Psychiatry Research 281 (2019) 112577

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The protective effect of edaravone on memory impairment induced by chronic sleep deprivation

Karem H. Alzoubi[a,*], Heba S. Al Mosabih[b], Amjad F. Mahasneh[b]

[a] Department of Clinical Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
[b] Department of Applied Biology, Jordan University of Science and Technology, Irbid, Jordan

ARTICLE INFO

Keywords:
Edaravone
Sleep deprivation
Memory
Maze
Oxidative stress

ABSTRACT

Sleep plays a critical role in body health maintenance, whereas sleep deprivation (SD) negatively affects cognitive function. Cognitive defects mainly memory impairment resulting from sleep deprivation were related to an increase in the level of oxidative stress in the body, including the brain hippocampus region. Edaravone is a potent free radical scavenger having antioxidant effect. In the current study, edaravone's ability to prevent SD induced cognitive impairment was tested in rats. Animals were sleep deprived 8 h/day for 4 weeks. Concurrently, edaravone was administrated intraperitoneally for four weeks. Animals performance during cognitive testing was evaluated to display if edaravone has a role in the prevention of sleep deprivation induced memory impairment. Additionally, the role of antioxidant biomarkers glutathione peroxidase (GPx), catalase, glutathione (GSH), oxidized glutathione (GSSG), GSH/GSSG in this effect was investigated. The results showed that SD impaired both short- and long- term memories, and chronic edaravone administration prevented such effect. Additionally, edaravone prevented decreases in hippocampal GPx, catalase, GSH/GSSG ratio and normalized increases in GSSG levels, which were impaired by SD model. In conclusion, current result showed a protective effect of edaravone administration against SD induction that could be related to edaravone's ability to normalizing mechanisms related to oxidative balance.

1. Introduction

Sleep is a naturally recurring status of the body and mind, in which awareness is altered, and sensory activity, most voluntary muscles activities, and interactions with surroundings are inhibited. During sleep, the body shifts into an anabolic state, which helps in restoring the nervous, immune, muscular and skeletal systems. Reduced metabolic rates leads to reduced reactive oxygen species (ROS) generation, which allows for restorative processes to take over during sleep. Thus, sleep combats free radicals accumulation in the brain via enhancing the endogenous antioxidant mechanisms efficiency (Bingham et al., 2007). Sleep is divided into two major phases: the rapid eye movement (REM) and the non-rapid eye movement (NREM). An essential cognitive benefit of sleep is to set newly acquired memory for long-term durations (Wagner and Born, 2008). In fact, REM sleep duration is increased after active learning processes (Siegel, 2001; Hornung et al., 2007).

Sleep deprivation is one of the sleep disorders, which represents the condition of not getting a sufficient amount of sleep. Currently, sleep deprivation is greatly expanding, affecting peoples work and social life (Basner et al., 2007; Hublin et al., 2001). Many studies showed the effect of sleep deprivation on memory and learning (Guan et al., 2004; Smith and Reviews, 1985; Stern and behavior, 1971). New studies demonstrated that REM-sleep deprivation might cause memory deficits by increasing the oxidative stress level in the hippocampus (Alzoubi et al., 2018a; Alzoubi et al., 2012b; Alzoubi et al., 2013c; Alzoubi et al., 2017; Ramanathan et al., 2002). This increase might be due to the accumulation of reactive oxygen species (ROS) during the wake circuit (Alzoubi et al., 2019a; Alzoubi et al., 2012b; Alzoubi et al., 2018c; Ramanathan et al., 2002; Silva et al., 2004).

Edaravone, 3 methyl-1- phenyl-2- pyrazolin-5-one, is a scavenger of free radicals, which passes the blood brain barrier, and can efficiently remove free radicals from the brain (Hara et al., 2015). Edaravone shows neuroprotective effects by inhibiting vascular endothelial cell injury and ameliorating neuronal damage in ischemic brain models (Banno et al., 2005). The application of edaravone in a mouse model of alzheimer disease was confirmed to decrease amyloid pathology and saving memory deficits (Jiao et al., 2015). Moreover, edaravone was recently shown to protect againist memory impairment and oxidative stress induced during the course of post-troumatic stress disorder (Alzoubi et al., 2019c). In this study, we investigated the possible

* Corresponding author.
E-mail address: khalzoubi@just.edu.jo (K.H. Alzoubi).

https://doi.org/10.1016/j.psychres.2019.112577
Received 6 June 2019; Received in revised form 20 September 2019; Accepted 22 September 2019
Available online 25 September 2019
0165-1781/

protective role of edaravone in learning and memory functions in Wistar male rats that were exposed to sleep-deprivation. To test this hypothesis, behavioral studies were conducted via using Radial Arms Water Maze (RAWM) to compare the cognitive functions of rats among different groups. Biochemical assays were executed to evaluate the interactive effect of chronic administration of edaravone on oxidative stress biomarkers.

2. Methods

Adult male Wistar rats weighing 150–200 g were obtained from Jordan University of Science and Technology (JUST) animal facility and were utilized in this study. Animals were kept in large plastic cages (seven to eight rats per cage; cage size, LXWXH in cm: 55 × 45 × 25) under optimum hygienic conditions. The animals were maintained at room temperature (24 ± 1 °C) with free access to water and food. They were identified by labeling their tails and they were housed in 12 hours light/dark cycle (light on 7:00 am). The whole experimental work was performed at the light phase as per the JUST Animal Care and Use Committee (ACUC) approval.

