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ORIGINAL ARTICLE

Role of Vitamin D in Memory Impairment Induced by Rapid Eye Movement Sleep Deprivation in Albino Rats

Shereen El-Arabi Bedear[1], Nadine A. Raafat[1], Radwa M. Al-Sayed[1], Shaimaa Ali Abuzeid[1*]
[1]Physiology department, Faculty of medicine, Zagazig University, Zagazig, Egypt.

[*]Corresponding author:
Shaimaa Ali Mohammad Abuzeid
Demonstrator in physiology department, Faculty of medicine, Zagazig University, Egypt.
E-mail: shaimaaa29@gmail.com

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ABSTRACT

Background: Chronic rapid eye movement (REM) sleep deprivation negatively impacts memory, which was related to oxidative stress-induced damage and decreased level of Brain-derived neurotrophic factor (BDNF). Vitamin D (vit D) is a neurosteroid known for its antioxidant properties. The current work is designed to assess the antioxidant role of vit D on the experimental model of REM sleep deprivation-induced memory impairment. Also, to investigate the modulatory effect of vit D on the possible expected disturbance in the level of BDNF associated with such condition.

Methods: Chronic sleep deprivation was induced via placing rats in a modified multiple platform apparatus for 8 h/day for 6 weeks. Concomitantly, vit D was administered to animals at doses of 500 IU/kg/day by oral gavage. After 6 weeks of treatment, the Morris water maze (MWM) was used to test for spatial learning and memory performance. The hippocampus was dissected; and levels/activities of antioxidant defense biomarkers, superoxide dismutase (SOD), malondialdehyde (MDA) and glutathione peroxidase (GPx) and BDNF levels were evaluated.

Results: Chronic REM sleep deprivation impaired spatial memory ($P<0.05$) which was prevented by vit D treatment, also vit D normalized sleep deprivation-induced decrease in hippocampal SOD ($P<0.05$) and BDNF ($p<0.001$) and increase in MDA ($p<0.001$).

Conclusions: Spatial memory impairment was induced by chronic REM sleep deprivation and vit D treatment prevented such impairment. This was possibly achieved via normalizing antioxidant defense mechanisms and BDNF level in the hippocampus.

Keywords: REM sleep deprivation; memory; Vitamin D; BDNF; Antioxidant.

INTRODUCTION

Sleep is essentially required for human physical and mental performance [1]. It is formed of two stages: non-rapid eye movement (NREM), and rapid eye movement (REM), also called paradoxical stage of sleep [2].

Sleep deprivation can be acute (several hours up to a week) or chronic (daily for several hours typically 3-8 hours/day that lasts for weeks or months). There is an evidence on human subjects and animals has shown that both acute and chronic REM-sleep deprivation resulted in memory defects in several behavioral tasks [3].

A recent study showed the correlation between REM-sleep deprivation and elevated hippocampal oxidative stress, which was correlated with impairment of cognitive functions [1] as the brain is more sensitive than other tissues to oxidative stress because of its poorer enzymatic antioxidant defense mechanisms [4].

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that has an important role in neuronal survival, differentiation and neurogenesis. BDNF is widely distributed within the hippocampus. It was revealed that its disturbance is associated with cognitive dysfunction [5].

Recent epidemiological evidence suggests that vitamin D is concerned with cognitive preservation including attention, memory orientation and executive functions, and inhibits brain dysfunction in disease models of multiple sclerosis and Alzheimer's disease [5].

Moreover, vitamin D has been found to reverse oxidative stress and neuro-inflammation that lead to cognitive impairments induced in

some models like high fat diet-induced obesity [5, 6]. Also, another study suggested a necessary role for vitamin D enhancing effect on acquisition and retrieval of streptozotocin-induced diabetic learning and memory impairment [7].

However, the ability of vitamin D to prevent or ameliorate oxidative stress biomarkers is controversial and its role on cognitive function is still not well elucidated so, there is a need for further and high-quality studies testing the cognitive enhancing effect of vitamin D [8].

