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Intra-Hippocampal Injection of Abscisic Acid Attenuates Learning and Memory Deficits, and Changes Oxidative Stress Indices in REM Sleep Deprived Rats

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ABSTRACT

This study evaluated whether intra-hippocampal administration of ABA can modulate learning and memory performance and oxidative stress biomarker activities in the cerebral cortex of rats exposed to rapid eye movement (REM) sleep deprivation. Adult male Wistar rats were cannulated in the CA1 area of the hippocampus. After recovery, the rats were subjected to REM sleep deprivation for 4 days. Then, the groups of REM sleep-deprived (SD) rats were treated with ABA (5, 10, and 15 µg) and ABA (10 µg) + bicuculline (Bic), a competitive GABAA receptor antagonist. Memory and learning were evaluated with the Morris water maze (MWM) and shuttle box tests. Moreover, alterations in catalase levels as an antioxidant enzyme, MDA, and H2O2 as oxidant biomarkers were determined in rat brain cortex. REM SD rats indicated noteworthy learning and memory deficits in both the MWM and shuttle box tests when compared to control rats. However, intra-CA1 injection of ABA (10 µg) decreased cognitive impairment in REM SD rats. Bic (1 µg/rat) could not change ABA (10 µg) effects. In addition, an increase in catalase activity and a decrease in MDA and H2O2 were indicated in the brain cortex of ABA (10 µg) and ABA+ Bic treated groups. Overall, the data showed ABA's aptitude to attenuate REM sleep deprivation-induced learning and memory disruption and oxidative damage in rats. Manipulation of the GABAA receptor failed to inhibit ABA effects in REM SD rats.

Keywords

sleep deprivation , abscisic acid , bicuculline, learning and memory , Rat

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Abbreviations

CAT: Catalase
REM: Rapid eye movement
STZ: Streptozotocin
Bic: Bicuculline
MWM: Morris water maze
MDA: Malondialdehyde
H2O2: Hydrogen peroxide
SD: Sleep deprivation

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Introduction

Sleep deprivation (SD) is a condition of inadequate sleep that can be considered a physiological disorder or a result of an inappropriate lifestyle [1, 2]. Sleep quality has a significant impact on the regulation of other physiological processes, including learning and memory [3, 4]. It has been shown that SD disrupts memory retrieval and consolidation by changing hippocampus structural constancy [5]. The patterns of rhythmic brain waves in non-rapid eye movement sleep also show a relationship with hippocampal activities [6]. Hippocampal-mediated learning and memory, as well as neurotransmitters, are affected by sleep quality [7, 8]. REM sleep deprivation could decline motor and sensory learning experiences in animals [9, 10].

Abscisic acid (ABA) is produced in all parts of plants and plays notable roles in their physiological functions, especially the regulation of stress responses [11, 12]. ABA is synthesized from pro-vitamin A carotenoids [13], which are found in high concentrations in plants [12]. Moreover, in animals, ABA is found in various brain areas including the hippocampus, cerebral cortex, and cerebellum [14, 15]. ABA receptors are peroxisome proliferator-activated receptors (PPARs) and lanthionine synthetase C-like protein 2 [16, 17]. ABA signalling shows variation, but changes in calcium concentration and activation of cyclic ADP-ribose are the most mutual pathways [18-20].

ABA exerts modulatory effects on a variety of physiological functions including nociception, anxiety and depression like behavior, sleep and learning and memory performances in rats [15, 21]. Central administration of ABA exhibited analgesic effect which is facilitated by the PPAR β/δ and opioid signalling [22]. Moreover, ABA meaningfully improved the pentobarbital-related sub hypnotic effects and also endorsed sleep induction. Such effects showed dependency with GABAA receptors and PPARβ/PPARγ signalling [23].

