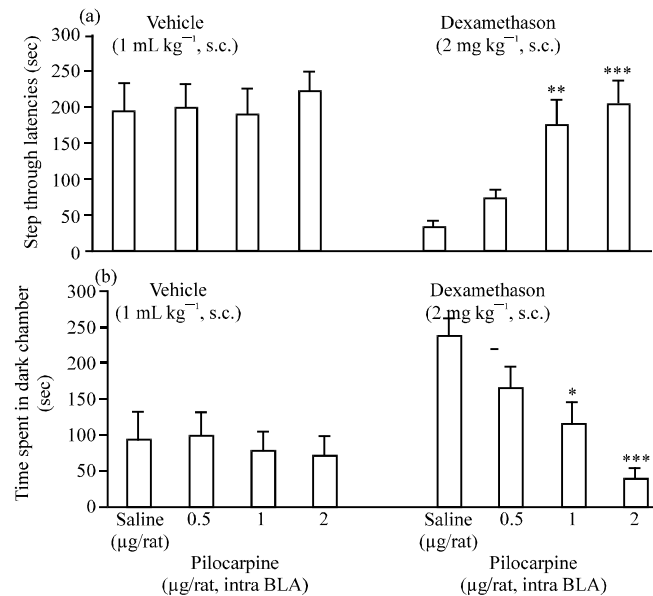


Fig. 2(a-d): The effect of pre- testing intraBLA microinjections of different doses of pilocarpine with or without dexamethasone on memory retrieval: Step through latencies (a) and Time spent in dark chamber(b). The animals trained in step through passive avoidance task and were tested 24 h later. They received of saline (1 µL rat<sup>-1</sup>, intraBLA) or pilocarpine (0.5, 1 and 2 µg/rat, intraBLA) plus vehicle (1 mL kg<sup>-1</sup>, s.c.), 35 and 30 min before testing, respectively. Each value represents the mean" S.E.M. of eight rats per group. \*p>0.05, \*\*p>0.01, \*\*\*p>0.001, compared with the dexamethasone/ saline group

and the groups that received the pilocarpine (0.5, 1, 2 µg/rat, intra BLA) plus effective dose of dexamethasone (2 mg kg<sup>-1</sup>, s.c.) (Within group comparison: treatment effect,  $F(1, 56) = 13.5$ ,  $p < 0.01$ ; dose effect,  $F(3, 56) = 4.3$ ,  $p < 0.01$ ; treatment  $\times$  dose interaction,  $F(3, 56) = 2.9$ ,  $p < 0.05$ ). Furthermore, one-way ANOVA indicated that there was no significant change among the groups that received different doses of pilocarpine (0.5, 1, 2 µg/rat, intra BLA) plus the vehicle ( $F(3, 28) = 0.19$ ,  $p > 0.05$ ) (Fig. 2a, left panel). One-way ANOVA revealed that the impairment effect of 2 mg kg<sup>-1</sup> of dexamethasone on memory retrieval was significantly reduced by same doses of pilocarpine ( $F(3, 28) = 9.73$ ,  $p < 0.001$ ) (Fig. 2a right panel).

Figure 2b shows the effect of pilocarpine (pre-testing injections) on the effect of dexamethasone on the time spent in the dark chamber. Two-way ANOVA indicated that there was an interaction effect on memory retrieval between the groups that received the pilocarpine (0.5, 1, 2 µg/rat, intra BLA) plus the vehicle (1 mL kg<sup>-1</sup>, s.c.) and the groups that received same doses of pilocarpine plus dexamethasone (2 mg kg<sup>-1</sup>, s.c.) (Within group comparison: treatment effect,  $F(1, 56) = 6.9$ ,  $p < 0.05$ ; dose effect,  $F(3, 56) = 5.4$ ,  $p < 0.01$ ; treatment  $\times$  dose interaction,  $F(3, 56) = 3.2$ ,  $p < 0.01$ ). One-way ANOVA revealed that There was no significant change among the groups that received ineffective doses of pilocarpine (0.5, 1, 2 µg/rat, intra BLA) plus the vehicle (:  $F(3, 28) = 0.17$ ,  $p > 0.05$ ) (Fig. 2b left panel). On the other hand, the impairment effect of dexamethasone (2 mg kg<sup>-1</sup>) on memory retrieval was reduced by same doses of pilocarpine ( $F(3, 28) = 10.47$ ,  $p < 0.001$ ) (Fig. 2a right).