METHODS

Fifty adult male albino rats weighing 150-200gm, aged 14 weeks old and supplied from the faculty of Veterinary Medicine, Zagazig University, were enrolled in the present study. Approval for this study was obtained from Institutional Review Board (IRB) NO 4294-4-2-2018, faculty of medicine, Zagazig University.

All animal experiments were with the ARRIVE guidelines and carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments. The rats had free access to water and chow, were kept at room temperature on a 12 h light/ dark cycle. After two weeks of acclimatization, rats were randomly divided into five equal groups (n=10 for each).

Group I: Control group: Rats were administered saline once daily for 6 weeks by oral gavage, ***group II: Vitamin D treated group****:* Rats received vitamin D3 treatment at a dose of 500 IU/kg per day by oral gavage. This dose of vitamin D was chosen according to the previous study suggesting the neuroprotective effects of this dose in animal models.**[5]**, ***group III: Wide platform (WPF) (stress control) group****:* Rats were allowed to use a wide platform to sleep on for 6 weeks with administration of saline once daily during the same period by oral gavage, ***group IV: Chronic sleep deprivation (SD) group:*** Rats were sleep-deprived 8h/day for 6weeks and were administered saline once daily by oral gavage and ***group V: Chronic sleep deprivation vitamin D treated (SD+vit D) group:*** Rats were sleep-deprived 8h/day for 6weeks and received vitamin D3 at a dose of 500 IU/kg per day by oral gavage. Groups I, II and III are considered control groups.

At the end of the sleep deprivation period, a Morris water maze (MWM) was performed on each rat for 8 days then the rats were sacrificed and the hippocampus was dissected then homogenized for biochemical assays. The whole 8-h sleep deprivation procedure was done during the day as rats are nocturnal animals.

The control, SD and WPF groups were administered saline once daily for 6 weeks by oral gavage. All manipulations including SD, vitamin D3 and normal saline administration were started on the same day and continued for 6 weeks.

Morris water maze training was carried out immediately after 6 weeks of treatment. SD and/or vitamin D treatments were continued throughout the MWM testing days. All the treatments were administered between 8:00 and 9:00 am. Right after dosing, both the SD and SD with vitamin D groups were subjected to REM-SD; 8 h/day for 6 weeks [9].

REM Sleep Deprivation Procedure

Chronic sleep deprivation was induced using columns-in-water (modified multiple platform) model. Briefly, animals were placed on platforms (24 platforms; 20cm high and 5cm diameter, 7cm apart edge-to-edge) arranged in 3 rows such that rats could move freely from one platform to another surrounded by water (24±1◦C) in an aquarium (2.29m×1.52m×56m). The water level in the aquarium was about 4cm below the edge of the platform. Loss of muscle tone during REM sleep caused animals to fall into the water, wake up and climb onto the platform again [10].

This method is applicable to deprive the animals from REM sleep and permit other stages. Several rats are deprived together in order to inhibit isolation stress. 20 rats were placed into the aquarium and 4 platforms were kept empty to decrease immobilization stress. Therefore, the animals were able to freely move and interact with each other [11].

To test the possible effects of stresses of the tank environment, wide platforms (diameter:12cm) were used to allow the WPF rats to sleep without falling in the water [10].

Behavioral Study

The maze was formed of a circular black pool 125 cm in diameter and 55 cm in height with a featureless interior surface. It was filled with opaque water that has been equilibrated to ambient temperatures of 19–22 °C to a depth of 20 cm. The pool was divided into four equal quadrants by imaginary two lines. The platform: The goal was circular (10 cm in diameter 20 cm in height) and transparent in order to be invisible. It was located in the middle of one of the quadrants. The maze was placed in a room with ample surrounding visual cues. These distal cues were not moving during testing as these were the animal's navigational reference points for locating the goal, independent of the start location.

Spatial acquisition (hidden platform): The animal was placed in the desired start position in the maze, facing the tank wall. The animal was

released into the water at water-level. A timer was started the moment that the animal was released. The timer was stopped when the animal reached the platform. A trial limit of 1 min per trial was the standard used. Animals not finding the platform within this time limit were either placed on the platform or guided to it.

