



# The effect of alpha lipoic acid on passive avoidance and social interaction memory, pain perception, and locomotor activity in REM sleep-deprived rats

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## Abstract

**Background** Evidence shows the vital role of sleep in the modulation of cognitive functions. Sleep deprivation (SD) can disrupt learning and memory processes. SD also affects pain perception and locomotor activity. Furthermore, alpha lipoic acid (ALA) may induce antioxidant and neuroprotective effects. ALA affects memory processes, pain subthreshold, and locomotor activity. The goal of the present study was to investigate the effect of REM (rapid-eye movement) SD and ALA on social and passive avoidance memory, locomotor activity, and pain perception.

**Methods** Multiple-platform apparatus was used to induce REM SD for 24 h. Three-chamber paradigm test, the shuttle box, locomotion apparatus, and hot plate were used to assess social interaction memory, passive avoidance memory, locomotor activity, and pain perception, respectively. ALA was injected intraperitoneally at the doses of 35 and 70 mg/kg.

**Results** 24 h REM SD impaired both types of memory. In addition, ALA (35 mg/kg) reversed REM SD-induced memory impairments. However, ALA (70 mg/kg) impaired social memory with no effect on REM SD-induced memory impairments. ALA (70 mg/kg) also decreased pain subthreshold in REM SD rats.

**Conclusion** REM SD impairs social interaction and passive avoidance memory. Furthermore, ALA may exhibit a dose-dependent manner in some cognitive tasks. ALA can induce a therapeutic effect at one dose, and an impairment effect at another dose (lower or higher), while the cognitive task and the conditions are equal.

**Keywords** Alpha lipoic acid (ALA) · Social interaction memory · Passive avoidance memory · Pain · Locomotor activity · Rat

## Introduction

Studies have reported the role of sleep in learning and memory processes [1, 2]. It has been shown that sleep is critically involved in the consolidation of newly acquired memories [3]. Previous research has revealed that sleep modulates neuronal activity during memory storage, and promotes memory consolidation [4]. Furthermore, sufficient sleep improves neuronal activity, synaptic renormalization, and synaptic neurotransmission in the brain [5, 6]. Many studies have reported the impairment effect of sleep deprivation (SD) on learning and memory. Indeed, there is a strong correlation between SD and memory impairment [7]. SD impairs learning and memory performance in different cognitive tasks [8]. A recent study has demonstrated that 24 h total or rapid eye movement (REM) SD attenuates the acquisition of passive avoidance memory in rats [9]. 24 h REM SD also impairs

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spatial memory retrieval in adolescent mice [10]. 12 h REM SD impairs consolidation, retrieval, and reconsolidation of novel object recognition memory in rats [11]. In addition, SD affects pain perception in rats [9, 12]. Our recent study has also shown that total SD decreases locomotor activity and induces analgesic effect [2].

On the other hand, alpha lipoic acid (ALA) is a natural antioxidant [13, 14]. ALA is highly efficient in combating free radicals, reducing lipid peroxidation, and scavenging reactive oxygen species (ROS) [15]. It has been suggested that ALA can be a potential option for the treatment of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) [15]. Also, ALA can improve memory function. For example, ALA improves spatial learning and memory deficit, and attenuates oxidative stress in a rat model of vascular dementia [16]. Alpha lipoic acid improves hippocampus-dependent memory impairment without altering A $\beta$  levels in Tg2576 mouse model of AD [17]. Previous study has shown that alpha lipoic acid protects the postoperative cognitive function and the structure of hippocampal neurons in mice [18]. Furthermore, ALA improves memory performance and reduces oxidative stress in SAMP8 mice [19]. Previous study has demonstrated that ALA improves fear memory and social novelty preference via affecting muscarinic receptors [20]. Alpha lipoic acid significantly improves spatial memory and hippocampal morphology in rats [21]. Additionally, it has been shown that alpha lipoic acid affects locomotor activity [22]. ALA can also induce a therapeutic effect for the treatment of pain [23]. It has been reported that systemic injection of ALA significantly suppresses the excitability of nociceptive wide-dynamic range neurons in spinal trigeminal nucleus caudalis of rats [24].

