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Original Article:

Restoration of Harmane Induced Memory Consolidation Deficit by Alpha-lipoic Acid in Male Mice

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Abstract

Introduction: there has been a growing number of publications focusing on the effect of beta-carbolines (e.g., harmane) on cognitive behaviors such as different stages of memory formation process. Moreover, several studies have stated that Alpha-lipoic acid (ALA) induces some molecular pathways effects including antioxidant effect and reduction of inflammation process. Thus, in the lines that follow, the question of whether ALA could alter memory consolidation deficit caused by harmane in the male NMRI mice will be addressed.

Materials and Methods: The data for this study were collected by step-down inhibitory avoidance task with one trial protocol for evaluation of memory consolidation. The ALA (35 mg/kg) was injected intraperitoneally immediately after training followed by subthreshold and effective doses of harmane (2.5, 5 and 10 mg/kg) with 15-minute interval period.

Results: The results show that post-training injection of the highest dose of harmane (10 mg/kg) lowers step-down latency, indicating the amnesia induced by harmane (P<.001). In addition, similar injection of subthreshold dose of ALA (35 mg/kg), 15 minutes before injection of subthreshold and effective doses of harmane, restores step-down latency caused by higher dose of harmane (P<.001) without its effect on the responses induced by subthreshold doses of harmane, indicating benefit effect of ALA on amnesia induced by harmane.

Conclusion: An implication of this study is the possibility that ALA can reverse the amnesia induced by harmane. Therefore, future studies on this topic such as molecular mechanisms are recommended.

Keywords: Alpha-lipoic acid, Beta-carboline, Memory consolidation, Mice

1. Introduction

Over the past decade, researchers have shown an increased interest in the effect of beta-carboline alkaloids on cognition and non-cognition behaviors [1-3]. Recent developments in beta-carboline alkaloids have heightened the need for investigating the effect of these compounds in physiological condition and abnormal phenomenon. It has been demonstrated that

beta-carbolines coumpounds such as harmane and norharmane have been implicated in Parkinson's disease, tremor, addiction, cancer and memory impariment. However, the externel sources of these compounds have been indentifed - such as tobacco- but they form normaly in the body tissues, endogenously. Interestingly, it is also observed that norharmane and harmane produce about 50-100 and 20 ng/kg body weight per day respectively, which are highily dependent of intake of precursors [2]. In some abnormal conditions, such as intake of alcohole or tobacco smoking, plasma level of these compounds will increase [2]. In contrast to these findings, some beneficial effects of beta-carboline alkaloids such as anticancer properties are proposed [1, 4].

Recently, considerable literature has gathered around the effect of beta-carboline alkaloids upon memory formation process. For example, Celikyurt et al revealed that pre-training infusion of harmane at highest dose impaired working memory and declarative memories [5]. Researches have consistently shown that also higher dose of harmane impaired memory acquisition in the mice through possible involvement of hippocampal serotonergic [6], dopaminergic [7], histaminergic [8] or nitrergic [9] systems. However, Goodwin in 2015 indicated that harmane and norharmane did not alter water maze performance (that using for spatial memory assessment) [10].

Evidence from a number of experimental studies has established that Alpha-lipoic acid (ALA) induced antioxidant effect and could improve cognitive functions or restored cognitive decline [11-18]. For example, Mahboob and et al showed that Alpha lipoic acid can improve memory formation process via hippocampus- and amygdala-dependent memory via muscarinic receptors [18]. In a new interesting article, Memudu et al postulated that ALA restored cognitive deficit and impairment of memory formation induced by scopolamine, as a model of Alzheimer's disease, because it could alleviate oxidative tissue damage via lowering reactive astrocytes proliferation and neuron chromatolysis, consequently repairing memory formation process [15]. According to the available data that Staykov et al published in 2022, ALA can alter acetylcholinesterase and monoamine levels in the hippocampus and prefrontal cortex following scopolamine induced dementia [11].

Given the reports above according which harmane at higher doses used induced amnesia and also the beneficial effect of ALA on cognitive process such as memory, the aim of this research has been to assess the effect of ALA on impairment of memory caused by harmane.

2. Materials and Methods

Animals

Male NMRI mice weighing 25-30 g were collected from the institute for cognitive sciences, Tehran, Iran. In the animal room the mice were held approximately five mice per cage. All experimental phenomenon was done under standard laboratory conditions between 9:00 am and 11:00 pm. The room temperature of the animal house was setup 22 ± 2 °C with 12/12-h light/dark cycle. In each experimental group ten animals were used. In accord with institutional guidelines for animal care and use, all interventions and behavioral assessments were deigned.