2.1. Animal groups and treatments

Seventy-five rats were randomly divided into five groups ($N = 15$/group): Control (control), Wide Platform (WPF), Chronic REM-Sleep Deprivation (SD), Edaravone, (Edaravone) and chronic Sleep Deprivation with Edaravone (Edaravone-SD). The control group received distilled water (the vehicle) intraperitoneally, and was not exposed to chronic REM-sleep deprivation. The SD group was exposed to REM-sleep deprivation and received distilled water intraperitoneally. The WPF group, which served as an internal control for possible stresses of the aquarium environment, where wide platforms were utilized permitting the rats to sleep in the aquarium. Animals in the WPF group received distilled water intraperitoneally. The Edaravone group, which recieved 3 ml/kg/day intraperitoneally, and was not exposed to REM-sleep deprivation. Finally, thechronic Sleep Deprivation with Edaravone (Edaravone-SD, $n = 15$), which recieved 3 ml/kg/day intraperitoneally, and was exposed to REM-sleep deprivation. Edaravone was obtained from Sigma-Aldrich (St. Louis, MI, USA). The edaravone dose regimen was based on previous work that showed its beneficial properties in conditions other than sleep deprivation (Alzoubi et al., 2019c; Zhang et al., 2018). As previously described (Alzoubi et al., 2019c), sleep deprivation and Edaravone administration were simultaneously started on the same day (day 1 of the experiment) and continued for four weeks and the behavioral test day, after allowing one-week acclimation for animals to get used to the new room, own new group and the researcher.

2.2. Induction of sleep deprivation

The SD and Edaravone-SD groups were exposed to REM-sleep deprivation 8 hours per day for 4 weeks by utilizing modified multiple platforms model (Alhaider et al., 2010a; Alhaider et al., 2011; Alzoubi et al., 2012b). A maximum of 10 rats were placed in a large glass aquarium that contains 20 platforms arranged in two rows. These platforms rise above water level by 2 cm at least, and had a surface diameter of 5 cm. The space between the two platforms (edge to edge) was 7 cm, which allowed animals to move freely among platforms. After a time the rats reach REM phase of sleep, they, then, loose muscle tone and fall into the water. Food and water were available for rats in pendent baskets from the aquarium surface. To test possible stresses of the aquarium environment, wide platforms with 12 cm diameter were utilized (the WPF group), which permitted the rats to sleep without falling into the water.

2.3. The radial arm water maze (RAWM)

The RAWM was used to test spatial learning and memory as previously described (Alzoubi et al., 2018a; Hei et al., 2018; Hutchinson et al., 2012; Mhaidat et al., 2015; Nuseir et al., 2017; Vanelzakker et al., 2011; Wolf et al., 2017). The learning phase consisted of two sessions of six trials each, separated by 5 min resting time. During the learning phase, each rat was given a one min to swim freely to the target arm but it was guided to the goal arm after having one minute without finding the goal arm. They were left in the target arm for 15 min to explore their location according to the visual cues. At 30 min of the final learning trial, short-term memory was tested. Then long term-memory was assessed at 5 h and 24 h of the final learning trial. In memory test, each rat was given one minute to locate the hidden platform. An error was recorded when the rat entered to the wrong arm.

2.4. Animals' brain dissection

All animals were executed by decapitation and the brain was removed and dissected immediately from the skull and placed over a filter paper saturated with normal saline, which is positioned on a cold glass plate filled with smashed ice. The isolated hippocampus was placed separately in a formerly labeled Eppendorf tube then transported to a box filled with liquid nitrogen. Finally, the samples were frozen at -80 °C until the analysis (Alzoubi et al., 2013a; Khabour et al., 2013).

2.5. Biochemical assays for oxidative stress biomarkers

The obtained hippocampus tissues were homogenized manually using a plastic pestle in 500 µl of phosphate buffer (lysis buffer) prepared by reconstitution of one phosphate buffered saline tablet (Sigma Chemical CO., Saint Louis, MO) and two tablets of protease inhibitor (Sigma Chemical CO., Saint Louis, MO) dissolved in 200 ml of distilled water. The homogenized tissues were centrifuged (15,000 x *g* for 10 minutes at 4 °C) in order to bring out the insoluble materials. The supernatant was gained and preserved for additional examination. The whole work was carried out over crushed ice. Total protein concentration in the obtained supernatant was examined by using existing commercial kit (Bio-Rad, Hercules, CA, USA). The activity of GPx was identified spectrophotometrically via cellular activity assay kit (CGP1, Sigma-Aldrich, MI, USA). Reduced and oxidized forms of glutathione (GSH and GSSG) were assessed in the homogenate tissue as instructed by glutathione assay kit (Sigma-Aldrich, MI, USA). Catalase enzyme level was examined in the hippocampal-homogenized tissue utilizing catalase assay kit (Cayman Chem, Ann Arbor, MI, USA). The whole process was carried out following the instructions of the kit, the microliter plate absorbance was measured using an automated reader (Epoch Microplate Spectrophotometer, Bio-Tek instruments, Highland Park, Winooski, USA).

3. Statistical analysis

All statistics were executed using the Graph Pad Prism (4.0) software. Two-way ANOVA; followed by Bonferroni posttest were used to compare the number of errors during the RAWM. Independent variables were time (repeated measures factor) and treatment (between-subjects factor) groups. Biochemical assays results were compared via one-way ANOVA; followed by Bonferroni posttest. Values were shown as mean ± SEM and $p < 0.05$ was considered as statistically significant.