According to the mentioned findings, the goal of the present study is to investigate the effect of alpha lipoic acid on passive avoidance and social interaction memory, locomotor activity, and pain perception in REM SD rats.

## Materials and methods

### Animals

Ninety-six male Wistar rats (180–220 g) were obtained from Institute for Cognitive Science Studies (ICSS). According to our previous studies, the rats were placed in Plexiglas cages in groups of four, and the standard temperature ( $22 \pm 2$  °C) and a stable light/dark cycle (12/12 h) were provided. The rats were free to access food and water, except during the experiments [9, 25]. Each experimental group consisted of eight rats and all the tests were done only during the light phase. The rats of each group were randomly selected. Our experimental protocol was approved by the Research and

Ethics Committee of the School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, and was done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals [26].

### Drug

Alpha lipoic acid (ALA) was purchased from Acros company (Acros organic, Thermo Fisher Scientific, United States) and was injected intraperitoneally at the doses of 35 and 70 mg/kg. The doses were chosen based on previous studies [21, 27–29]. The half-life of ALA is about 30 min [30]. The vehicle of ALA was 0.1% NaOH [27].

### REM sleep deprivation apparatus

The multiple-platform apparatus (BorjSanatAzma Co, Tehran, Iran) was used to induce REM SD. The multiple-platform apparatus was a water tank (90 × 50 × 50 cm) with several circular platforms with 7 cm diagonal. The surface of the platforms was 2 cm above the water. The rats were placed in the apparatus and during the experiment, they were free to move through the tank. When the rats fell asleep, and when the REM phase began, they fell into the water and woke up (due to REM-induced muscles relaxation). This process induced REM SD in rats. Note that, platforms with a larger diagonal (15 cm) were provided for sham of REM SD rats, in which the rats had normal sleep. The temperature of the water was standard and monitored during the experiment [2]. Duration of REM SD was 24 h. Note that, we did not use EEG (electroencephalogram) to assess the efficiency of the apparatus to induce REM SD, but our previous studies have shown that the rats are deprived from REM sleep during using this apparatus [2, 9]. Also, this apparatus had a limitation. In addition to complete deprivation of REM sleep, non-REM sleep is also decreased about 30% during using this apparatus [2, 31].

### Three-chamber paradigm test

The three-chamber paradigm test, also known as Crawley's sociability and preference for social novelty evaluates social behavior [32]. This apparatus was a rectangular three-chamber box, and each chamber was 19 × 45 cm with dividing walls. Each rat was placed in the apparatus by two equal wire glass-like compartments with removable tops. The compartments held the familiar/stranger rats. The time spent in each chamber was manually measured and all the processes were recorded by a camera. This test consisted of three phases:

### Habituation phase

Right and left chambers of the rectangular three-chamber box were isolated, while the empty chamber was in the center. Each rat was placed in the empty chamber to adaptation, with two doorways closed.

### Social affiliation and sociability phase

A control rat (stranger 1) was placed inside a wire cup that was positioned in one of the side spaces, to assess social affiliation. After that, the walls between the chambers were removed and the rat could freely move to all the chambers. Duration of direct interaction between the subject rat and the stranger 1 was recorded. This phase lasted 10 min.

### Social novelty/preference and social memory phase

A second control rat (stranger 2) was placed inside the other wire cup on the opposite side, to evaluate the behavior of the test rat in the presence of the stranger 1 (a familiar), when compared with stranger 2 (a novel). This phase lasted 10 min.

### Shuttle box apparatus

Shuttle box apparatus consisted of two equal-sized compartments (25 × 25 × 25 cm), including a light and a dark compartment. The two compartments had a grid floor and Plexiglas walls. The Plexiglas walls were separated by a door. For adaptation, we put the rats into the apparatus for 5 min, 24 h before training. In the training session, we put the rat into the light compartment for 1 min. After opening the door, when the rat entered the dark compartment, the door was closed and an electric footshock (0.5 mA, 50 Hz) was delivered for 2 s through the grid floor. 20 s later, the rat was transferred to its cage. 24 h after training, the test session was performed. In this session, we put the rat into the light compartment. The rat's step-through latency to enter the dark compartment was evaluated. The cut-off time was 300 s.

