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Research report

The locus coeruleus involves in consolidation and memory retrieval, but not in acquisition of inhibitory avoidance learning task

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Abstract

The locus coeruleus (LC) located at the level of the pons, is involved in cognitive functions such as learning and memory. The bilateral lidocaine-induced reversible inactivation of this nucleus has been considered in order to study its role in the phases of memory processing (acquisition, consolidation and retention) without any interference with the function of the same structure either during earlier and/or later phases of the same process. In this study, inhibitory avoidance (IA) learning task used to find the LC function in acquisition, consolidation and retrieval. Saline or lidocaine 4% (0.5 μl/side) microinjected into the LC, for assessing the acquisition (5 min before training), consolidation (5, 90 and 360 min after training) and memory retrieval, 5 min before testing. The retention test was done 24 h after learning. Our results indicated that: (1) The bilateral functional inactivation of LC before training did not affect acquisition, but affected subsequent memory retention 24 h later in IA task. (2) The lidocaine-induced inactivation of LC only 5 min after training impaired consolidation but did not affect it after 90 or 360 min. (3) Inactivation of the LC, 5 min before pre-retrieval test, impaired memory retrieval in IA task. In conclusion, it seems that the nucleus locus coeruleus does not affect acquisition while it involves in the memory consolidation and retrieval of inhibitory avoidance learning task.
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Keywords: Locus coeruleus; Learning and memory; Reversible inactivation; Inhibitory avoidance task; Lidocaine; Rat

1. Introduction

The locus coeruleus (LC) is a distinct cluster of neurons located near the wall of fourth ventricle at the level of the pons. It is the largest group of norepinephrine (NE)-containing neurons in the brain [26]. The locus coeruleus–norepinephrine (LC–NE) neurons have a diverse set of efferent projections throughout the brain regions (with the exception of the basal ganglia) and provides noradrenergic fiber distribution within and across the cerebral [33] and subcortical structures such as brainstem and hippocampus [29,33,36,59]. On the other hand, the LC receives inputs from CNS structures, substantially more restricted set of afferents arising from the prepositus hypoglossus and paragigantocellularis nuclei [5,8,10]. These unique anatomical properties indicate a possible role for this system in behavioral and cognitive functions [48].

Previous studies based on lesion and pharmacological manipulations have indicated that the LC–NE system has been implicated in several behavioral functions, including sleep/waking cycles [34], learning, memory and cognitive performances [16,24,30,45]. Crow [16] have previously proposed hypothesis that the LC plays an important role in establishing the synaptic changes underlying learning and memory. It has been indicated that electrical and chemical stimulation of the noradrenergic neurons in LC increase the NE release in the forebrain and as a result enhances memory retrieval [22,49,55]. While, electrical or chemical impairments and NE inhibition

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do not affect acquisition and consolidation of different kinds of learning [21,50,61]. Indeed, the electrical stimulation of the LC improved the early stages of acquisition and extinction of a food-reinforced task [60]. Moreover, Chen et al. [9] suggested that electrical stimulation of the LC, significantly improves the memory consolidation processes of inhibitory avoidance learning. Several studies have shown that LC or its forebrain projection fiber system is not engaged in learning and consolidation i.e., animals with very little NE in the forebrain do well in learning and retrieving many challenging cognitive tasks [51,57]. Some investigations have shown the negative effect of the LC on learning and memory for example, animals with NE depletion learned some learning tasks with food reward and also a two-way active avoidance task more quickly [28,43]. While, degeneration of the LC and its efferent projection throughout the cerebral cortex and the limbic system caused a two-way active avoidance [4,19] and different spatial memory [23,37] impairments.

Although there have been many studies in this regard, the role of LC in learning and memory has not been fully investigated. Therefore, in this study, we used the local microinjection of lidocaine to show the role of LC in the acquisition, consolidation and retrieval memory to provide more information about the function of LC–NE neurons on the three related but distinct types of explicit memory process (encoding, consolidation, and retrieval) in the inhibitory avoidance learning task in rats.