The animal was left on the platform during the inter-trial interval (ITI) (60s), therefore the rat could orient to its position in space and remember the position of the goal in relation to surrounding cues. The animal was placed in the maze at a new start location and the trial was repeated until the animal had the desired number of trials for that day, towel dried then was put in a holding cage till the whole group finished the trials then they were returned to the homecage. Animals were given four trials per day. The trials were repeated on the next subsequent five days.

Reference Memory:

Probe Trial: The platform was removed. The animal was placed in a novel start position in the maze, facing the tank wall, for example, 180° from the original platform position. A novel start position was used during the probe trial to ensure that its spatial preference is a reflection of the memory of the goal location rather than for a specific swim path. The animal was removed after a fixed interval (60s). Percent time in the target quadrant was estimated as an indication of such memory (Morris Water Maze) [12].

Hippocampus dissection:

On the last day of the study, the animals were sacrificed by decapitation and the brain was removed immediately and washed with ice-cold saline. After that, the hippocampus was quickly dissected and weighed. Hippocampi were stored at a temperature of -80°C for biochemical analysis [13].

Biochemical studies:

Estimation of BDNF by Immunoassay: according to manufacturers' instruction. Estimation of Lipid Peroxide (Malondialdehyde) (MDA) by a colorimetric method according to Ohkawa et al. [14]. Superoxide Dismutase (SOD) by a colorimetric method according to Nishikimi et al. [15]. Estimation of Glutathione Peroxidase was according to Paglia and Valentine [16].

Statistical analysis

The collected data were entered, presented and analyzed by computer using a database software program, Statistical Package for Social Science (SPSS) version 20 (IBM, 20).

For quantitative variables, mean and standard deviation were computed. median and range were computed in case of not normally distributed data (non-parametric data).

Analysis of variance (ANOVA), one-way ANOVA test was used for comparison of means of more than two groups in normally distributed data and Kruskal Wallis test was used in case of not normally distributed data.

Mann Whitney test was used to calculate the difference between quantitative variables in two groups in not normally distributed data. For all above mentioned statistical tests, the threshold of significance is fixed at a 5% level (p-value). Where P-value of <0.05 indicates significant results, and the smaller the P-value obtained the more significant are the results.

RESULTS

The Effect of Chronic REM-Sleep Deprivation and vitamin D on Learning and Memory: Hidden platform task in all experimental animals:

Figure (1) shows different days of training regarding escape latency time among all studied groups. In the learning (acquisition) phase (first and second day of the hidden course), there was no significant difference in the median value of escape latency time among all groups ($p>0.05$). On the third, fourth and fifth days of the hidden platform task, there was a significant increase in the median value of escape latency time between the SD and all other groups ($p<0.05$). However, no significant difference was observed in the median values of escape latency time (time of finding platform) between all other groups ($p>0.05$).

Figure (2) shows time spent in target quadrant in the probe step. On the probe trial of MWM test (the sixth day of the test), which evaluated how well the experimental groups learned and stabilized the platform position during the five days of hidden training, by using one-way ANOVA and post hoc analyses, there was a significant decrease in the mean value of time spent in the target quadrant between SD group compared with other groups ($p<0.001$). However, there was no significant difference between all other groups ($p>0.05$).

The effect of chronic sleep deprivation and vitamin D on hippocampal tissue oxidant and antioxidant stress markers:

Figure (3) shows hippocampal levels of SOD enzymatic activity (U/gm tissue) in all studied groups. By using the Mann Whitney test, sleep-deprived group showed a significant decrease in the median value of the hippocampal activity of SOD as compared to the other groups ($p<0.001$). However, there was no significant difference between all other groups ($p>0.05$).

Figure (4) shows hippocampal levels of MDA (nmol/gm tissue) in all studied groups. By

using the Mann Whitney test, sleep-deprived group showed a significant increase in the median value of hippocampal MDA level as compared to the other groups ($p<0.001$). However, there was no significant difference between all other groups ($p>0.05$).

Figure (5) shows hippocampal levels of GPx enzymatic activity (U/gm tissue) in all studied groups. No significant change was observed in the median value of GPx activity level among all groups ($p>0.05$).