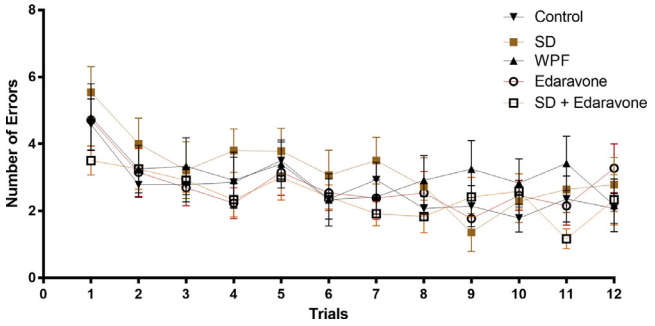

Fig. 1. Animals' performance during RAWM. Comparison of rats' performance during the acquisition phase, number of errors made by each animal declines with continuous learning without significant difference among all groups. Each point is the mean ± SEM of 15 rats.

4. Result

4.1. The effect of chronic sleep deprivation and edaravone on learning and memory

After four weeks of sleep deprivation, learning and memory tasks were assessed using RAWM model. At the beginning of the learning trials, rats in all groups showed a higher number of errors, and then the number gradually started to decrease while the rats were doing more trials. Results showed no significant differences ($F(1, 70) = 0.71$, $p > 0.05$, Fig. 1) among all groups, demonstrating that sleep deprivation did not impair learning.

Memory tests of RAWM displayed that sleep deprivation impairs both short-term and long-term memories. In all memory tests, number of errors made by SD rats was substantially higher than the number of errors made by the other groups (namely, the Edaravone-SD group;

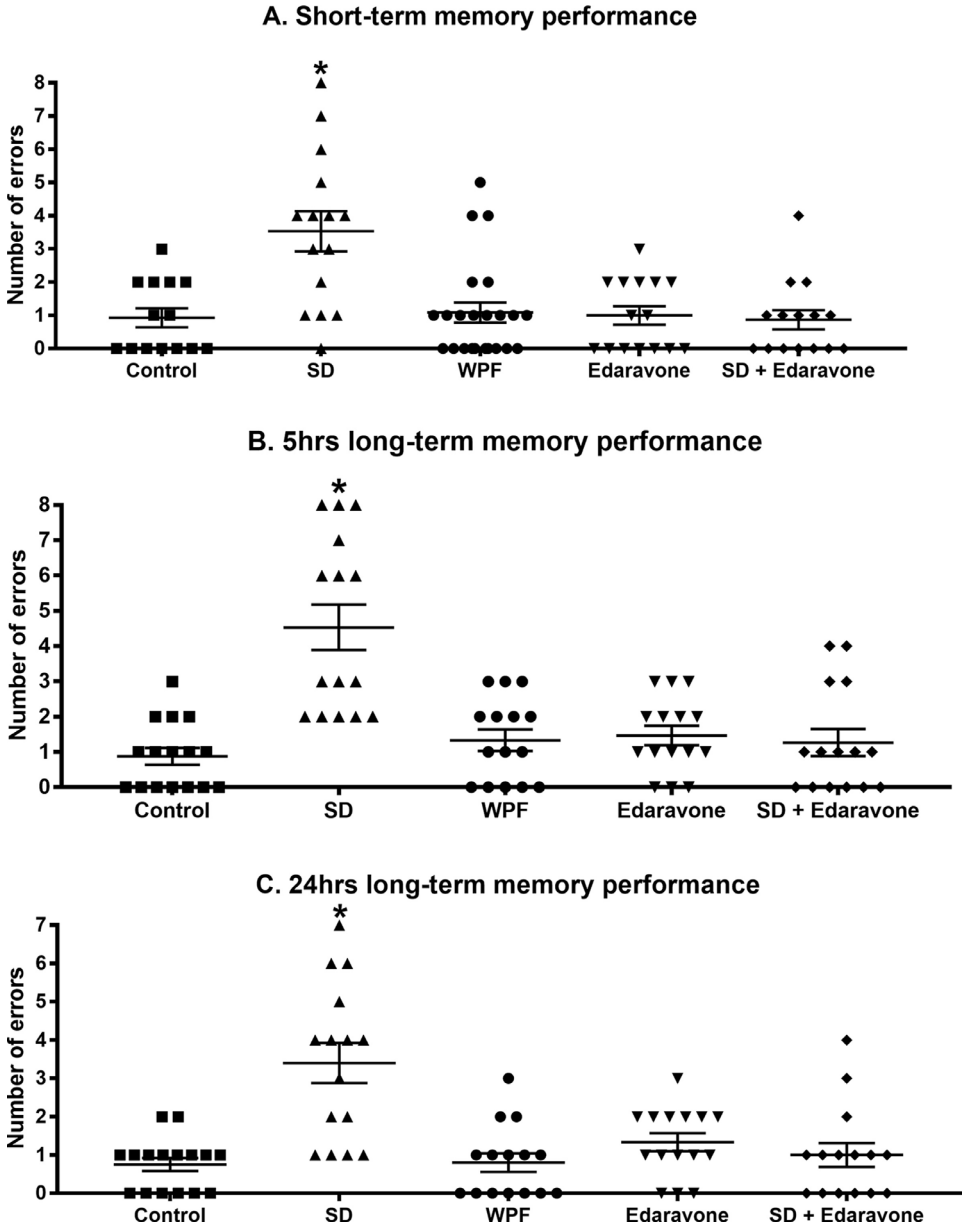

Fig. 2. Animals' performance during RAWM, short-term (30 min) memory test and long-term memory test (5 h and 24 h). The SD group showed a significant elevation in a number of errors compared to other groups. Administration of edaravone protected animals from short-term and long-term memory deficits. Edaravone treatment conserved spatial memory against cognitive impairments induced by SD. Data of each experimental group are presented as mean ± SEM of 15 rats. * Indicates significant difference from other groups ($p < 0.05$).