2. Material and methods

2.1. Animals

Adult male Wister rats weighing 220–250 g purchased from the breeding colony of the Pasteur Institute of Iran, Tehran. In each cage three rats were housed and maintained at a constant temperature of 23 ± 1 °C with a 12:12-h light/dark cycle beginning with lights on at 7:00 A.M. Food and water were available ad libitum in the home cages.

2.2. Surgery

Rats received surgery after at least 2 weeks from being in the animal house. Approximately 12 days prior to the initiation of the behavioral experiments, rats were anaesthetized with i.p. injection of a mixture of ketamine (100 mg/kg) and xylazine (2.5 mg/kg) and were implanted bilaterally with two cannulae (15 mm, 23-gauge) aimed at a site 1 mm above the LC (AP: −6.3 mm from bregma; at angle of 25° to the vertical, ML = ±1.2 mm and DV = 7.1 mm with respect to the skull at the midline) according to the atlas of Paxinos and Watson [47]. Two screws were inserted into the skull and cannulae were fixed to them with dental cement. Then, the cannulae were closed with stylets. Three rats were housed per cage for up to 5 days following surgery as a recovery period.

2.3. Microinjection procedure

Before injection, animals were restrained by hand and cannulae stylets were removed and replaced with the injection needles (30-gauge) connected to a short piece of polyethylene tubing (PE-20) and a 1-μl Hamilton syringe. Needles were inserted 1 mm beyond the tip of the cannulae and placed just above the LC to prevent it from mechanical damage. Then 0.5 μl of saline or 4% lidocaine hydrochloride (Bayer) was injected over 1 min. Needles were left in place for another 60 s before they were slowly withdrawn. In microinjection studies, it has been found that a 1–4% concentration of lidocaine is necessary to inactivate tissue [6,33,52]. The volume of injection is based on another study in which 0.5 μl of lidocaine, as a fully reversible sodium channel inhibitor, was injected into the LC to inactivate it for 30–45 min [35].

2.4. Apparatus

The inhibitory avoidance (IA) apparatus (Modified shuttle box) consisted of illuminated (20 cm × 40 cm × 20 cm) and dark (20 cm × 40 cm × 20 cm) chambers with walls made of opaque plastic. The floor of both chambers was made of stainless steel rods (3 mm diameter) spaced 1 cm apart. The floor of the dark chamber could be electrified. A rectangular opening (8 cm × 8 cm) located between the two chambers and can be closed by an opaque guillotine door.

2.5. Training

First, all experimental groups were given two trials to habituate them to the apparatus. For these trials, rats were placed in a lighted compartment of apparatus facing away from the door and 5 s later, the guillotine door was raised. After the rats entered the dark compartment, the door was closed and animals were taken from the dark compartment into their home cage. The habituation trial was repeated after 30 min and followed after the same interval by the first acquisition trial. The entrance latency to the dark compartment, step through latency (STL), was recorded when the animal placed all four paws in the dark compartment. After the animal had spontaneously entered the dark compartment, the guillotine door was lowered and a 50 Hz square wave, 1 mA constant current shock was applied for 1 s. In Experiment 1, the rat was retained in the apparatus and received a foot shock each time it re-entered the dark compartment. Training was terminated when the rat remained in the light compartment for 120 consecutive seconds. The number of trials (entries into the dark chamber) was recorded. In Experiments 2 and 3, the rat was removed from the dark compartment after 20 s, and received appropriate treatments, if necessary by injecting saline, lidocaine or sometimes without any injections, and then placed into its home cage. The non-shocked control animals were handled in the same way but received no electrical shock upon entering the dark compartment and were not given the second test.

2.6. Retention test

The retention test was performed 24 h after the IA acquisition trial. The rat was placed in a lighted chamber as in IA training and 5 s later, the guillotine door was raised, and STL and the time spent in dark compartment (TDC) were recorded up to 600 s. If animal did not enter the dark compartment within 600 s, the retention test was terminated and a ceiling score of 600 s was assigned. IA acquisition and retrieval trials were performed from 8:00 to 11:00 h.