The main goal of the present study was to evaluate if intra-hippocampal treatment of ABA can alter learning and memory performance in rats exposed to REM-SD. Moreover, bicuculline was used to assess the possible association of ABA with the GABA A receptor. In a previous study, pretreatment with bicuculline was found to block ABA's ability to extend sleep duration in a rat model of pentobarbital-induced sleep. Bicuculline is a competitive GABAA receptor antagonist that blocks GABA's inhibitory effects by preventing chloride ion influx, leading to increased neuronal excitability and potential seizure activity[24]. The alteration of pro-oxidant/antioxidant biomarkers was also assessed in the cerebral cortex of SD rats.

Abbreviations-Cont'd

PPARs: Peroxisome proliferator-activated receptors
ABA: Abscisic acid
ROS: Reactive oxygen species
CGRP: Calcitonin gene-related peptide

Results

PA test

The SD group showed an increase in the number of acquisition trials when compared with the control group ($p < 0.001$) (Fig. 1A). However, the number of acquisition trials was significantly decreased in SD groups post-treated with ABA (10 µg and 15 µg) ($p < 0.001$). No major alteration in acquisition trials was found in SD rats post-treated with Bic +ABA (10 µg) as compared to SD+ABA (10 µg) group. In addition, an increase in the step-through latency and a decline in time spent in the dark cavity were determined in the SD group ($p < .001$). ABA (10 µg) was able to increase the step-through latency and decrease time spent in a dark chamber in SD rats ($p < 0.001$). In addition, no significant alteration was found in the SD rats' response infused with Bic + ABA (10 µg) as compared with the ABA (10 µg) group (Fig. 1B and 1C).

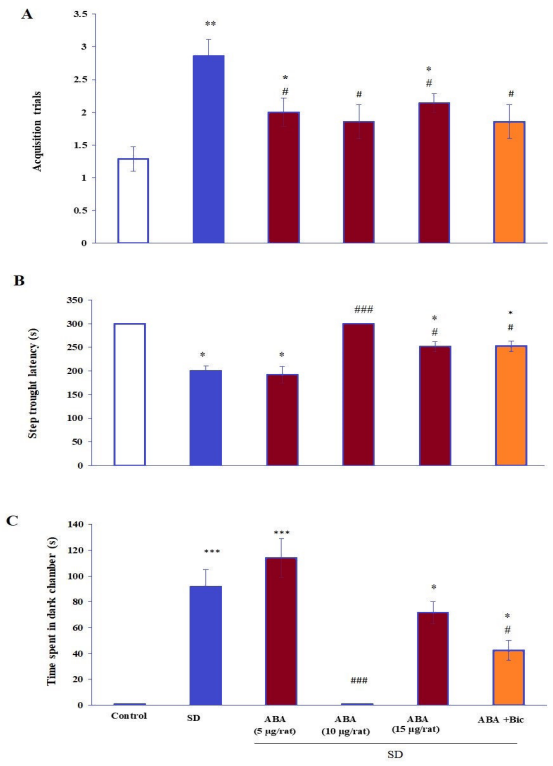

Figure 1.
The effect of intra-hippocampal administration of ABA (5, 10, and 15 µg/rat) or Bic+ABA (10 µg/rat) on the number of acquisition trials (A), step through latency (B), and time spent in a dark chamber (C) in passive avoidance test in SD rats. Values are expressed as mean ± SEM. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ versus control groups, # $p < 0.05$, ## $p < 0.01$, and ### $p < 0.001$ versus SD group

MWM test

In acquisition trials, the latency time to catch the concealed platform was pointedly increased in the SD group in comparison to the control group ($p < 0.001$). Intra-hippocampal infusion of ABA (10 µg / rat) expressively decreased the latency time to catch the concealed stage in the SD rats ($p < 0.01$) (Fig. 2A). Moreover, SD+Bic+ABA (10 µg /rat) and SD+ ABA (10 µg /rat) treated groups show no change the latency to discover the hidden platform. Moreover, the groups showed major differences in space moved to touch the concealed platform on the acquisition test. As shown in Fig. 2B, the distance trekked to touch the hidden stage was meaningfully increased in the SD group ($p < 0.001$). Besides, the SD group treated with ABA (10 µg/rat) traveled a lower distance to reach the hidden platform as compared to the SD group ($p < 0.001$). In the SD group injected with Bic+ ABA (10 µg/rat) the distance traveled to find the platform showed no difference as compared to the ABA (10 µg/rat) group (Fig. 2B).