### Rats' locomotion apparatus

The rats' locomotion apparatus (BorjSanatAzma Co, Tehran, Iran) was used to assess locomotor activity. This apparatus consisted of transparent Perspex container (with a height of 40 × 30 × 30 cm) and a gray Perspex panel (with a thickness of 2.2 × 30 × 30 cm) with 16 photocells which divided the apparatus into sixteen equal-sized squares. Locomotor

activities of the rats were assessed as the number of movements from one square to another square during 300 s [33].

### Hot plate apparatus

Hot plate apparatus was used to assess pain subthreshold. This apparatus was a sheet getting hot by electric current (BorjSanatAzma Co, Tehran, Iran). Before the experiment, hot plate sheet was cleaned by ethanol 70%. Then, the rats were placed on the apparatus. The start time was determined and as soon as the rats started to lick their paws or change their steps, their pain tolerance was evaluated. The temperature of the apparatus was set at 50 °C. The cut-off time was 60 s [34].

### Experimental groups

This study consisted of 12 groups (each group consisted of 8 rats).

Non-SD groups consisted of:

Group 1 (control): The rats had no any intervention.

Group 2 (vehicle): The rats received intraperitoneal injection of NaOH (0.1 µl/g) for three consecutive days.

Group 3 (ALA 35 mg/kg): The rats received intraperitoneal injection of ALA at the dose of 35 mg/kg for three consecutive days.

Group 4 (ALA 70 mg/kg): The rats received intraperitoneal injection of ALA at the dose of 70 mg/kg for three consecutive days.

Sham-SD groups consisted of:

Group 5 (Control): The rats were placed in REM SD apparatus (when the apparatus was off) without drug injection.

Group 6 (Vehicle): The rats received intraperitoneal injection of NaOH (0.1 µl/g) for three consecutive days and then, they were placed in REM SD apparatus (when the apparatus was off).

Group 7 (ALA 35 mg/kg): The rats received intraperitoneal injection of ALA at the dose of 35 mg/kg for three consecutive days and then, they were placed in REM SD apparatus (when the apparatus was off).

Group 8 (ALA 70 mg/kg): The rats received intraperitoneal injection of ALA at the dose of 70 mg/kg for three consecutive days and then, they were placed in REM SD apparatus (when the apparatus was off).

SD groups consisted of:

Group 9 (Control): The rats were placed in REM SD apparatus (when the apparatus was on) without drug injection.

Group 10 (Vehicle): The rats received intraperitoneal injection of NaOH (0.1 µl/g) for three consecutive days and then, they were placed in REM SD apparatus (when the apparatus was on).

Group 11 (ALA 35 mg/kg): The rats received intraperitoneal injection of ALA at the dose of 35 mg/kg for three consecutive days and then, they were placed in REM SD apparatus (when the apparatus was on).

Group 12 (ALA 70 mg/kg): The rats received intraperitoneal injection of ALA at the dose of 70 mg/kg for three consecutive days and then, they were placed in REM SD apparatus (when the apparatus was on).

We have provided a graphical scheme that shows the order of experiments and procedures in (Fig. 1). The time interval between the experiments of the fifth day was 5 min [27].

### Statistical analyses

Statistical analyses were done using SPSS software (V. 24.0). The results are indicated as Mean  $\pm$  S.E.M considering normal distribution of data. The normal distribution of the results was checked by the Kolmogorov–Smirnov test. Two-way ANOVA was used to analyze the results of social interaction memory test. One-way ANOVA was used to analyze the results of passive avoidance memory, pain subthreshold, and locomotor activity. For all behavioral tests, more analyses were done to compare two groups using Tukey's post hoc test. In all comparisons,  $p < 0.05$  was considered as statistically significant [2].