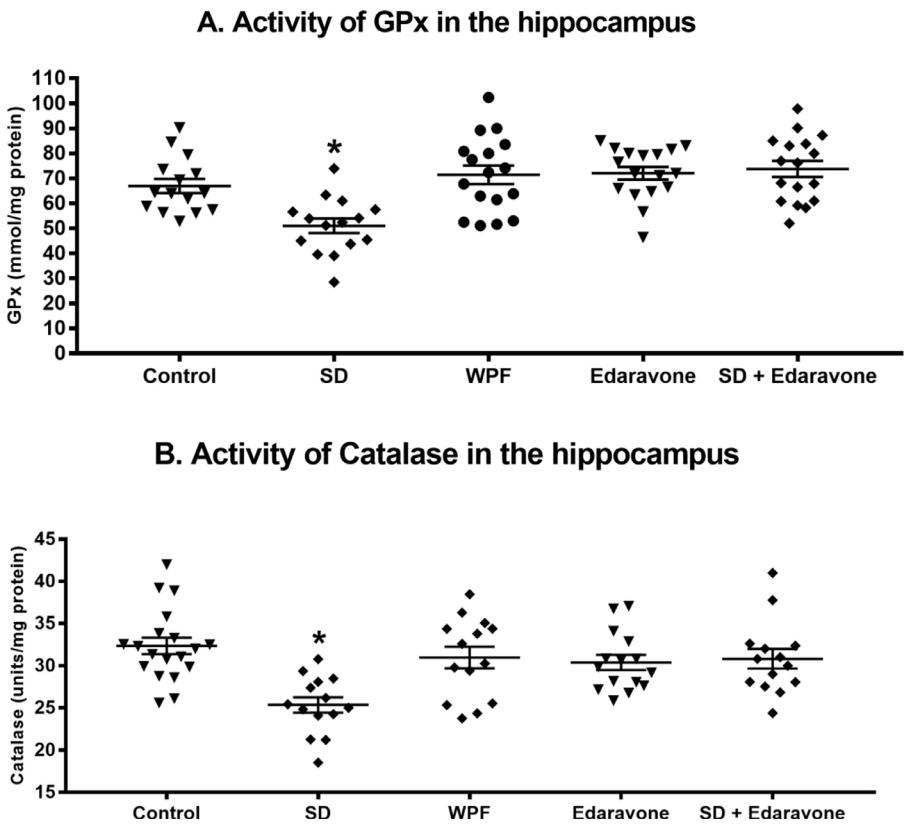

Fig. 3. The effect of SD and Edaravone on hippocampal oxidative stress enzymes. A. Hippocampal GPx Activity: There is a significant reduction in GPx activity in SD group compared to other groups. On the other hand, chronic treatment with edaravone normalized activity of GPx during chronic sleep deprivation. (B) Hippocampal Catalase Activity: Treatment with edaravone restored the activity of catalase during chronic sleep deprivation. Data of each experimental group are presented as mean ± SEM of 15 rats. * Indicate significant difference ($p < 0.05$) from other groups.

short-term memory test: $F(4, 71) = 9.06, p < 0.001$, Fig. 2A, long-term 5hr memory test: $F(4, 71) = 14.25, p < 0.001$, Fig. 2B, long-term 24 h memory test: $F(4, 71) = 12.20, p < 0.001$, Fig. 2C). Moreover, the groups with edaravone administration (Edaravone and Edaravone-SD) displayed a similar number of errors as compared to those made by the control and WPF rats.

4.2. The effect of sleep deprivation and edaravone on the hippocampal oxidative stress biomarkers

4.2.1. Hippocampus glutathione (GPx) activity

The GPx activity was significantly decreased in the SD group in comparison to the control, Edaravone and Edaravone-SD groups ($F(4, 71) = 8.76, p < 0.01$; Fig. 3 **A**). No significant difference was detected among the other groups (WPF, Edaravone, and Edaravone-SD) and the control group, indicating that edaravone preserved GPx activity in chronically sleep-deprived rats.

4.2.2. Hippocampus catalase activity

The SD significantly decreased catalase activity compared with the control, Edaravone and Edaravone-SD groups ($F(4, 71) = 6.41$, $p < 0.01$, Fig. 3 B). On the other hand, catalase activities in Edaravone and Edaravone-SD groups were similar to that of the control and WPF groups. This indicates that edaravone normalized hippocampal catalase activity, which was impaired by chronic sleep deprivation.

4.2.3. Levels of GSSG, GSH, and GSH/GSSG ratio

No significant change was detected in the levels of reduced GSH among the different experimental groups (Fig. 4A). The SD group showed elevation in oxidized GSSG levels ($F(4, 70) = 17.75, p < 0.001$, Fig. 4 B), and reduction in GSH/GSSG ratio compared to other groups, namely, the Edaravone-SD group ($F(1, 69) = 3.75, p < 0.05$, Fig. 4 C). On the other hand, no significant difference was observed in GSSG level, and the ratio of GSH/GSSG among control, WPF, Edaravone, and Edaravone- SD groups, indicating that Edaravone treatment normalized the difference in the GSSG levels, and GSH/GSSG ratio.

5. Discussion

The current study showed the potential protective role of chronic edaravone administration against SD induced memory impairment. Sleep deprivation is mainly REM sleep loss. The REM sleep was shown to be essential for memory consolidation (Harrison and Horne, 2000). Several lines of evidence indicate that SD interferes with memory in the hippocampus. Sleep deprivation was previously related with memory impairment in both human (Mograss et al., 2009; Polzella and Memory, 1975; Turner et al., 2007) and animal studies (Alkadhi et al., 2013; Alzoubi et al., 2013b; Alzoubi et al., 2019b; Alzoubi et al., 2017; Mhaidat et al., 2015; Zagaar et al., 2013). Through using SD-model and RAWM for memory testing at current study; current results showed that SD is corresponding to short- and long- term memory impairment induced by sleep deprivation, and to be related to the induction of oxidative stress damage in the hippocampus. It was previously reported that twenty-four hours of acute sleep deprivation using modified multiple platform model resulted in short-term memory impairments (Aleisa et al., 2011; Alhaider et al., 2010b; Alkadhi et al., 2013; Zagaar et al., 2013). Current data are consistent with other previous studies showing that cognitive and spatial memory impairment in rats exposed to chronic SD using RAWM (Alzoubi et al., 2013b; Alzoubi et al., 2013d; Alzoubi et al., 2016b). Accordingly, both acute and chronic sleep deprivation can disturb spatial memory formation.