Fig.3 indicates the results of the probe trial. The figure indicated that time spent and the traveled distance in the object zone significantly decreased in the SD group than the control group ($p <0.001$) (Fig. 3A). Moreover, ABA weakened the effects of SD on the time spent in the object area ($p <0.05$) (Fig. 3A). Further, ABA meaningfully improved distance traveled in the

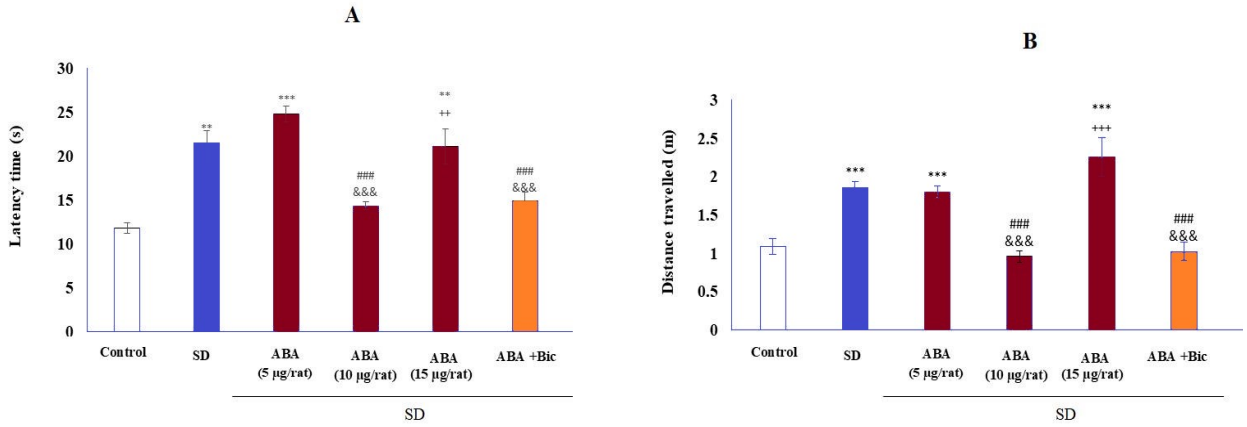

Figure 2.
The effect of intra-hippocampal administration of ABA (5, 10, and 15 µg/rat) or Bic+ABA (10 µg/rat) on the escape latency time (A) and distance travelled to find the hidden platform in the MWM test in SD rats. Values are expressed as mean ± SEM. ** $p < 0.01$ and *** $p < 0.001$ versus control groups, ### $p < 0.001$ versus SD group, &&& $p < 0.001$ versus SD + ABA (5 µg/rat) group, ++ $p < 0.01$, +++$p < 0.001$ versus SD + ABA (10 µg/rat) group