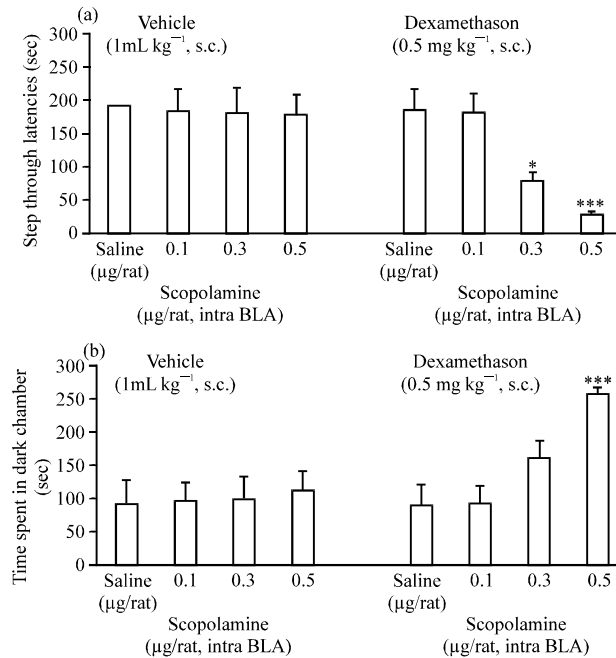


Fig. 3(a-d): The effect of pre-testing of intra-BLA microinjections of different doses of scopolamine with or without dexamethasone on the memory retrieval: Step through latencies (a) and time spent in dark chamber (b). The animals trained in the step through passive avoidance task and were tested 24 h later. They received saline (1 µL/rat, intraBLA) or scopolamine (0.1, 0.3 and 0.5 µg/rat, intraBLA), 35 min before testing and the ineffective dose of dexamethasone (0.5 mg kg<sup>-1</sup>, s.c.) 5 min later. Each value represents the mean SEM of eight rats per group. \*p>0.05, \*\*\*p>0.001, compared with the saline/ dexamethasone group

**Effect of scopolamine on the effect of dexamethasone on memory retrieval:** Figure 3a shows the effect of pre-testing administration of scopolamine on the dexamethasone effect on step-through latencies. Two-way ANOVA showed that there was an interaction effect on memory retrieval between the groups that received the scopolamine (0.1, 0.3, 0.5 µg/rat, intra BLA) plus the vehicle (1 mL kg<sup>-1</sup>, s.c.) and the groups that received the scopolamine (0.1, 0.3 and 0.5 µg/rat, intra BLA) plus ineffective dose of dexamethasone (0.5 mg kg<sup>-1</sup>, s.c.) (Within group comparison: Treatment effect,  $F(1, 56) = 9.7$ ,  $p < 0.01$ ; dose effect,  $F(3, 56) = 3.9$ ,  $p < 0.01$ ; treatment  $\times$  dose interaction,  $F(3, 56) = 3.03$ ,  $p < 0.01$ ). On the other hand, one-way ANOVA indicated that there was no significant change among the groups that received different doses of scopolamine (0.1, 0.3, 0.5 µg/rat, intra BLA) plus the vehicle ( $F(3, 28) = 0.03$ ,  $p > 0.05$ ) (Fig. 3a left panel). While, the impairment effect of ineffective dose of dexamethasone (0.5 mg kg<sup>-1</sup>, s.c.) on memory retrieval was significantly increased by same ineffective doses of scopolamine ( $F(3, 28) = 10.83$ ,  $p < 0.001$ ) (Fig. 2a right panel).

Figure 2b shows the effect of scopolamine on the effect of dexamethasone on the time spent in the dark chamber. Two-way ANOVA showed that there was a significant difference between the groups that received the scopolamine (0.1, 0.3, 0.5 µg rat<sup>-1</sup>, intra BLA) plus the vehicle (1 mL kg<sup>-1</sup>, s.c.) and the groups that received same doses of scopolamine plus ineffective dose of dexamethasone (0.5 mg kg<sup>-1</sup>, s.c.) (Within group comparison: treatment effect,  $F(1, 56) = 6.03$ ,

$p < 0.01$ ; dose effect,  $F(3, 56) = 4.6$ ,  $p < 0.05$ ; treatment  $\times$  dose interaction,  $F(3, 56) = 3.01$ ,  $p < 0.05$ . There was no significant change among the groups that received different doses of scopolamine (0.1, 0.3, 0.5  $\mu\text{g}/\text{rat}$ , intra BLA) plus the vehicle ( $F(3, 28) = 0.03$ ,  $p > 0.05$ ) (Fig. 2b left panel). Whiles, co-administration of the ineffective doses of dexamethasone (0.5  $\text{mg kg}^{-1}$ ) with ineffective doses of scopolamine decreased the memory retrieval ( $F(3, 28) = 9.94$   $p < 0.001$ ) (Fig. 2a right).

## DISCUSSION

Glucocorticoids have known to modulate memory retrieval in different kinds of emotionally arousing tasks, including inhibitory avoidance, contextual and fear conditioning, water-maze in laboratory animals (De Quervain *et al.*, 2009). The findings of our experiments showed that systemic subcutaneous injection of moderate dose of dexamethasone before testing reduces retrieval in the passive avoidance memory. These results are in accordance with other investigations (Rashidy-Pour *et al.*, 2004; Sajadi *et al.*, 2006, 2007; Rashidy-Pour *et al.*, 2009). Of course administration of post-training of dexamethasone or other GRs agonists enhance memory consolidation (De Quervain *et al.*, 2009). These effects of dexamethasone can mediate via genomic and nongenomic mechanisms (Venturella *et al.*, 2005). Several studies have shown that certain neurotransmitters and neuropeptide systems, including noradrenergic, GABAergic and opioidergic systems, are involved in these effects of glucocorticoids (Pare, 2003; McGaugh and Roozendaal, 2008; Vafaei *et al.*, 2008). In this study, we determined the involvement of BLA mAChRs mechanisms in the effect of dexamethasone on memory retrieval.