## Results

### The effect of ALA on social affiliation and social memory

*Social affiliation and sociability:* The results of two-way ANOVA for non-SD groups revealed that the effect of stranger 1 ( $F_{1,56} = 69.52$ ,  $p = 0.000$ ), ALA dose ( $F_{3,56} = 12.27$ ,  $p = 0.000$ ), and the interaction between stranger 1 and ALA ( $F_{3,56} = 7.41$ ,  $p = 0.000$ ) were significant. Tukey's post hoc test showed that there was a significant difference between empty and stranger 1 in control ( $p = 0.000$ ), vehicle ( $p = 0.000$ ), and ALA (35 mg/kg,  $p = 0.000$ ) group, but not ALA (70 mg/kg,  $p = 0.849$ ) group, indicated social affiliation and sociability impairment in rats which received ALA (70 mg/kg). The results of two-way ANOVA for sham-SD groups revealed that the effect of stranger 1 ( $F_{1,56} = 72.52$ ,  $p = 0.000$ ) and the interaction between stranger 1 and ALA ( $F_{3,56} = 3.79$ ,  $p = 0.015$ ) were significant, while the effect of ALA dose ( $F_{3,56} = 2.45$ ,  $p = 0.073$ ) was not significant. Tukey's post hoc test showed that there was a significant difference between empty and stranger 1 in control ( $p = 0.000$ ), vehicle ( $p = 0.000$ ), and ALA (35 mg/kg,  $p = 0.000$ ) group, but not ALA (70 mg/kg,  $p = 0.313$ ) group, indicated social affiliation and sociability impairment in rats which received ALA (70 mg/kg). Furthermore, the results of two-way ANOVA for SD groups revealed that only the interaction between stranger 1 and ALA ( $F_{3,56} = 3.46$ ,  $p = 0.022$ ) was significant, while the effect of stranger 1 ( $F_{1,56} = 0.64$ ,  $p = 0.425$ ) and ALA dose ( $F_{3,56} = 1.63$ ,  $p = 0.193$ ) were not

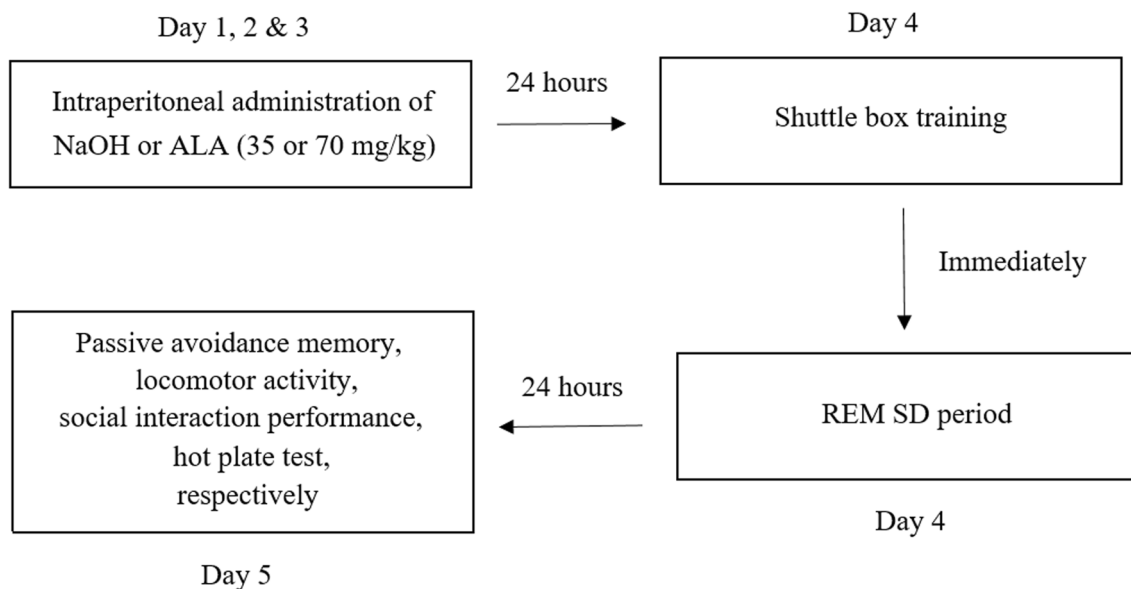


Fig. 1 Outline of experimental design (The time interval between the experiments of the day 5 was 5 min)

significant. Tukey's post hoc test showed that there was a significant difference between empty and stranger 1 in only ALA (35 mg/kg,  $p=0.004$ ) group, indicated social affiliation and sociability impairment in control, vehicle, and ALA (70 mg/kg) SD rats (Fig. 2, left panel).