The Effect of Chronic REM-Sleep Deprivation and vitamin D Treatment on Hippocampus BDNF

Figure (6) shows hippocampal levels of BDNF (ng/ml) in all studied groups. There was a significant decrease in the mean value of BDNF in SD group when compared with other groups (control, vitamin D treated, WPF and SD+vit D) ($p<0.01$, <0.05, <0.05 and <0.001 respectively). However, there was no significant difference between all other groups.

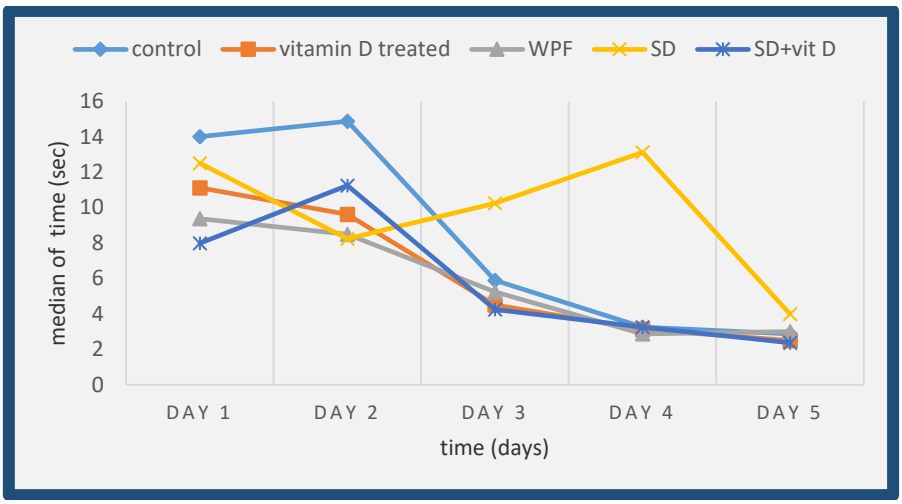

Figure (1): Time (sec) spent to reach the hidden platform in different days of the memory test in the different studied groups.

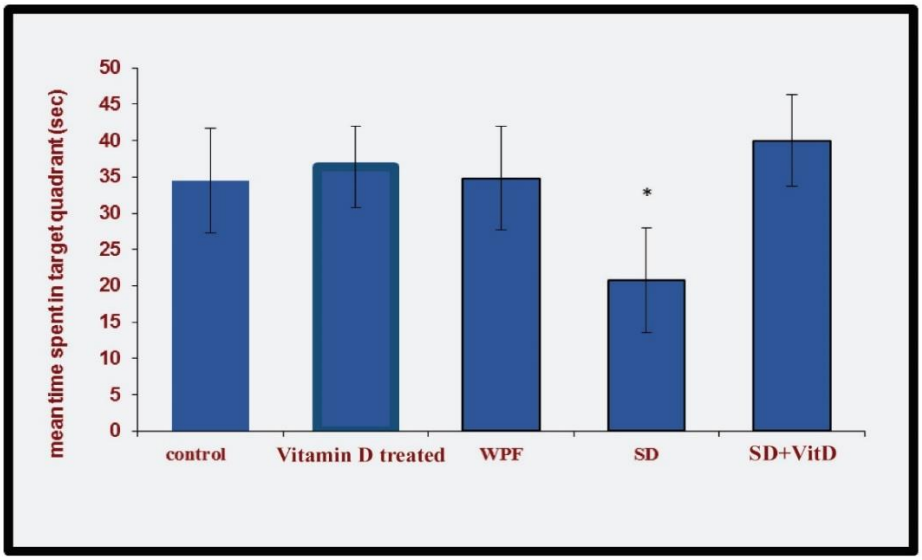

Figure (2): Illustrates mean value (±SD) of time spent in target quadrant in all studied groups. *=significant vs all other groups.