2.7. Experimental protocol

2.7.1. Experiment 1

The aim of this experiment was to determine the effect of pre-training reversible inactivation of the LC on IA acquisition and retention. Seventeen rats divided into two experimental groups: shocked-saline (SS) control group ($n = 8$) receiving intra-LC injection of saline, 5 min before the acquisition trial, and shocked-lidocaine (SL) test group ($n = 9$) receiving intra-LC injection of 4% lidocaine. The number of trials to IA acquisition, STL and TDC during the retrieval test were recorded.

2.7.2. Experiment 2

The aim of this experiment was to determine the effect of post-training reversible inactivation of the LC on IA consolidation. Sixty-three rats divided into seven experimental groups: NS, non-shocked control group ($n = 9$), SS-5 ($n = 9$), SS-90 ($n = 9$), SS-360 ($n = 9$), shocked-saline groups receiving intra-LC injection of saline and lidocaine group SL-5 ($n = 9$), SL-90 ($n = 9$), SL-360 ($n = 9$), shocked-lidocaine groups receiving intra-LC injection of lidocaine 5, 90, 360 min after foot shock or training, respectively. STL and TDC during the retrieval test were recorded in all groups.

2.7.3. Experiment 3

The aim of this experiment was to determine the effect of pre-retrieval reversible inactivation of the LC on the IA retention test. Thirty-two rats divided into four groups, NS ($n = 8$), NSL ($n = 8$), RS ($n = 8$), and RL ($n = 8$). RS and RL

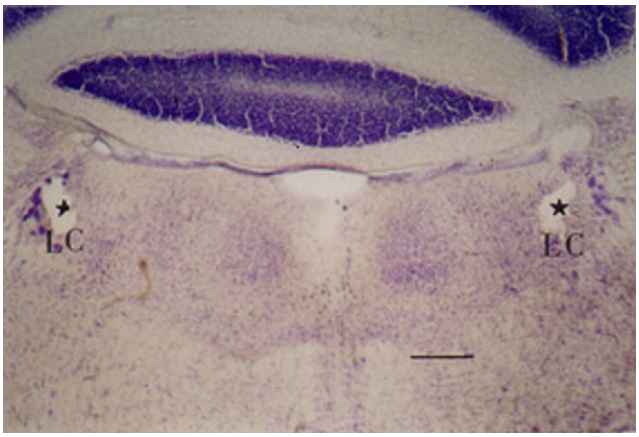

Fig. 1. A typical photo micrograph of a coronal section through the injection site (asterisks) in the LC. The tip of the injection needles can be seen on the right and left sides. Scale bar = 300 μm.

groups received intra-LC injection of saline or lidocaine (4%), 5 min before the retrieval test, respectively. The NS group comprised naive rats that were tested in the step through latency apparatus without any treatments. The NSL group comprised naive rats that were tested in the apparatus without any preliminary treatments but received lidocaine, 5 min before the retrieval test. STL and TDC during the retrieval test were recorded in all groups.