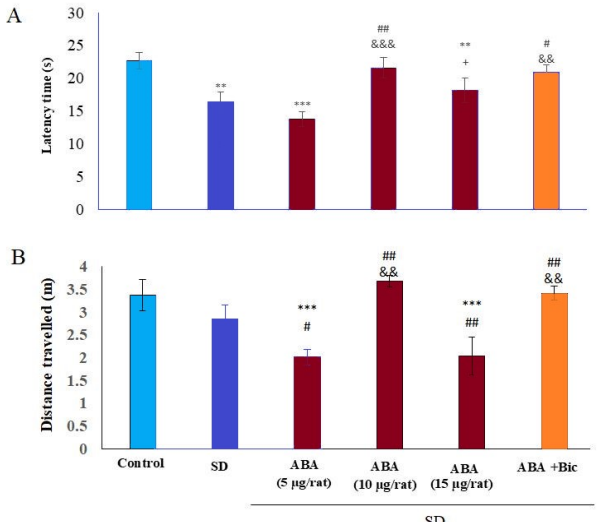

Figure 3
The effect of intra-hippocampal administration of ABA (5, 10, and 15 µg/rat) or Bic+ABA (10 µg/rat) on the duration time (A), and distance travelled in target zone in SD rats in probe trial of MWM test. Values are expressed as mean ± SEM. ** $p < 0.01$ and *** $p < 0.001$ versus control groups, # $p < 0.05$, ## $p < 0.01$ versus SD group, && $p < 0.05$, &&& $p < 0.001$ versus SD + ABA (5 µg/rat) group, + $p < 0.05$ versus SD + ABA (10 µg/rat) group

object area in SD-treated rats ($p < 0.01$) (Fig. 3B). As notated in Fig. 3, SD rats infused with Bic + ABA show no significant difference in spent time and distance traveled in the target quadrat in comparison to ABA (10 µg/rat) group ($p < 0.05$).

Biochemical assay

The activity of the antioxidant enzyme CAT was significantly decreased in the SD group when compared with control rats. As shown in Fig. 4A, ABA at 10 µg/rat and Bic+ABA (10 µg/rat) were able to increase CAT activity in the SD group. Moreover, there were significant increases in the activity of pro-oxidant biomarker H2O2 and MDA concentration in the cerebral cortex of the SD group as compared to the control group. However, post-treatment of SD rats with ABA (10 µg/rat) or Bic+ABA significantly attenuated H2O2 activity and MDA level in the cerebral cortex (Fig. 4B and 4C).

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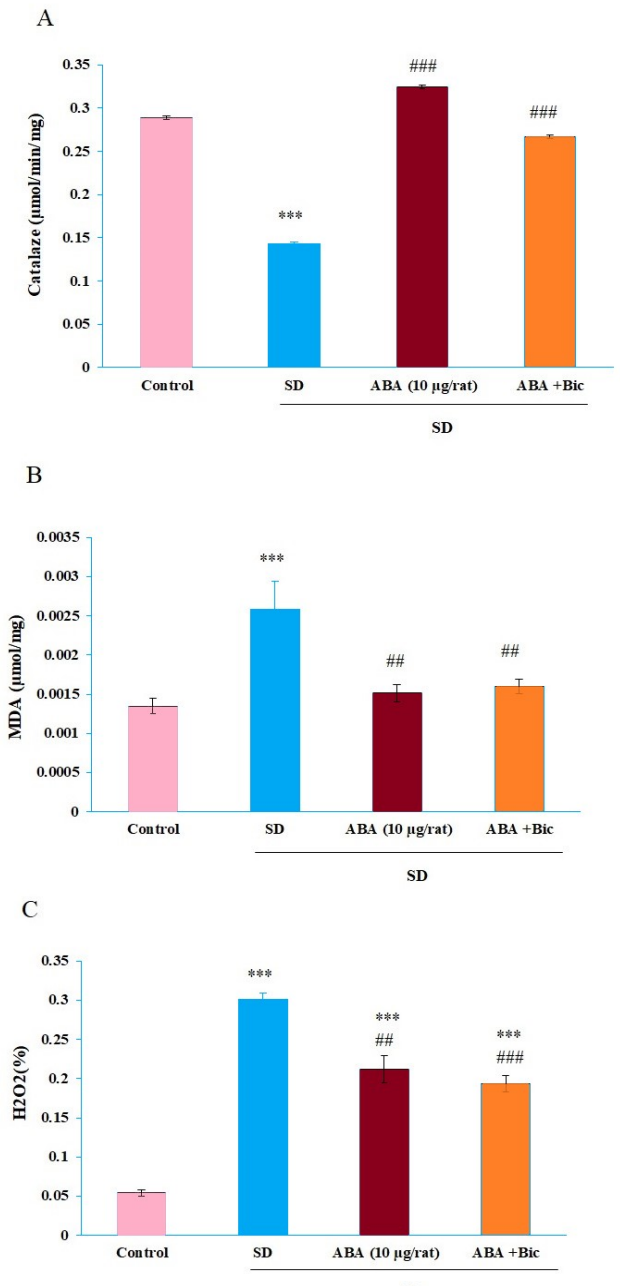