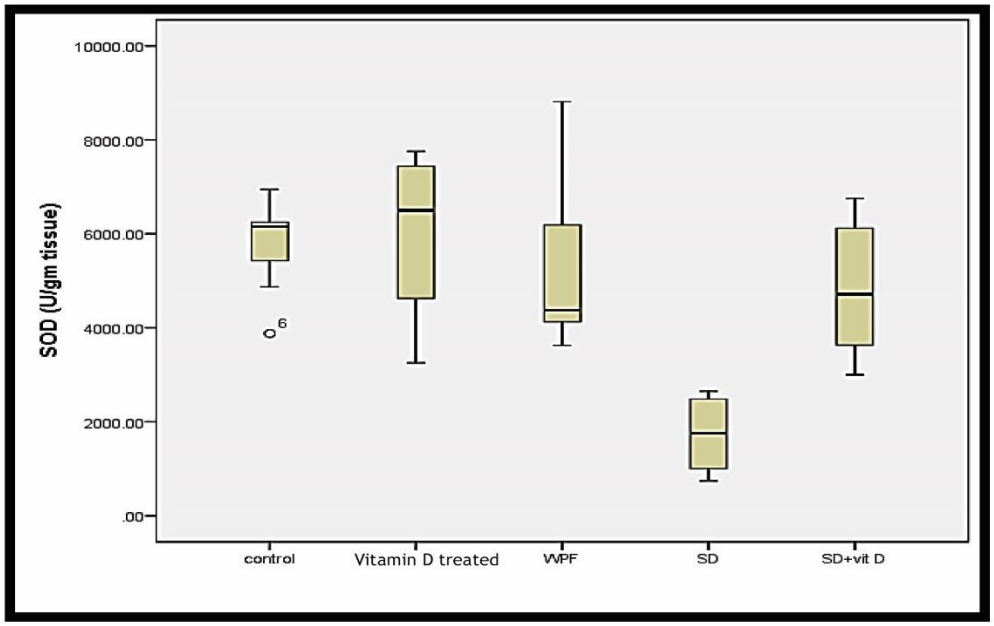

Figure (3): Box plot showing SOD enzymatic activity level in hippocampus among studied groups.