**Social memory and novelty:** The results of two-way ANOVA for non-SD groups revealed that the effect of stranger 2 ( $F_{1,56}=29.86$ ,  $p=0.000$ ), ALA dose ( $F_{3,56}=21.16$ ,  $p=0.000$ ), and the interaction between stranger 2 and ALA ( $F_{3,56}=4.66$ ,  $p=0.006$ ) were significant. Tukey's post hoc test showed that there was a significant difference between stranger 1 and 2 in control ( $p=0.000$ ), vehicle ( $p=0.002$ ), and ALA (35 mg/kg,  $p=0.000$ ) group, but not ALA (70 mg/kg,  $p=0.812$ ) group, indicated social affiliation and sociability impairment in rats which received ALA (70 mg/kg). The results of two-way ANOVA for sham-SD groups revealed that the effect of stranger 2 ( $F_{1,56}=16.75$ ,  $p=0.000$ ), ALA dose ( $F_{3,56}=9.33$ ,  $p=0.000$ ), and the interaction between stranger 2 and ALA ( $F_{3,56}=3.90$ ,  $p=0.013$ ) were significant. Tukey's post hoc test showed that there was a significant difference between stranger 1 and 2 in control ( $p=0.000$ ), vehicle ( $p=0.011$ ), and ALA (35 mg/kg,  $p=0.000$ ) group, but not ALA (70 mg/kg,  $p=0.716$ ) group, indicated social affiliation and sociability impairment in rats which received ALA (70 mg/kg). Furthermore, the results of two-way ANOVA for SD groups revealed that only the effect of ALA dose ( $F_{3,56}=6.35$ ,  $p=0.001$ ) was significant, while the effect of stranger 2 ( $F_{1,56}=1.16$ ,  $p=0.286$ ) and the interaction between stranger 2 and ALA ( $F_{3,56}=2.16$ ,  $p=0.102$ ) were not significant. Tukey's post hoc test showed that there was a significant difference between

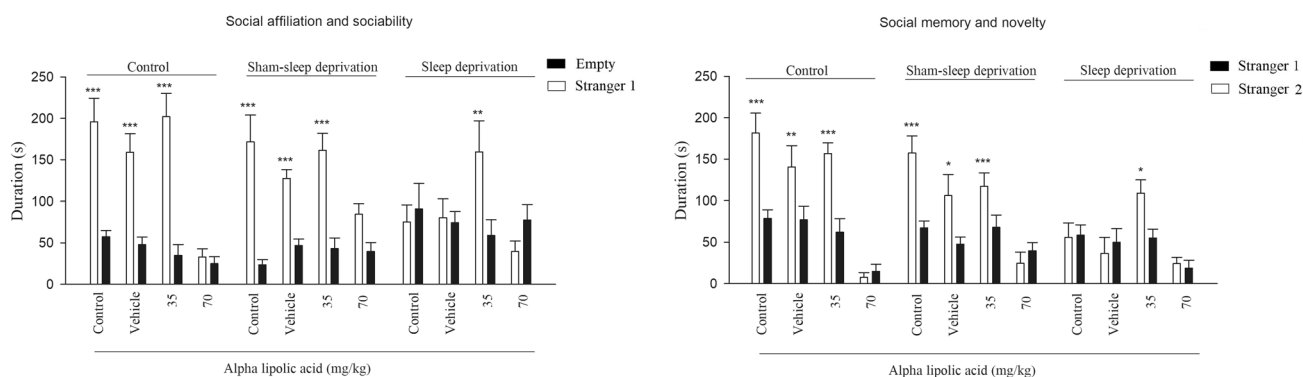
stranger 1 and 2 in only ALA (35 mg/kg,  $p=0.016$ ) group, indicated social affiliation and sociability impairment in control, vehicle, and ALA (70 mg/kg) SD rats (Fig. 2, right panel).