Figure 4.
The effect of intra-hippocampal administration of ABA (10 µg/rat) or Bic+ABA (10 µg/rat) on the activity of CAT enzyme (A), MDA concentration (B) and H2O2 activity in the cerebral cortex of rats. Values are expressed as mean ± SEM. ** p <0.01 and *** p <0.001 versus control groups, # p <0.05, ## p <0.01 versus SD group, && p <0.05, &&& p <0.001 versus SD + ABA (5 µg/rat) group, + p <0.05 versus SD + ABA (10 µg/rat) group

Discussion

The present study showed the deteriorating effects of REM sleep deprivation on the memory and learning performance of rats assessed in the MWM and shuttle box tests. However, intra-CA1 microinjection of ABA decreased SD-induced learning and memory deficiency in rats. Moreover, the sleep-deprived rats indicated a disruption in oxidant/antioxidant biomarkers verified by a decrease in CAT activity and increases in lipid peroxidation and H2O2 production in the cerebral cortex, which was prevented by ABA (10 µg) treatment. The ABA effects in behavioral and biochemical experiments did not diminish with the GABA receptors antagonist bicuculline.

The importance of sleep quality on cognitive performance, especially hippocampal-depended learning and memory has been strongly supported by evidence from clinical and experimental studies [25]. In this study, the rats' learning and memory performances were assessed after a continuous 72 h period of REM SD. The 72-hour REM sleep deprivation period in rats reflects severe sleep loss but is not directly equivalent to 72 hours in humans due to differences in metabolism and sleep architecture. In humans, this timeframe would likely correspond to several days of significant sleep restriction or chronic sleep disruption rather than total sleep deprivation. Rodent models typically involve more intense and compressed sleep deprivation protocols compared to human studies. To bridge the gap between rodent and human studies, future research could explore the effects of varying durations of REM sleep deprivation in animal models and attempt to correlate these findings with human studies involving partial sleep restriction or chronic sleep fragmentation. Learning and memory changes following SD are highly dependent on the lasting duration of the SD. In line with our result, most studies showed the highest detrimental effects of SD on memory performance when it lasted for 72 h. Nevertheless, in some cases, shorter terms of SD lasting for 24 or 48 hours have been associated with no alteration or even increases in hippocampal synaptic plasticity and memory impairment [26-28]. The mechanism(s) underlying different effects of SD lasting on learning and memory function are complex and still not well understood.

For the first time, this study shows ABA's ability to increase learning and memory performance in SD rats. The efficacy of ABA interventions on sleep, learning, and memory has been demonstrated in previous studies conducted on rodents. It has been indicated that ABA decreases onset time and prolongs sleep duration in a rat model of pentobarbital-induced sleep [23]. Moreover, ABA treatment reduced learning and memory deficits in rat models of STZ-induced Alzheimer's disease [29]. In addition, ABA infusion decreased learning and memory deficits in MWM and shuttle box tasks in STZ diabetic rats[30]. The mechanism(s) of ABA involvement to attenuate sleep deprivation weakening effects on learning and memory is not understood. It is postulated the effects might be intended by manipulation of related neurotransmit-

ters and distinct neural networks within the brain.

The data showed pharmacological blockage of the GABAA receptor with bicuculline did not inhibit ABA efficiency on learning and memory performances in sleep-deprived rats. In a related study, pretreatment with bicuculline could obstruct ABA impending to prolong sleep duration in a rat model of pentobarbital-induced sleep [23]. This duality suggests that ABA could engage different pathways—supporting both sleep recovery and neurocognitive resilience—depending on the physiological or experimental conditions.