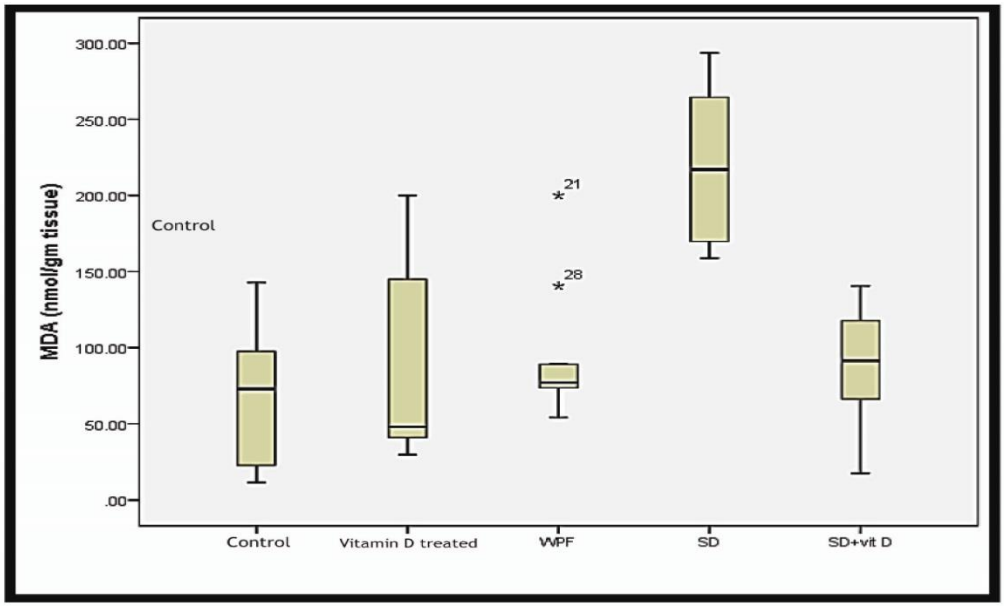

Figure (4): Box plot shows MDA level in hippocampus among studied groups

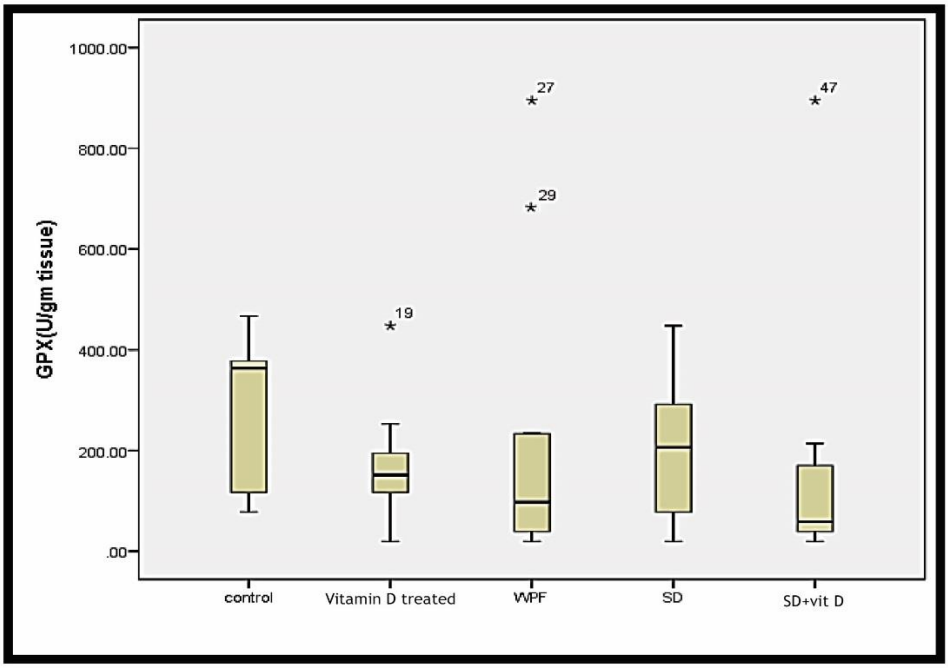

Figure (5): Box plot shows GPx enzymatic activity level in hippocampus among studied groups.

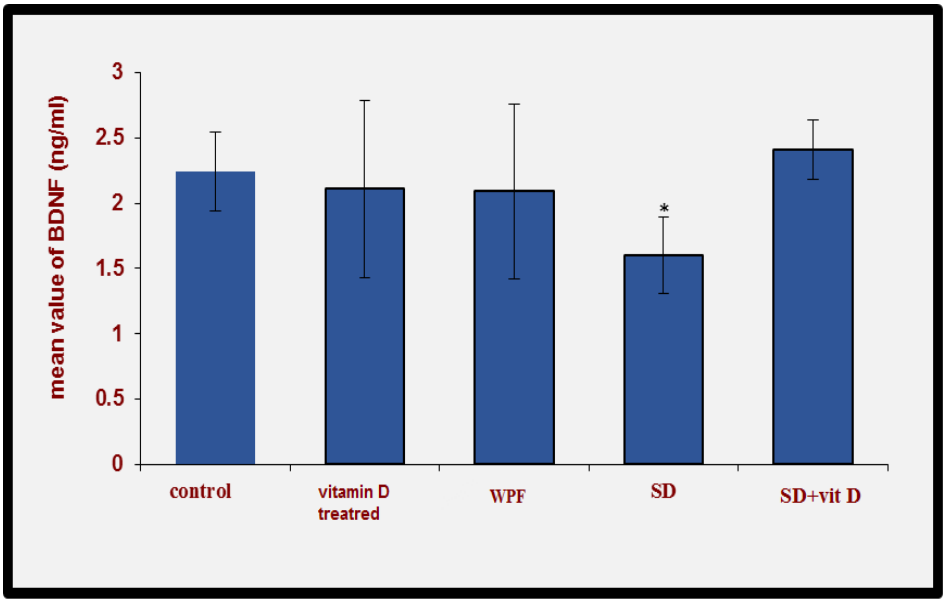

Figure (6): Illustrates the mean value of BDNF in all studied groups.
*=significant vs all other groups.