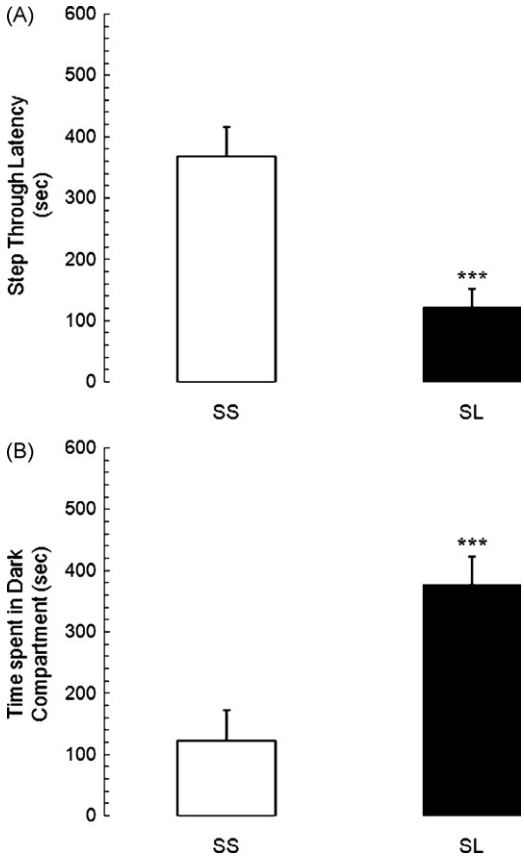

Fig. 2. The effect of pre-training reversible inactivation of the LC on IA retention. Ordinate: mean ± S.E.M. Step through latency (A), and time spent in dark compartment (B) during the retrieval test performed 1 day after IA acquisition. SS, control group receiving saline 5 min before acquisition trials; SL, test group receiving lidocaine 5 min before acquisition trials. ***$P < 0.001$ different from shocked-saline (SS) group.

2.7.4. Experiment 4

The effect of reversible inactivation of the LC on locomotor activity was determined in this experiment. Immediately after saline ($n = 6$) or lidocaine ($n = 6$) injections into the LC, rats were placed in the activity monitoring apparatus (Opto-varimex auto track system) and their locomotor activity was recorded up to 45 min after injection.

2.8. Histological procedure

At the end of each experiment, rats were deeply anaesthetized with sodium pentobarbital. The brain was removed and kept in 10% formalin for at least 7 days and sectioned (40 μm) coronally. The sections were stained with thionin followed by histological verification of the needle's location in the injection. A representative photomicrograph illustrating the location of cannulae and injection needle aimed at the LC has shown in Fig. 1. The volume of lidocaine injected into the LC in these experiments has been reported to spread from 0.5 to 1.5 mm from the site of injection. Therefore, cannulae positioned more than 0.5 mm from the intended site of injection were not included into the statistical analysis. The numbers of animals in the present work were 117 rats in main experimental groups (plus 12 rats on locomotor activity), individually 9 rats in each group. In five cases, one from Experiment 1, four from Experiment 3 cannulae tips that were not in the LC area was excluded from statistical analysis.

2.9. Statistical analysis

Significant difference in Experiment 1 was measured by unpaired Student's *t*-test or Mann–Whitney *U*-test. In the second and third experiments either one-way ANOVA (for parametric data) followed by the Tukey's test or the Kruskal–Wallis test (nonparametric ANOVA test) followed by Dunn's test for multiple comparisons was performed. All results are shown as the mean ± S.E.M (standard error of mean). The level $P < 0.05$ was considered significantly.

3. Results

3.1. Experiment 1. Effect of pre-training reversible inactivation of the LC on IA acquisition and retention

The unpaired *t*-test indicated that before the acquisition trial, there is no significant difference in the step through latency between SS (1.13 ± 0.13; $n = 8$) and SL (1.22 ± 0.15; $n = 9$) groups. Lidocaine-induced inactivation of the LC before the acquisition trial had no effect on the number of trials up to acquisition in SS and SL groups (number of trials up to acquisition in both groups = 1), so the all of the animals demonstrated acquisition, but we would just be cautious regarding statements that there is no role of the LC in acquisition based on these data. On the other hand, the effect of pre-training reversible inactivation of the LC on IA retention has summarized in Fig. 2. According to Mann–Whitney *U*-test, there was a significant difference in STL ($P < 0.001$) and TDC ($P < 0.001$) between SS and SL groups.