### The effect of ALA on passive avoidance memory

The results of one-way ANOVA revealed that there were no any significant differences between control ( $F_{3,28}=0.50$ ,  $p=0.684$ ) and sham-SD ( $F_{3,28}=1.67$ ,  $p=0.196$ ) groups, while there was a significant difference between SD groups ( $F_{3,28}=3.70$ ,  $p=0.023$ ). Tukey's post hoc test revealed that REM SD impaired passive avoidance memory ( $p=0.003$ ) and ALA at the dose of 35 mg/kg reversed REM SD-induced passive avoidance memory impairment ( $p=0.023$ ). ALA only at the dose of 35 mg/kg (but not 70 mg/kg) could restore REM SD-induced memory deficit (Fig. 3).

### The effect of ALA on pain perception and locomotor activity

The results of one-way ANOVA revealed that there were no any significant differences between control ( $F_{3,28}=0.15$ ,  $p=0.930$ ) and sham-SD ( $F_{3,28}=2.09$ ,  $p=0.081$ ) groups, while there was a significant difference between SD groups ( $F_{3,28}=2.94$ ,  $p=0.047$ ). Tukey's post hoc test revealed that ALA at the dose of 70 mg/kg decreased the pain sub-threshold in REM SD rats ( $p=0.040$ ). It should be noted that, the results of locomotor activity were not significant in all groups. The interventions did not alter locomotor activity of rats in all the experimental groups (Fig. 4).

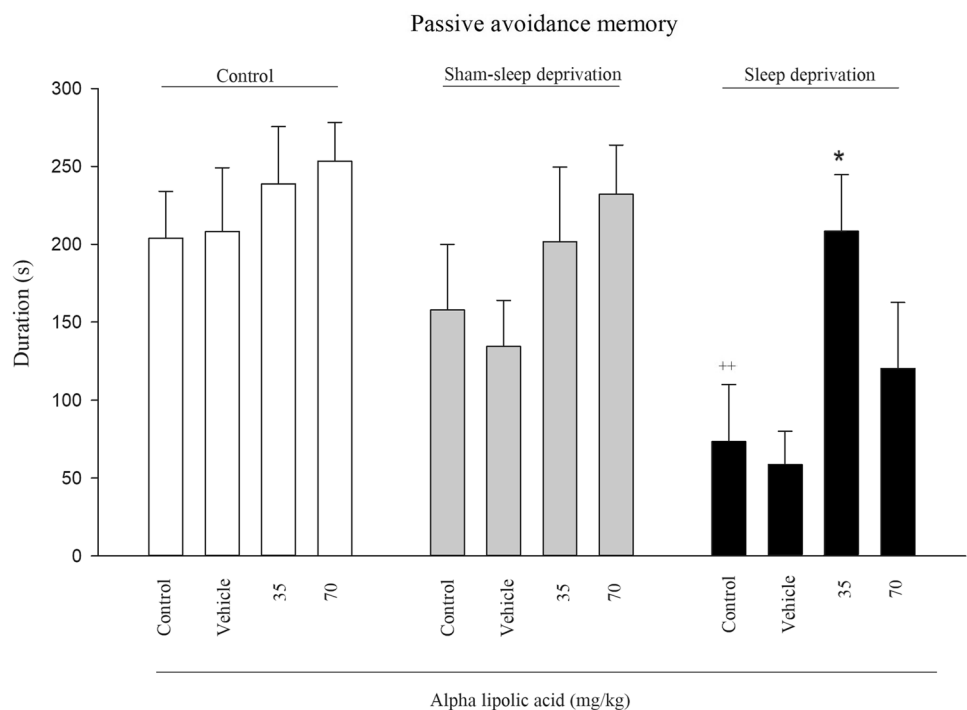


**Fig. 2** Impact of sleep deprivation on social affiliation and social memory. Two-way ANOVA was used to analyze the results of social affiliation and memory, and Tukey's post hoc test was used to compare two groups. REM SD impaired social affiliation and sociability,