Oxidative stress has been related to cognitive impairments in many health conditions such as aging (Nicolle et al., 2001), Alzheimer's disease (Butterfield et al., 2001; Lauderback et al., 2001; Markesbery and Medicine, 1997), Parkinson's disease (Alzoubi et al., 2018e), Post-traumatic stress disorder (Alquraan et al., 2019; Alzoubi et al., 2018a; Alzoubi et al., 2019a; Alzoubi et al., 2018b), and hyperhomocysteinemia (Alzoubi et al., 2018d). In fact, majority of records underling cognitive impairment in Alzheimer disease associated that impairment to oxidative stress via decreased levels of antioxidant enzymes

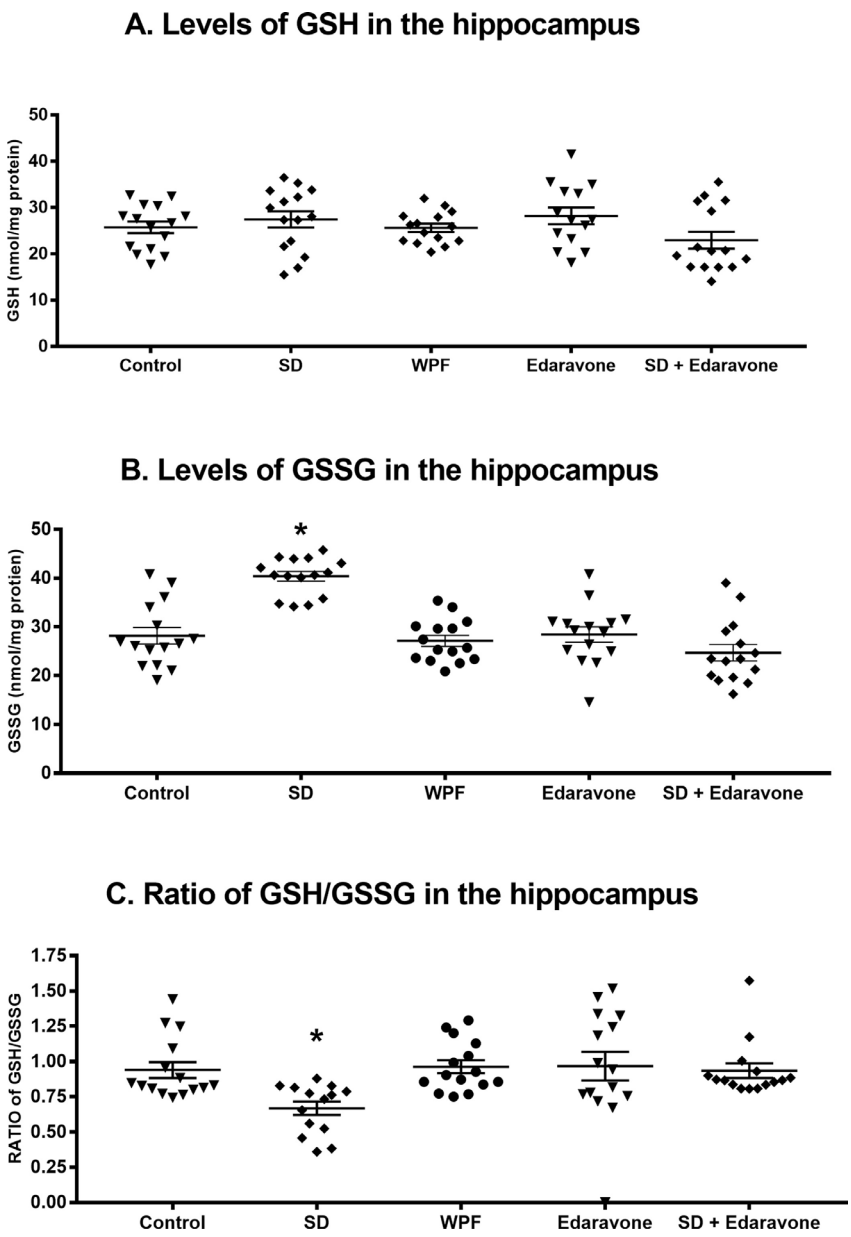

Fig. 4. Effect of Edaravone and SD on the levels of GSH, GSSG and GSH/GSSG in the hippocampus: (A) Hippocampal GSH Levels: There was no change in the levels of GSH among all experimental groups. (B) Hippocampal GSSG levels: The SD group showed a significant elevation in the hippocampal GSSG level compared to other groups. Edaravone treatment normalized the increment in the GSSG level in sleep-deprived rats. (C) Hippocampal GSH/GSSG ratio: The ratio between hippocampal GSH and GSSG (GSH/GSSG) was significantly decreased in the SD group compared to other groups. This reduction was normalized by chronic edaravone administration. Data of each experimental group are presented as Mean ± SEM of 15 rats. *Indicates a significant difference compared to other groups ($p < 0.05$).