3.2. Experiment 2. Effect of post-training reversible inactivation of the LC on IA consolidation

One-way ANOVA indicated that there is no significant difference in step through latency before the acquisition trial among the different experimental groups [$F(6,62) = 0.061$; n.s.]. Fig. 3 shows the results of the retrieval test performed 24 h after train-

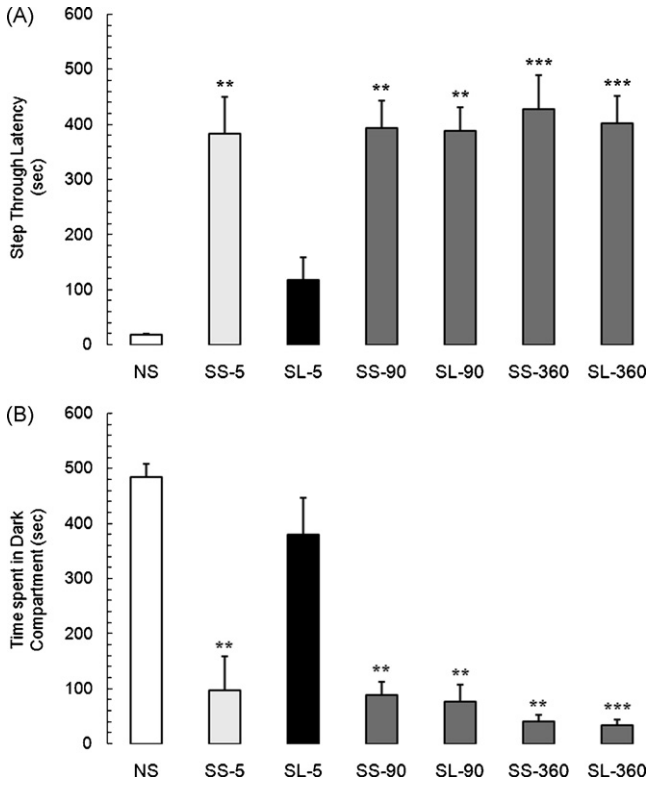

Fig. 3. The effect of post-training reversible inactivation of the LC on IA consolidation. Ordinate: mean ± S.E.M. Step through latency (A), and time spent in dark compartment (B) during the retrieval test performed 1 day after IA acquisition. NS, non-shocked control group and SS-5 shocked control groups receiving intra-LC injection of saline 5 min after the acquisition trial; SL-5, SL-90, and SL-360, shocked animals receiving intra-LC injection of lidocaine 5, 90, and 360 min after the acquisition trial, respectively; SS-90, and SS-360, shocked animals receiving intra-LC injection of saline 90 and 360 min after the acquisition trial, respectively. $^{**}P<0.01$, $^{***}P<0.001$ different from SL-5 (shocked-lidocaine) group.

ing and after lidocaine injection. Kruskal–Wallis test indicated that there was significant differences in STL [$F(6,62)=16.12$; $P<0.0001$] between groups in the retrieval test. Dunn's multiple comparison test showed that STL in groups which received lidocaine 5 min after training (SL-5) was significantly different from saline-control and experimental groups (Fig. 3A). On the other hand, there were significant differences between the NS group and SS-5 ($P<0.001$), SL-5 ($P<0.03$), SS-90 ($P<0.001$), SL-90 ($P<0.001$), SS-360 ($P<0.001$) and SL-360 ($P<0.001$) groups, as well. Kruskal–Wallis test indicated that there was significant differences in TDC [$F(6,62)=17.64$; $P<0.0001$] between groups in the retrieval test. Dunn's multiple comparison test showed that TDC in groups which received lidocaine 5 min after training, were significantly different from control and experimental groups (Fig. 3B). There was no significant difference between the SL-90 and SL-360 groups. Taken together, these results revealed that post-training inactivation of the LC, time dependently impairs IA consolidation. Also spontaneous activity of the LC seems to be necessary for memory consolidation at least 5 min after the acquisition trial.