DISCUSSION

Results of the present work revealed that chronic REM-sleep deprivation in rats caused memory impairment in them represented by significant increases in escape latency time on the third, fourth and fifth days and decreases in time of the MWM probe test. Also, there was an increase in hippocampal tissue MDA levels associated with decreases in enzyme activity of SOD and BDNF levels, while no change was observed in GPx levels.

In concordance with these findings, previous studies described an impairment in short- and long-term memory in rats by chronic sleep deprivation which is confirmed by their observations that animals in the chronic sleep-deprived groups made significantly more errors in finding the hidden platform than controls in the radial arm water maze (RAWM) [17].

The impaired performance of sleep-deprived animals in the present study seems to be related to sleep deprivation rather than the stress of the procedure, since there was no memory deficit in the stress-control group (WPF). In agreement with this finding, Mhaidat et al. [9] also found in their studies that there was no

significant difference between rats in the stress control group versus the sleep deprivation group in their performance in RAWM.

On the other hand, current results showed that chronic sleep deprivation did not alter spatial learning as there was no significant difference between all studied groups in the first and second days of the escape latency time in the hidden phase.

Supporting this finding, Alzoubi et al. [10] performed behavior test through the RAWM test and found that all the animal groups learned the location of the submerged platform, as determined by the marked reduction of errors in the learning phase with no significant difference among these groups in all learning trials.

In contrast with the present results, Walsh et al. [18] noted that rats in the REM sleep deprivation and control groups performed similarly across training trials and probe trial measures in MWM so, they concluded that REM sleep deprivation didn't affect memory. They proposed that the discrepancies between the results of the previous studies and their study could be attributed to the incomplete sleep deprivation, overtraining, pre-training, floor effects, maze geometry and differences in REM sleep deprivation protocols and these factors could contribute to the lack of effect of concurrent REM sleep deprivation on either initial spatial learning or reversal learning in the MWM.

Regarding the effects of sleep deprivation on oxidative stress, the current study showed that REM-sleep deprivation for 8hrs/day for 6 weeks caused a significant increase in hippocampal MDA level and a significant decrease in enzyme activity of SOD while no change was revealed in GPx level.

These data were in agreement with Ramanathan et al. [19] who observed that REM-sleep deprivation increases hippocampal oxidative stress by reducing SOD activity in the hippocampus and brainstem.

Furthermore, Silva et al. [13] showed that hippocampal level of lipid peroxidation was significantly high in the sleep-deprived animals for 72 hours which was associated with memory deficits displayed through the RAWM test. They reported that this increase was prevented by repeated treatment with the antioxidant agents; melatonin and vitamin E.

However, the current study revealed that there was no significant difference in the level of GPX between different groups and this came in agreement with Singh et al. [20] who also found that paradoxical sleep deprivation did not affect GPx level in any of the brain regions examined both in adult and old animals.

The brain is more liable than any other tissue to oxidative stress because of its poorer enzymatic antioxidant defense mechanisms [7]. In addition to this, the brain is rich in polyunsaturated fatty acids that make neuronal cells easily vulnerable to oxidative attack [21].

The present work revealed that REM sleep deprivation for 6 weeks caused a significant decrease in hippocampal BDNF. These findings were in agreement with Schmitt et al. [22] who demonstrated that sleep deprivation resulted in a reduction in the expression of BDNF and its protein levels in the hippocampus, whereas no changes were observed in the expression of these molecules in the neo-cortex.

A possible explanation for the harmful effect of sleep deprivation on the memory could be the decrease in the main regulatory proteins for BDNF expression and its mechanism of action; CREB, extracellular signal-regulated kinase (ERK) and calcium/calmodulin-dependent protein kinase IV (CaMKIV) [10]. The decrease in BDNF leads to deficits in LTP, the most studied form of synaptic plasticity and the mechanism underlying learning and memory [3].