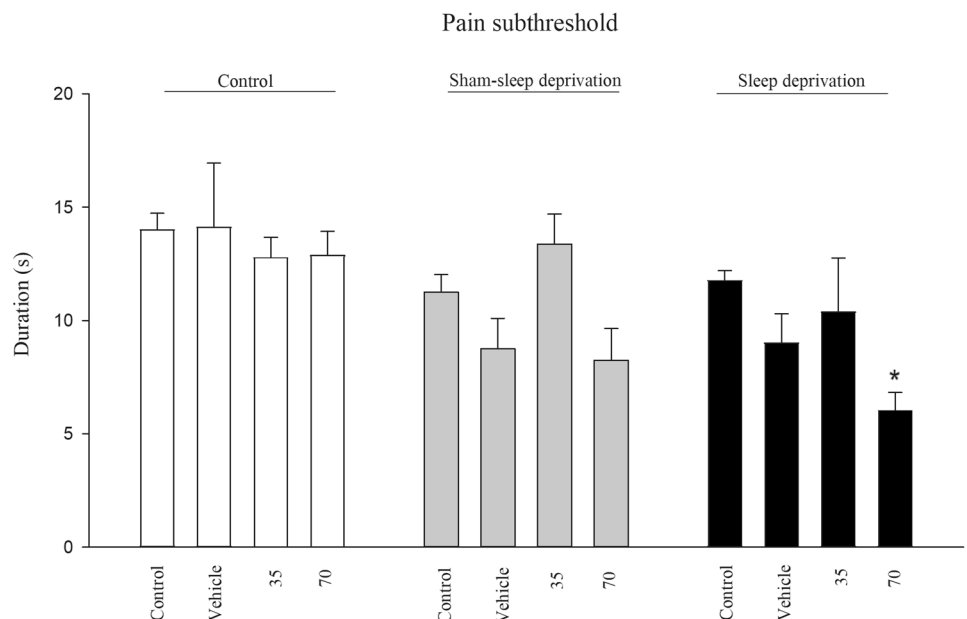
and social memory and novelty, while ALA (35 mg/kg) reversed this effect. [\*\*\* $p<0.001$ , \*\* $p<0.01$  and \* $p<0.05$  compared with empty for social affiliation and sociability, and with stranger 1 for social memory and novelty]



**Fig. 3** Impact of sleep deprivation on passive avoidance memory. One-way ANOVA was used to analyze the results of passive avoidance memory, and Tukey's post hoc test was used to compare two groups. REM SD impaired passive avoidance memory, while ALA (35 mg/kg) reversed this effect. [ $++p < 0.01$  compared with the control group and  $*p < 0.05$  compared with the related control group]



**Fig. 4** Impact of sleep deprivation on pain subthreshold. One-way ANOVA was used to analyze the results of pain subthreshold, and Tukey's post hoc test was used to compare two groups. ALA (70 mg/kg) decreased pain subthreshold. [ $*p < 0.05$  compared with the related control group]



## Discussion

In the present study, 24 h REM SD impaired social and passive avoidance memory. As mentioned, sleep is involved in the consolidation of new memories [3]. Many studies have shown the impairment effect of total or REM SD on learning and memory processes [2, 10, 35]. Synaptic plasticity is an important mechanism that underlies

SD-induced memory impairment [36]. It has been reported that SD enhances long-term depression (LTD) in the hippocampus and attenuates synaptic plasticity [37]. Previous study has shown that REM SD impairs memory via altering the hippocampal expression of genes that are related to synaptic plasticity [38]. Furthermore, SD disrupts memory processing via increasing autophagy in the hippocampus [39]. SD via increasing oxidative stress in the brain impairs memory function [40]. SD also decreases

antioxidant activity and increases oxidative stress in the hippocampus [40, 41]. REM sleep regulates memory processes that are correlated with protein synthesis and PKA (protein kinase A) [42]. Interestingly, REM SD attenuates synaptic plasticity via reduction of PKA and CREB (cAMP response element-binding protein) activity [43]. Given these proposed mechanisms, REM SD impaired memory performance.