(Butterfield et al., 2001; Lauderback et al., 2001; Lovell and Markesbery, 2001; Markesbery and Lovell, 1998; Markesbery and Medicine, 1997). It was previously shown that SD elevates rats hippocampal oxidative stress via reducing glutathione levels and enhancing GSSG/GSH ratio, decreasing catalase activity (Alzoubi et al., 2016a; Alzoubi et al., 2012a; Alzoubi et al., 2018c; Alzoubi et al., 2019b; Silva et al., 2004). The antioxidant enzymes activities, GPx and catalase were decreased through SD. Moreover, the GSH/GSSG ratio reduced the scavenging consequence of glutathione in the hippocampus. The defected antioxidant defense mechanisms boost the oxidative stress level in the hippocampus and deliver a reasonable description for the memory impairment accompanying SD. Current results indicate that chronic sleep deprivation decrease the antioxidant defense mechanism, namely, GSH/GSSG ratio, GPx, catalase and perhaps contribution to cause impairment of both short- and long–term memory.

Edaravone, is a free radical scavenger, which passes blood brain barrier, and can efficiently remove free radicals from the brain (Hara et al., 2015). Results of current study show that the administration of edaravone as a protective antioxidant agent, prevented short- and long- term memory impairment that was induced by chronic sleep deprivation through normalizing oxidative stress biomarkers levels and antioxidant enzymes in the hippocampus such as GPx, catalase, and GSH/GSSG ratio. Thus, Edaravone might prevent memory impairment during chronic sleep deprivation via its antioxidant property. This conclusion is consistent with other studies, for example, edaravone prevented memory impairment and normalized the level of GSSG, GPx, and catalase levels during post- traumatic stress disorder (PTSD) (Alzoubi et al., 2019d). In another study, it was shown that Edaravone suppressed several oxidative stress markers such as oxidized lipids and proteins and elevates antioxidant markers such as SOD and GPx in the brain of AD mice (Jiao et al., 2015). Finally, Edaravone inhibited lipid peroxide accumulation by scavenging free radicals generated during brain ischemia/reperfusion (Yoshida et al., 2006).

Generally, recent results displayed a protective effect of edaravone against SD- induced short and 5 h long-term memory dysfunction, and this protective role of Edaravone against could be attained by restoring oxidative stress in the hippocampus of SD animal.

Declaration of Competing Interest

Authors declare no conflict of interest.

Acknowledgments

The study was funded by grant no. 527/2018 to KA from the Deanship of Research of the Jordan University of Science and Technology.