GABAergic synapses are profoundly founded on hippocampus CA1 pyramidal neurons [31, 32]. While the baseline GABA levels in the hippocampus improve learning and memory performance, an increase in GABAA receptor activity has been shown to decline network excitability and reduce synaptic plasticity in the CA1 area [33, 34]. Indeed, memory retrieval is impeded by the glutamate and GABA concentration balance in the brain [35]. In the rats subjected to SD impairment of memory performance has been associated with imbalances in Glu/GABA ratio [36]. Although this study did not find ABA interfering with the GABAA receptor, however, more data are still required to describe the details of ABA's impact on the GABAergic system to modulate the learning and memory of SD-exposed rats.

In the present study, REM sleep deprivation increased oxidative stress damage defined by increases in lipid peroxidation and H2O2 levels, and a decrease in CAT activity in the cerebral cortex of rats. However, post-treatment with ABA (10 µg/rat), which was the most effective dose to increase learning and memory behaviors, could inhibit oxidative stress imbalances in SD rats. This data is supported by many previous studies that display ABA antioxidant capacity in rodents. Oral treatment with ABA in drinking water increased antioxidant defence systems indices and decreased MDA levels in many tissues of rats [37]. Moreover, intra-lateral ventricles infusion of ABA increased feeding behavior and increased the antioxidant enzymes activity, while attenuated stress oxidative enzymes [38]. In a mouse model of thioacetamide-induced hepatic fibrosis ABA treatment decreased oxidative stress enlargements and inflammation by induction of NF-κB signaling path [39]. Indeed, this study data support an association between ABA antioxidant properties and reduction of REM-SD induced learning and memory deficits.

It has been shown that as a isoprenoid plant hormone compound, ABA binds to PPARs and activates several intracellular signaling molecules essential in the regulation of learning and memory performance [16]. Pretreatment with PPAR β/δ antagonist was able to suppress ABA anti-nociceptive effects in rats [16]. Moreover, ABA decreased diabetes-induced learning and memory deficit in rats via intonation of PPARγ receptors [30]. In addition, PPARγ receptors antagonist prevented the ability of ABA to increase sleep duration in a rat model of pentobarbital-induced sleep [23]. On the other hand, motivation of PPARγ receptors with ABA modifies calcium channel activity and induces PI3K/PKC pathway in rat's brain to modulate learning and memory and anxiety-like behavior [40]. Possibly ABA efficiency on learning and memory responses in SD rats is at least partially mediated by manipulations of the PPARs system and induction of the downstream signaling molecules involved in learning and memory performance.

Our study primarily focused on learning and memory performance using specific behavioral tests (e.g., acquisition trials). While these tests provide valuable insights, they may not fully capture the broader spectrum of cognitive functions affected by sleep deprivation or ABA treatment. While oxidative stress biomarkers (catalase, MDA, H2O2) were evaluated, other potential mechanisms (e.g., neuroinflammation, synaptic plasticity) were not explored, leaving gaps in understanding ABA's comprehensive effects.

Conclusions

Overall, the data of this study showed the potential of intra-hippocampal administration of ABA to increase antioxidant indices in the brain and attenuate learning and memory deficits in RAM-SD rats. Pretreatment infusion with GABAA receptors antagonist did not change ABA-induced responses.

Materials & Methods

Animals

Adult male Wistar rats (2 months) weighing 230–270 grams were used in this study. The animals were contained four per cage in a room with a temperature of 23 ± 2 °C under a 12-h light/dark cycle with limitless entrance to food and water. All trial procedures were permitted by the Animal Research Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran.

Surgery and microinjection

Rats were profoundly anesthetized with a mixture of ketamine (100 mg) and xylazine (5 mg) and placed in a stereotaxic apparatus (Estoelting CO, USA). Guide cannulae were bilaterally inserted in the CA1 region (3.8 mm posterior to the bregma, 2.2 mm lateral from the midline, and 3.2 mm depth to the cortical surface). Afterward, rats were kept separately and endorsed for 1 week to recover from surgery before treatments [41]. The drugs (1 µL each side) were delivered using a 27-gauge stainless steel needle devoted to a Hamilton micro-syringe.