Memory measurement and apparatus

There are a number of apparatus available for measuring the memory formation process in the mice. An inhibitory avoidance device was used for measurement of memory formation in this study. This method is particularly useful for measurement of different parts of declarative memory formation such as acquisition, consolidation and retrieval sessions. In this method, the mice learn to avoid dangerous places. Briefly, in this method, the device contained a plexiglas box (30 × 30 × 40 cm^3) with a floor that comprised of parallel stainless steel bars. A plastic platform (4 × 4 × 4 cm^3) was located in the center of box.

In the first day of memory formation, each mouse was gently located on the platform of device, then immediately after the mouse stepped down from the platform and put all four paws on the grid floor, 15 s electric shocks were delivered (1 Hz, 0.5 s and 50 VDC) [19, 20]. Twenty-four hours after training day, the mouse was also located in the platform and its latency to put all four paws on the grid floor were measured as memory retrieval index. The cut-off for this section was set 300 second. All drugs were intraperitoneally injected immediately after training.

Drugs treatment

Alpha lipoic acid (ALA) was obtained from Acros company (Acros organic, Thermo Fisher Scientific, United States). ALA's vehicle was .1% NaOH. Moreover, ALA was injected at the dose of 35 mg/kg, immediately after training. Harmane HCl was purchased from Sigma (St. Louise, MO). The harmane

was dissolved in sterile 0.9% NaCl and injected at doses of 2.5, 5 and 10 mg/kg, 15 minutes after ALA injection [6-9].

Statistical analysis

The Kruskal–Wallis nonparametric analysis accompanied by a two-tailed Mann–Whitney U test were used to show statistical difference between groups. Ten mice were used in each group. The data were presented as medians ± interquartile in each group. The P<.05 was considered to be statistically significant level for all intervention.

Experiment 1

In the first evaluation, immediately after training the animals received saline (10 ml/kg). 15 minutes after previous treatment, the treated groups also received saline (10 ml/kg) or harmane at doses of 2.5, 5 and 10 mg/kg, intraperitoneally. The aim of this design was detecting the effect of harmane on memory consolidation by itself.

Experiment 2

In the second evaluation, the animals received saline (10 ml/kg) or subthreshold dose of ALA (35 mg/kg) immediately after training. 15 minutes after previous treatment, the treated animals also received saline (10 ml/kg) or subthreshold and effective doses of harmane (2.5, 5 and 10 mg/kg). The purpose of this experiment was evaluation of the effect of ALA on memory consolidation deficit induced by harmane

3. Results

Effects of harmane on memory consolidation formation

The Kruskal–Wallis analysis, H (3) = 11.45, P<.001, Figure 1; left panel, indicated that post-training infusion of harmane altered the latency time for step-down device. Further analysis by Mann-Whitney's U-test indicated that harmane at higher dose (10 mg/kg) caused memory consolidation deficit (Table 1).

The effect of ALA on memory consolidation deficit caused by harmane

The similar analysis for Kruskal–Wallis analysis demonstrated that post-training injection of a sub-threshold dose of ALA (35 mg/kg) restored the amnesia caused by higher dose of harmane, H (3) = 15.241, P< 0.001, Figure 1; right panel.

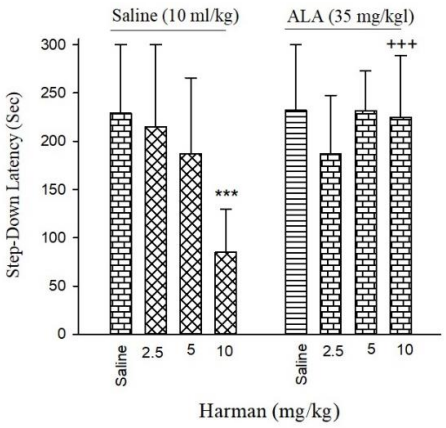

Figure 1. the effect of harmane in presence and absence of ALA on memory consolidation formation is summarized in the figure 1. Fig.1, left and right panels present the effects of post-training administration of ALA (35 mg/kg) 15 min before injection of subthreshold and effective doses of harmane (2.5, 5 and 10 mg/kg) on memory consolidation formation. The step-down latency bars are represented with median and quartile. ***P<.001 showing that significantly level when the treated group compared to group that received saline. +++P<.001 as compared to saline/harmane (10 mg/kg) group

Table 1. Drugs administration schedules and main qualitative results under the different experimental conditions