In contrast, Fujihara et al. [23] suggested the possibility that short-term disturbance of the sleep/wake cycle and, hence, the partial reduction of sleep duration, might exert a potential influence on neuronal and glial cells as an internal stressor, resulting in the elevation of BDNF gene expression in rat hippocampus.

On another aspect, the results obtained from the administration of vitamin D to the sleep-deprived rats revealed that vitamin D protected against chronic sleep deprivation induced impairment of memory and normalized oxidative stress marker, MDA, antioxidant enzyme activity, SOD, and BDNF levels.

In line with these findings, Moghadamnia et al. [7] investigated the effect of vitamin D on the acquisition and retention of memory and learning in streptozotocin-induced diabetic mice and they reported that vitamin D has a potential role in the treatment of diabetes-associated cognitive deficits through its physiological effects on Ca^{2+} homeostasis. They assumed that brain calcium-binding proteins are modulated by vitamin D which is in addition to their calcium-buffering functions; are required for normal signaling of calcium in synapses and are involved in synaptic plasticity, long-term potentiation, and memory formation.

Additionally, the findings of Taghizadeh et al. [24] study revealed that a vitamin D-free

diet was associated with lower performance in the spatial task as the rats who received a vitamin D-free diet never located the maze target in about 21% of trials. Moreover, they required a longer time to learn the place of the hidden platform compared to the controls.

Moreover, weekly dietary intake of vitamin D was found to be associated with cognitive performance in older women [25]. Also, Pettersen [26] found that a high dose of vitamin D supplementation significantly enhanced performance on nonverbal (visual) memory, compared with low dose supplementation.

Contrary to these findings, Dean et al. [27] indicated that vitamin D supplementation did not influence cognitive functioning in healthy young adults with vitamin D deficiency. Moreover, it was shown that there was no relationship between serum vitamin D and cognitive functioning in young to middle-aged adults [28].

It is possible that these discrepancies in the vitamin D literature can be attributed to cross-sectional study designs, inadequate statistical adjustment, heterogeneity in cognitive function measures and variation across vitamin deficiency cut-off values used in different studies as according to some authorities, persons are at risk of vitamin deficiency at serum 25(OH)D3 concentrations 30 nmol/l. Some argue that optimal levels of serum 25(OH)D3 concentrations are 50 nmol/l, and persons below this level should be considered at high risk and targeted for treatment. Similarly, there have been some authorities that recommend serum 25(OH)D3 levels of 75–80 nmol/l or higher [8].

Vitamin D has been shown to act as a neuro-protective agent in many ways; it decreases the production of tumor necrosis factor-*a*, interleukin-6, and nitric oxide (NO) in the microglial cell line, indicating its direct anti-inflammatory properties [29].

Hajiluian et al. [6] evaluated the neuro-protective effects of vitamin D on a high fat diet (HFD) induced obese rats and evaluated that vitamin D reversed HFD induced oxidative stress and neuro-inflammation that led to cognitive impairments via elevation of SOD, GPX and decline in the MDA concentrations and reduction of inflammatory biomarkers in rats' hippocampi.

Regarding the antioxidant role of vitamin D, Mokhtari et al. [30] clarified that it regulates the oxidative stress through the following mechanisms; induction of expression of several molecules involved in the antioxidant defense system including GSH, GSH peroxidase and SOD, and suppression of expression of NADPH oxidase also it acts as a direct antioxidant of the membrane via scavenging hydrogen peroxide and superoxide radicals, thus protecting cells against lipid peroxidation and membrane breakdown.

Vitamin D supplementation did not show significant effects on SOD activity and MDA in subjects with juvenile idiopathic arthritis [31] and in pregnant women at risk for pre-eclampsia [32].

In addition, vitamin D administration was associated with a significantly high level of hippocampal BDNF concentration in rat model of Alzheimer's disease [33] and high fat diet-induced obese rats [5], whereas, in another study by Pirotta et al. [34], no effects of vitamin D on serum BDNF in old adults were reported. They assumed that there were some limitations in their study that restricted the ability to detect significant differences between groups like the small sample size, short duration of the trial and the relatively healthy older adults they included in the study.

Conflicts of interest: None.

Financial disclosure: None.

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