References

Aleisa, A.M., Alzoubi, K.H., Alkadhi, K.A., 2011. Post-learning REM sleep deprivation impairs long-term memory: reversal by acute nicotine treatment. Neurosci. Lett. 499 (1), 28–31.
Alhaider, I.A., Aleisa, A.M., Tran, T.T., Alkadhi, K.A., 2010a. Caffeine prevents sleep loss-induced deficits in long-term potentiation and related signaling molecules in the dentate gyrus. Eur. J. Neurosci. 31 (8), 1368–1376.
Alhaider, I.A., Aleisa, A.M., Tran, T.T., Alkadhi, K.A., 2011. Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. Mol. Cell Neurosci. 46 (4), 742–751.
Alhaider, I.A., Aleisa, A.M., Tran, T.T., Alzoubi, K.H., Alkadhi, K.A., 2010b. Chronic caffeine treatment prevents sleep deprivation-induced impairment of cognitive function and synaptic plasticity. Sleep 33 (4), 437–444.
Alkadhi, K., Zagaar, M., Alhaider, I., Salim, S., Aleisa, A., 2013. Neurobiological consequences of sleep deprivation. Curr. Neuropharmacol. 11 (3), 231–249.
Alquraan, L., Alzoubi, K.H., Hammad, H., Rababa'h, S.Y., Mayyas, F., 2019. Omega-3 fatty acids prevent post-traumatic stress disorder-induced memory impairment. Biomolecules 9 (3), pii: E100.
Alzoubi, K., Abdul-Razzak, K., Khabour, O., Al-Tuweiq, G., Alzubi, M., Alkadhi, K.A., 2013a. Caffeine prevents cognitive impairment induced by chronic psychosocial stress and/or high fat–high carbohydrate diet. Behav. Brain Res. 237, 7–14.
Alzoubi, K.H., Al-Ibbini, A.M., Nuseir, K.Q., 2018a. Prevention of memory impairment induced by post-traumatic stress disorder by cerebrolysin. Psychiatry Res. 270, 430–437.
Alzoubi, K.H., Al Subeh, Z.Y., Khabour, O.F., 2019a. Molecular targets for the interactive effect of etazolate during post-traumatic stress disorder: Role of oxidative stress, BDNF and histones. Behav. Brain Res. 369, 111930.
Alzoubi, K.H., Khabour, O.F., Ahmed, M., 2018b. Pentoxifylline prevents post-traumatic stress disorder induced memory impairment. Brain Res. Bull. 139, 263–268.
Alzoubi, K.H., Khabour, O.F., Albawaana, A.S., Alhashimi, F.H., Athamneh, R.Y., 2016a. Tempol prevents chronic sleep-deprivation induced memory impairment. Brain Res. Bull. 120, 144–150.
Alzoubi, K.H., Khabour, O.F., Rashid, B.A., Damaj, I.M., Salah, H.A., 2012a. The neuroprotective effect of vitamin E on chronic sleep deprivation-induced memory impairment: the role of oxidative stress. Behav. Brain Res. 226 (1), 205–210.
Alzoubi, K.H., Khabour, O.F., Rashid, B.A., Damaj, I.M., Salah, H.A, 2012b. The neuroprotective effect of vitamin E on chronic sleep deprivation-induced memory impairment: the role of oxidative stress. Behav. Brain Res. 226 (1), 205–210.
Alzoubi, K.H., Khabour, O.F., Salah, H.A., Abu Rashid, B.E., 2013b. The combined effect of sleep deprivation and Western diet on spatial learning and memory: role of BDNF and oxidative stress. J. Mol. Neurosci. 50 (1), 124–133.
Alzoubi, K.H., Khabour, O.F., Salah, H.A., Rashid, B.E., 2013c. The combined effect of sleep deprivation and Western diet on spatial learning and memory: role of BDNF and oxidative stress. J. Mol. Neurosci. 50 (1), 124–133.
Alzoubi, K.H., Khabour, O.F., Tashtoush, N.H., Al-Azzam, S.I., Mhaidat, N.M., 2013d. Evaluation of the effect of pentoxifylline on sleep-deprivation induced memory impairment. Hippocampus 23 (9), 812–819.
Alzoubi, K.H., Malkawi, B.S., Khabour, O.F., El-Elimat, T., Alali, F.Q., 2018c. Arbutus andrachne L. Reverses sleep deprivation-induced memory impairments in rats. Mol. Neurobiol. 55 (2), 1150–1156.
Alzoubi, K.H., Mayyas, F., Abu Zamzam, H.I., 2019b. Omega-3 fatty acids protects against chronic sleep-deprivation induced memory impairment. Life Sci. 227, 1–7.
Alzoubi, K.H., Mayyas, F.A., Khabour, O.F., Bani Salama, F.M., Alhashimi, F.H., Mhaidat, N.M., 2016b. Chronic melatonin treatment prevents memory impairment induced by chronic sleep deprivation. Mol. Neurobiol. 53 (5), 3439–3447.
Alzoubi, K.H., Mhaidat, N.M., Obaid, E.A., Khabour, O.F., 2018d. Caffeine prevents memory impairment induced by hyperhomocysteinemia. J. Mol. Neurosci. 66 (2), 222–228.
Alzoubi, K.H., Mokhemer, E., Abuirmeileh, A.N., 2018e. Beneficial effect of etazolate on depression-like behavior and, learning, and memory impairment in a model of Parkinson's disease. Behav. Brain Res. 350, 109–115.
Alzoubi, K.H., Rababa'h, A.M., Owaisi, A., Khabour, O.F., 2017. L-carnitine prevents memory impairment induced by chronic REM-sleep deprivation. Brain Res. Bull. 131, 176–182.
Alzoubi, K.H., Shatnawi, A., Al-Qudah, M.A., Alfaqih, M.A., 2019c. Edaravone prevents memory impairment in an animal model of post-traumatic distress. Behav. Pharmacol. 30 (2 and 3-Special Issue), 201–207.
Alzoubi, K.H., Shatnawi, A., Al-Qudah, M.A., Alfaqih, M.A, 2019d. Edaravone prevents memory impairment in an animal model of post-traumatic distress. Behav. Pharmacol. 30 (2), 201–207.
Banno, M., Mizuno, T., Kato, H., Zhang, G., Kawanokuchi, J., Wang, J., Kuno, R., Jin, S., Takeuchi, H., Suzumura, A., 2005. The radical scavenger edaravone prevents oxidative neurotoxicity induced by peroxynitrite and activated microglia. Neuropharmacology 48 (2), 283–290.
Basner, M., Fomberstein, K.M., Razavi, F.M., Banks, S., William, J.H., Rosa, R.R., Dinges, D.F, 2007. American time use survey: sleep time and its relationship to waking activities. Sleep. 30 (9), 1085–1095.
Bingham, R., Sejnowski, T., Siegel, J., Dyken, M.E., Czeisler, C., Shaw, P., Greenspan, R., Panda, S., Low, P., Stickgold, R., 2007. Waking Up to Sleep, Several Conference Videos. The Science Network.
Butterfield, D.A., Drake, J., Pocernich, C., Castegna, A., 2001. Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid β-peptide. Trends Mol. Med. 7 (12), 548–554.
Guan, Z., Peng, X., Fang, J., 2004. Sleep deprivation impairs spatial memory and decreases extracellular signal-regulated kinase phosphorylation in the hippocampus. Brain Res. 1018 (1), 38–47.
Hara, N., Chijiiwa, M., Yara, M., Ishida, Y., Ogiwara, Y., Inazu, M., Kuroda, M., Karlsson, M., Sjovall, F., Elmér, E., 2015. Metabolomic analyses of brain tissue in sepsis induced by cecal ligation reveal specific redox alterations—protective effects of the oxygen radical scavenger edaravone. Shock 44 (6), 578–584.
Harrison, Y., Horne, J.A., 2000. Sleep loss and temporal memory. Q.J. Exp. Psychol. A. 53 (1), 271–279.
Hei, Y., Chen, R., Yi, X., Wei, L., Long, Q., Liu, W., 2018. The expression of hippocampal NRG1/ErbB4 correlates with neuronal apoptosis, but not with glial activation during chronic cerebral hypoperfusion. Front Aging Neurosci. 10, 149.
Hornung, O.P., Regen, F., Danker-Hopfe, H., Schredl, M., Heuser, I., 2007. The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. Biol. Psychiatry 61 (6), 750–757.
Hublin, C., Kaprio, J., Partinen, M., Koskenvuo, M., 2001. Insufficient sleep—a population-based study in adults. Sleep 24 (4), 392–400.
Hutchinson, K.M., McLaughlin, K.J., Wright, R.L., Bryce Ortiz, J., Anouti, D.P., Mika, A., Diamond, D.M., Conrad, C.D., 2012. Environmental enrichment protects against the effects of chronic stress on cognitive and morphological measures of hippocampal integrity. Neurobiol. Learn Mem. 97 (2), 250–260.
Jiao, S.-S., Yao, X.-Q., Liu, Y.-H., Wang, Q.-H., Zeng, F., Lu, J.-J., Liu, J., Zhu, C., Shen, L.-L., Liu, C.-H., 2015. Edaravone alleviates Alzheimer's disease-type pathologies and cognitive deficits. Proc. Natl. Acad. Sci. USA 112 (16), 5225–5230.
Khabour, O.F., Alzoubi, K.H., Alomari, M.A., Alzubi, M.A., 2013. Changes in spatial memory and BDNF expression to simultaneous dietary restriction and forced exercise. Brain Res. Bull. 90, 19–24.
Lauderback, C.M., Hackett, J.M., Huang, F.F., Keller, J.N., Szweda, L.I., Markesbery, W.R., Butterfield, D.A., 2001. The glial glutamate transporter, GLT-1, is oxidatively modified by 4-hydroxy-2-nonenal in the Alzheimer's disease brain: the role of Aβ1–42. J. Neurochem. 78 (2), 413–416.
Lovell, M.A., Markesbery, W.R., 2001. Ratio of 8-hydroxyguanine in intact DNA to free 8-hydroxyguanine is increased in Alzheimer disease ventricular cerebrospinal fluid. Arch. Neurol. 58 (3), 392–396.
Markesbery, W., Lovell, M.J., 1998. Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease. Neurobiol. Aging 19 (1), 33–36.
Markesbery, W.R., 1997. Oxidative stress hypothesis in Alzheimer's disease. Free Radic. Biol. Med. 23 (1), 134–147.
Mhaidat, N.M., Alzoubi, K.H., Khabour, O.F., Tashtoush, N.H., Banihani, S.A., Abdul-razzak, K.K., 2015. Exploring the effect of vitamin C on sleep deprivation induced memory impairment. Brain Res. Bull. 113, 41–47.
Mograss, M., Guillem, F., Brazzini-Poisson, V., Godbout, R., 2009. The effects of total sleep deprivation on recognition memory processes: a study of event-related potential. Neurobiol. Learn Mem. 91 (4), 343–352.
Nicolle, M., Gonzalez, J., Sugaya, K., Baskerville, K., Bryan, D., Lund, K., Gallagher, M., McKinney, M., 2001. Signatures of hippocampal oxidative stress in aged spatial learning-impaired rodents. Neuroscience 107 (3), 415–431.
Nuseir, K.Q., Alzoubi, K.H., Alhusban, A., Bawaane, A., Al-Azzani, M., Khabour, O.F., 2017. Sucrose and naltrexone prevent increased pain sensitivity and impaired long-term memory induced by repetitive neonatal noxious stimulation: role of BDNF and beta-endorphin. Physiol. Behav. 179, 213–219.
Polzella, D.J., 1975. Effects of sleep deprivation on short-term recognition memory. J. Exp. Psychol. Hum. Learn. 1 (2), 194.
Ramanathan, L., Gulyani, S., Nienhuis, R., Siegel, J.M., 2002. Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. Neuroreport 13 (11), 1387–1390.
Siegel, J.M., 2004. The neurotransmitters of sleep. J. Clin. Psychiatry 65 (Suppl 16), 4–7.
Silva, R., Abilio, V., Takatsu, A., Kameda, S., Grassl, C., Chehin, A., Medrano, W., Calzavara, M., Registro, S., Andersen, M.J., 2004. Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice. Neuropharmacology 46 (6), 895–903.
Smith, C., 1985. Sleep states and learning: a review of the animal literature. Neurosci. Biobehav. Rev. 9 (2), 157–168.
Stern, W.C., 1971. Acquisition impairments following rapid eye movement sleep deprivation in rats. Physiol. Behav 7 (3), 345–352.
Turner, T.H., Drummond, S., Salamat, J.S., Brown, G.G., 2007. Effects of 42 hr of total sleep deprivation on component processes of verbal working memory. Neuropsychology 21 (6), 787.
Vanelzakker, M.B., Zoladz, P.R., Thompson, V.M., Park, C.R., Halonen, J.D., Spencer, R.L., Diamond, D.M., 2011. Influence of pre-training predator stress on the expression of c-fos mRNA in the hippocampus, amygdala, and striatum following long-term spatial memory retrieval. Front Behav. Neurosci. 5, 30.
Wagner, U., Born, J., 2008. Memory consolidation during sleep: interactive effects of sleep stages and HPA regulation. Stress 11 (1), 28–41.