Experiment	Figure 1	Post-training and immediately after training (i.p.)	Post-training treatment (i.p.) 15 min after before injection	Step-Down latency
1	Left Side	Saline (10 ml/kg)	Saline (10 ml/kg) or Harmane (2.5, 5 and 10 mg/kg)	Decreased (Amnesia)
2	Right Side	ALA (35 mg/kg)	Saline (10 ml/kg) or Harmane (2.5, 5 and 10 mg/kg)	Increased (restoration of amnesia)

4. Discussion

First aim of this study was to examine the effect of harmane on memory consolidation process. The most important result was that higher dose of harmane impaired memory consolidation. This result is consistent with those of Nasehi et al reporting that pre-training infusion of harmane and harmaline reduced memory acquisition [6, 21]. Some studies indicated that these interesting results of beta-carbolines on

memory formation could be due to unsaturation of pyridine ring of harmane [19] and decrease of neuronal excitation induced by harmaline [21]. These differences can be explained in part by the modulatory effect of harmane on behaviors. For example, Smith et al revealed that harmane induced a general effect through the body such as elevated of ACTH and corticosterone concentrations level in the plasma, noradrenaline in the prefrontal cortex and serotonin in hypothalamus, amygdala, hippocampus and prefrontal cortex as well as decrease of serotonin and dopamine turnover in the prefrontal region [22]. This finding is contrary to previous studies which have suggested that harmane could not alter short- and long- term memories formation [23]. A greater focus on harmane's effects in the brain by Moura et al could produce interesting findings that the affinity of beta-carbolines are highly dependent on substitutions and ring saturation [19]. It seems that harmane could not improve learning and memory, because it has a fully unsaturated pyridine ring without substitution in C7 [23].

Further statistical tests revealed that subthreshold dose of Alpha-lipoic acid (ALA) reversed the amnesia induced by harmane. This finding is consistent with that of Ghafour-Broujerdi (2021) who reported that ALA restored the amnesia induced by scopolamine in the mice [17]. Moreover, several studeis indicated that ALA can contribute to treatment of neurodegenerative disorders, because it increases the activity of cholinergic system [18] and also decreases the reactive astrocytes proliferation, thus improving memory formation [15].

There are several possible explanations for the effect of ALA on brain function. Abdul et al demonestrated that using ALA in chronic pahse reduced inflammation induced by diet-induced obesity in the male mice [24]. Apart from beneficial effect of ALA on cognitive function, a new study by Di Tucci et all showed that ALA induced positive effects in multiple processes from oocyte maturation to fertilization, embryo development and reproductive outcomes [25]. A clinical trials indicated that ALA blocked nuclear factor kappa B, chelates divalent transient metal ions and also expression of adenosine monophosphate-activated protein kinase [26]. It seems that ALA could inhibit activation of NF-kB and decrease fas-ligand in matrix metalloproteinase-2 of Diabetes Mellitus patinents [27]. Kelishadi et all proposed a new mechanisem for ALA, they maintained that ALA as a supplemet can improve mitochondrial and endothelial functions in the patinent with in episodic migraines [28]. Ko in 2021 proposed other mechanisems for ALA in the cells: ALA alterd formation of proteints that are invoved in the synaptic plasticity of long-tem potantiation phenomenon such as calmodulin-dependent protein kinase II, cyclic AMP response element-binding protein, as well as insulin-related pathway proteins in the cerebral cortex or hippocampus (as main regions for mamory formation) in diabetes mellitus (type 2) and high-fat diet male rats [29]. Yet, ALA regulates antioxidant balance and reduces inflammation, protein nitrosative damag, oxidative/glycative stress, and apoptosis, critically in the hypothalamus of rats with insulin-resistant [30]. Najafi in an interesting narrative review indicated that ALA can elevate insulin secretion, glucose transport and insulin sensitivity throught activation of PI3K/Akt pathway, inasmuch as ALA can treat central obesity via developing adiponectin levels and biogenesis of mitochondry and stimulauts of SIRT1 mechanisms for reduction of food intake [31]. Moreover, ALA could reduce cell apoptosis in Alzheimer's disorder and downregulated the phosphorylation-mediated degradation of beta-catenin as well as GSK3beta [32].

5. Conclusion

Returning to the question posed at the beginning of this study, this study set out to explore the influence of ALA on memory consolidation deficit caused by harmane. The current data highlight the importance of ALA for decreasing the effect of harmane on memory formation; however, there is no data for this subject directly. Some molecular pathways have been proposed for ALA effect such as its effect as antioxidant balance, reducing inflammation, protein nitrosative damage, oxidative/glycative stress and apoptosis.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this study. No human was enrolled. Animals were treated in compliance with the guidelines established by cognitive and neuroscience research center (CNRC), Islamic Azad University Tehran, Iran.

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Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflict of interest.

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