3.3. Experiment 3. Effect of reversible inactivation of the LC before the retention test on IA retrieval

One-way ANOVA indicated that there is no significant difference in step through latency before the acquisition trial among the different experimental groups [$F(3,31)=0.131$; n.s.] and thus confirmed their uniformity. Fig. 4 shows the result of the retrieval test. Kruskal–Wallis test indicated that there are significant differences in STL [$F(3,31)=21.86$; $P<0.0001$] and TDC [$F(3,31)=35.97$; $P<0.0001$) between groups in the retrieval test. Dunnet's multiple comparison test showed that there were significant differences in STL and TDC among between RS as a control group and experimental groups. However, there was no significant difference in STL and TDC between groups that received lidocaine before the retention test (RL), NS and NSL groups. These results revealed that reversible inactivation of the LC before the retrieval test impairs IA retrieval.

3.4. Experiment 4. Effect of reversible inactivation of the LC on locomotor activity

Unpaired *t*-test showed no significant difference between the distance traveled by lidocaine- and saline-treated groups. It indicates that functional inactivation of the LC has no effect on locomotor activity (Fig. 5).

4. Discussion

In this study, the reversible bilateral inactivation of LC on different processes of IA learning has been studied chronologically for the first time. The main obtained results from the present study are: (1) The bilateral functional inactivation of LC before training did not affect acquisition, but affected subsequent memory retention 24 h later in IA task. (2) Reversible inactivation of the LC only 5 min after training impaired consolidation but did not affect it after 90 or 360 min. (3) Inactivation of the LC, 5 min before memory retention test, impaired memory retrieval in IA task. Our findings of the first set of experiments is in agreement with previous experiences that have shown the electrical and chemical impairments of LC did not affect IA learning [4,15,57]. Furthermore, both inhibiting the NE synthesis and chemical impairment of the LC before IA learning did not affect acquisition [17] as well. Meanwhile degeneration of the LC and its efferent projection throughout cerebral cortex and limbic system caused a two-way active avoidance and spatial learning task impairments [3,4,19]. Nevertheless, our study shows that the LC is not involved in acquisition, indeed it is involved in other processes of memory like consolidation and retrieval in IA learning task.

In the second set of experiments, our results showed that inactivation of the LC, only 5 min after training, impaired consolidation. On the other hand, our data in retention test in Experiment 1 confirms the results of Experiment 2 that LC involves in memory consolidation process. Our data support the findings of previous studies that the LC stimulation-induced NE release in target structures such as amygdale and hippocampus, is involved in the memory consolidation [11]. Nielson et

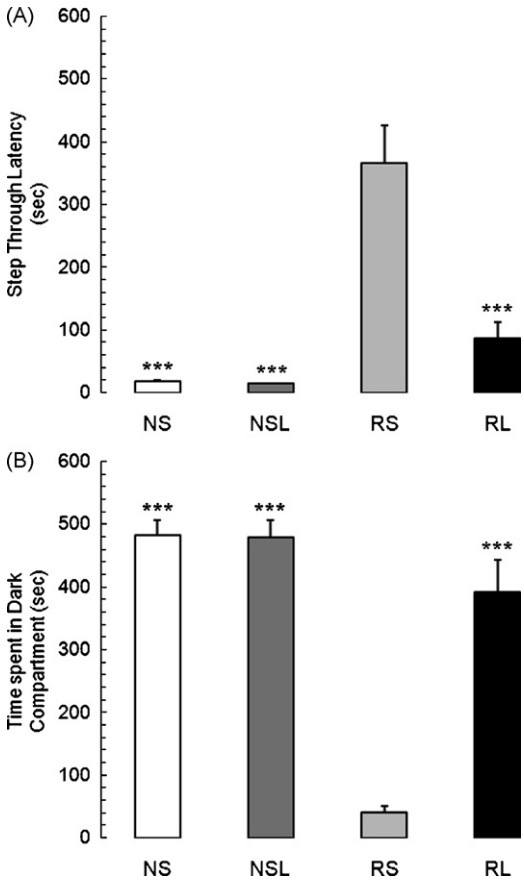

Fig. 4. The effect of reversible inactivation of the LC before retention test on IA retention. Ordinate: mean ± S.E.M. Step through latency (A), and the time spent in dark compartment (B) during the retrieval test performed 1 day after IA acquisition. NS, non-shocked control group; NSL, non-shocked group receiving intra-LC injection of lidocaine; RS and RL, shocked animals receiving intra-LC injection of saline or lidocaine 5 min before retrieval test. ***$P < 0.001$ different from retrieval-saline (RS) group.