On the other hand, our results showed that alpha lipoic acid (ALA) at the lower dose (35 mg/kg) reversed REM SD-induced social and passive avoidance memory impairment, while at the higher dose (70 mg/kg) impaired social memory, with no effect on REM SD-induced social and passive avoidance memory impairment. ALA has antioxidant and anti-inflammatory effects [44]. ALA is used as a therapeutic agent for disorders that are related to oxidative stress [45]. As mentioned, ALA is highly efficient in combating free radicals, reducing lipid peroxidation, and scavenging ROS [15]. Some studies have shown the improvement effect of alpha lipoic acid on memory performance. For example, previous study has reported that alpha lipoic acid improves fear memory and social novelty preference [20]. Alpha lipoic acid improves spatial memory and hippocampal morphology in rats [21]. In addition, ALA attenuates spatial learning and memory impairment induced by hepatectomy [18]. ALA also prevents radiation-induced spatial memory impairment [46]. Previous study has demonstrated that ALA reverses the impairment effect of ketamine on social interaction memory [47]. As we know, alpha lipoic acid has antioxidant properties [48]. ALA also affects oxidative stress. For example, it has been shown that ALA reduces the level of Malondialdehyde (biomarker of oxidative stress) following ketamine administration [49]. ALA reduces lipid peroxidation and oxidative damage of proteins, and improves non-enzymatic antioxidant capacity [50]. Furthermore, previous study has revealed that ALA decreases ROS accumulation induced by Antimycin A [51]. Note that, many studies have reported that oxidative stress is involved in memory impairment [52, 53]. Alpha lipoic acid can also improve the structure of hippocampal neurons and synapses, and the number of intersections in the hippocampus [21]. Previous study has shown that ALA improves long-term potentiation (LTP) and antioxidant activity in aged rats [54]. Interestingly, ALA enhances the phosphorylation of CREB [51], that is involved in memory processing [55]. As mentioned, SD can impair memory performance via increasing oxidative stress in the brain [40]. Given these proposed mechanisms, alpha lipoic acid (35 mg/kg) improved social and passive avoidance memory in REM SD rats.

On the contrary, alpha lipoic acid (70 mg/kg) impaired social and passive avoidance memory, with no effect on REM SD-induced memory impairments. It seems that

alpha lipoic acid can show a dualistic manner or a dose-dependent effect. Considering some studies showing that alpha lipoic acid reduces oxidative stress, a recent study has shown a different result. This study [56] has shown that ALA increases ROS accumulation and oxidative damages. Furthermore, [56] have reported that ALA decreases CREB phosphorylation. Both these effects can induce negative impact on memory processing. According to the results of the present study that showed alpha lipoic acid impaired memory only at higher dose (70 mg/kg), we suggest that alpha lipoic acid may induce a dose-dependent effect on memory. Alpha lipoic acid at higher doses may increase oxidative damages. Also, it can attenuate CREB activity and disrupt memory performance.

Finally, the results showed that alpha lipoic acid (70 mg/kg) decreased the pain subthreshold in REM SD rats. Many studies have reported that ALA reduces neuropathic and other types of pain [23, 57, 58]. However, in the present study, ALA increased pain perception. For this effect, we can point to the possible dose-dependent effect of alpha lipoic acid. Previous study has shown that ALA induces antinociceptive effects in a dose-dependent manner in morphine-treated rats [58]. However, there are not enough studies to better discuss the possible effect of ALA on pain perception and more detailed studies are needed.

## Conclusion

As the results showed, REM SD impaired social interaction memory and passive avoidance memory. ALA at the dose of 35 mg/kg reversed REM SD-induced memory impairments, while at the dose of 70 mg/kg did not show this effect. In addition, ALA (70 mg/kg) impaired social interaction memory in control and sham-SD rats. ALA (70 mg/kg) also decreased pain subthreshold in REM SD rats. We suggested that oxidative stress and free radicals may be involved in REM SD-induced memory impairment, and ALA at lower dose may attenuate oxidative stress. Furthermore, ALA may induce a dose-dependent effect. We suggested that the higher dose of ALA may increase oxidative stress and impair memory performance. Additionally, the role of CREB phosphorylation can be important.

**Author contributions** MSM collected animal data and conducted the experiments. SV wrote the manuscript, managed the literature search, and prepared the revised version. ZM analyzed data and prepared figures. MN and MRZ designed the study. All authors have approved the final manuscript.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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