Wolf, G., Lotan, A., Lifschytz, T., Ben-Ari, H., Kreisel Merzel, T., Tatarskyy, P., Valitzky, M., Mernick, B., Avidan, E., Koroukhov, N., Lerer, B., 2017. Differentially severe cognitive effects of compromised cerebral blood flow in aged mice: association with myelin degradation and microglia activation. Front Aging Neurosci. 9, 191.

Yoshida, H., Yanai, H., Namiki, Y., Fukatsu-Sasaki, K., Furutani, N., Tada, N., 2006. Neuroprotective effects of edaravone: a novel free radical scavenger in cerebrovascular injury. CNS Drug Rev. 12 (1), 9–20.

Zagaar, M., Dao, A., Levine, A., Alhaider, I., Alkadhi, K., 2013. Regular exercise prevents sleep deprivation associated impairment of long-term memory and synaptic plasticity in the CA1 area of the hippocampus. Sleep 36 (5), 751–761.

Zhang, D., Xiao, Y., Lv, P., Teng, Z., Dong, Y., Qi, Q., Liu, Z., 2018. Edaravone attenuates oxidative stress induced by chronic cerebral hypoperfusion injury: role of ERK/Nrf2/HO-1 signaling pathway. Neurol. Res. 40 (1), 1–10.