al. [46] suggested that chronic (15 days) administration of propranolol, β-adrenergic antagonist, impaired consolidation in the inhibitory avoidance task. It has also been shown that deficiency in the neonatal central NE impaired the IA consolidation in postnatal rats [14]. In addition, the LC stimulation [9] and its target structures [25,39] immediately after learning, improved consolidation in IA learning [25,39]. In contrast with the previous statements, there are evidences indicating that electrical and chemical LC impairments, did not affect consolidation of the Morris water maze task [20,50,61]. It is probably a difference between our result and the results from previous findings according to their tasks. As a result, there is a possibility that foot shock is the strongest factor in creating stress in memory consolidation in comparison with the Morris water maze task.

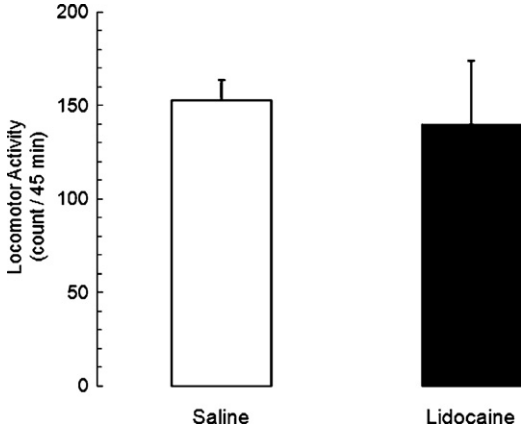

Fig. 5. The effect of reversible inactivation of LC on locomotor activity. Ordinate: mean ± S.E.M. distance traveled during 45 min.

The second set of experiments also indicated that the LC inactivation, only 5 min after training affected the memory consolidation while 90 or 360 min after training could not affect it. Gold et al. [27] have shown that memory consolidation improves after immediately administration of NE and during a short time after IA learning tasks while consolidation cannot be affected at 10, 20 and 30 min following training. The bilateral impairment of LC increased the memory consolidation from 3–6 to 40 h in the rodents [63]. The reason for these discrepancies in time and differences in results may be due to varying patterns of depletion by the different neurotoxins used and the different modes of administrations and also the task used may also have important in revealing deficits with LC manipulations.

The obtained results from the third set of experiments showed that bilateral inactivation of the LC, 5 min before retrieval test impaired memory retention in the IA learning. There is some debate about the significance of the noradrenergic system in the retrieval process and in long-term memory [16,21,54]. Several line of evidences have shown that electrical stimulation of LC or dorsal noradrenergic bundle (DNB) before the retention test, facilitated memory retrieval in linear maze for food reinforcement [22,23,54,56]. In addition, α2 adrenergic antagonist injection before the retention test decreased IA retrieval impairment in the aged rats [49]. It has been suggested that animals with very little NE in the forebrain do well in learning and retention of the challenging cognitive tasks [51,57]. Sara [53] has indicated that NE deficiency in the forebrain cannot affect memory retrieval. It seems that the improvement of electrical and chemical impairments takes a lot of time, so brain's function and its compensated mechanisms might be the reason for the response. In the fourth set of experiments, our results indicated that the LC has a role in learning and memory and the changes in memory consolidation and retrieval are not related to locomotor activities.

Finally, according to our findings in this study, it seems that the nucleus locus coeruleus does not affect acquisition of the IA learning task while it affects memory consolidation and retrieval. These results are in agreement with the previous studies that suggested that the nucleus locus coeruleus is the source of noradrenergic neural system in transferring the short-term memory into the long-term memory in IA learning.

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