Experimental design

The animals were randomly separated into six experimental groups

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(n=7) as follows: control (untreated rats); sleep deprivation (SD): located in small platform; SD + ABA groups: treated intra-CA1 with ABA (5, 10, and 15 µg/ rat) and then located on small platform; SD + ABA (10 µg/ rat) + bicuculline (1 µg/rat): treated intra-CA1 with ABA and bicuculline and then located on small platform. The groups were exposed to SD procedures for 72 h and then injected with specific treatments. Ten minutes after intra-hippocampal injection, the rats were verified in MWM and Shuttle box tests, respectively.

Sleep deprivation (SD)

In the first tests, the single small platform method of SD was used. Animals were sited on a single stage in the center of a water cistern. The water reached up to 2 cm under the shallow of the stage. Based on the multiple small platform method, five stages (each 5 cm diameter) were used. In this method, the stages were spread out (8–10 cm apart) so that animals were able to simply travel amongst them but could not lie through any two. The control group was tested using the single large stage method, where the size of the stage was enlarged to 15.2 cm to to ensure sleep. All the treatments lasted 72 hours [42].

Learning and memory assessment

1. MWM

In this study, all the experimental groups were subjected to four days of training trials in the MWM, as defined previously [43]. A video camera was attached straight overhead the water maze pool, and the tracking system of Any maze was provided to assess the time to reach the concealed platform (the escape latency) and the length of the swim (traveled distance) of each rat in training time. Twenty-four hours later, the rats were evaluated in the probe trial, in which the escape platform was detached from the pool, and the animal was permitted to swim for 60 sec. The total time spent and the number of visits across the past position of the platform were measured to appraise spatial memory.

2. Shuttle box test

The apparatus encompassed identical-sized light and dark partitions that were separated by a sliding guillotine door. The floor of the dark and light partitions consisted of a stainless-steel shock grid. This test was divided into training and memory stages. In the instruction phase, each animal was positioned in the lightened partition, and after 5 seconds, the gate was unlocked and the rats were indorsed to transfer freely into the dark space. Upon entry into the dark chamber, the door was barred and the rat was assumed 1 mA electrical shock in 1 second. The instruction trial was completed when the rat endured in the light hall for 5 continuous min. Twenty-four hours later, in stage 2 (retrieval session), each rat was positioned on the light side of the box. Ensuing 30 s acclimatization, the door was raised. The number of electrical shock trial, latency to enter the dark chamber initial time spent to wholly enter the dark room (STL), as well as whole time consumed in the dark box were important in the passive avoidance test [44].

Biochemical assay

The rats were euthanized with CO2. The brains were detached, and the separated brain regions, hippocampus and prefrontal lobe, were kept in liquid nitrogen for assessment of biochemical parameters. Brain malondialdehyde (MDA) and hydrogen peroxide (H2O2) assay were evaluated as lipid peroxidation products and oxidative stress index [26, 45]. Moreover, the measurement of catalase enzyme activity was done as an index of antioxidant activity [46].

Statistical analysis

The results are expressed as the mean ± SEM. The statistical analyses were performed using SPSS (version 22) software. One-way analysis of variance (ANOVA) was used to evaluate significant variations among groups. Tukey's Post hoc assessment was conducted to explore the differences between the groups. A significance level of $p < 0.05$ was adopted for all tests.

Authors' Contributions

Md. Taimur Islam conceived the idea, designed the experiments and drafted the first version of the manuscript; Mohosina Mou, Nusrat Binte Rafique, Minhaz Ahmed and Md. Selim Jahangir Saurov performed the sample collection and laboratory experiment; Robius Sani Sadi edited the manuscript; Anup Kumar Talukder participated in the data analysis and edited the manuscript; Ziban Chandra Das and Md. Golam Haider reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors have no competing interests to declare.

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