Numerous evidences have been shown that cholinergic system may affect memory formation through a process involving the amygdala. Post- training intra-amygdala microinjections of muscarinic cholinergic agonists and antagonists enhance and impair memory, respectively, for inhibitory avoidance task and other kinds of memory models (Introini-Collison *et al.*, 1996; Power and McGaugh, 2002; Power *et al.*, 2003). There are functional interactions of central cholinergic and glucocorticoids (Helm *et al.*, 2002). Cholinergic dysfunctions have also been reported by chronic treatment of corticosterone (Tizabi *et al.*, 1989; Douma *et al.*, 1999).

BLA activation is critical for mediating effects of glucocorticoids and cholinergic agent on memory, because BLA lesions eliminate these effects (Roozendaal *et al.*, 1996; Takahashi and Goh, 1998; McGaugh *et al.*, 2002; Duvarci and Pare, 2007).

The results of present study showed that pre-test bilateral microinjections of the low doses of pilocarpine or scopolamine into the BLA by themselves had no effect on the retention latencies. This may be in agreement with other studies that pre-test systemic administration of low doses of these drugs did not affect the memory retrieval in passive avoidance task (Boccia *et al.*, 2003; Rezayof *et al.*, 2009). However, it has been shown that the muscarinic system of the BLA is important for improvement of memory (Power *et al.*, 2003) and the injections of mAChRs agonist and antagonists into the amygdala impair learning and memory in a variety of behavioral tasks (Rezayof *et al.*, 2009). In these study intra-BLA microinjections of ineffective doses of pilocarpine reversed memory impairment effect of dexamethasone (2  $\text{mg kg}^{-1}$ ). On the other hand, administration of the lower dose of the pre-test of dexamethasone (0.5  $\text{mg kg}^{-1}$ ) alone did not affect memory retrieval but pre-test co-administration of ineffective doses of scopolamine (IntraBLA) with this dose of dexamethasone, significantly impaired the memory retrieval and mimicked the effects of pre-test administration of a higher dose of dexamethasone (2  $\text{mg kg}^{-1}$ , s.c.) treatment. The interaction between glucocorticoids and the cholinergic system in memory formation has been reported by other investigations. The BLA muscarinic activity is important for the memory



enhancement effect of glucocorticoids (Dalmaz *et al.*, 1993), For instance, The intra-BLA infusion of atropine, other mAChRs antagonist, impairs the improvement effect of dexamethasone on memory formation, when these drugs are co-administered after training (Power *et al.*, 2000).

There is possibility that impairment effect of glucocorticoids on memory retrieval is mediated indirectly, in ways other than through direct glucocorticoids-cholinergic interaction in the BLA, via other neurotransmitter systems such as noradrenergic. Central noradrenergic system is important for memory formation (Moazedi *et al.*, 2008a). Several lines of evidence indicate that noradrenergic activity in the BLA has an important role in mediating effects of other neurotransmitter systems and hormones on retrieval. Noradrenergic receptors of BLA mediate the effect of the glucocorticoids on retrieval (Roozendaal *et al.*, 2006). On the other hand, the muscarinic cholinergic and noradrenergic systems interact for storage and retrieval memory in the amygdala (Dalmaz *et al.*, 1993; Introini-Collison *et al.*, 1996).

Power *et al.* (2003) are reported that the memory-enhancing effect of  $\beta$ -adrenoreceptor agonists block with intra amygdala microinjection of atropine. Studies also have shown that opiodergic system modulates memory processes in many region of the brain including amygdale (McGaugh, 2004; Rezayof *et al.*, 2009; Bodnar, 2010). Studies also have been shown that central glutamatergic is involved in learning and memory. Because, BLA has a high density of glutamate receptors (Moazedi *et al.*, 2008b; Rezayof *et al.*, 2011), perhaps these receptor mediate the effect of mAChRs.

On the other hand, there are close relation between the BLA cholinergic and other neurotransmitter systems including, opiodergic (McGaugh *et al.*, 2002; Rashidy-Pour *et al.*, 2004; Rezayof *et al.*, 2009), dopaminergic (Hajisoltani *et al.*, 2011) and GABAergic (Rassouli *et al.*, 2010; Zarrindast *et al.*, 2004, 2010). Therefore, these systems also may be mediating the effect of mAChRs in the BLA.

## CONCLUSION

In summary, the present study shows that moderate doses of dexamethasone impaired retrieval in the passive avoidance type of memory. It can be inferred that the mechanisms of muscarinic receptors of the basolateral amygdala may directly or indirectly, through other neurotransmitters systems, be involved in the impairment effect of dexamethasone on memory retrieval.

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