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Omega-3 fatty acids protects against chronic sleep-deprivation induced memory impairment

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ABSTRACT

Aims: The current study aims to evaluate the possible protective effect of omega-3 fatty acids on memory impairment induced by sleep-deprivation in rats.

Materials and methods: Animals were chronically sleep deprived using the modified multiple platform model (8 h/day for 8 weeks). Omega-3 fatty acids were administered as fish oil via oral gavage at a daily dose of 100 mg omega-3 PUFA/100 g BWT. The spatial learning and memory were evaluated using the radial arm water maze (RAWM). Additionally, the following oxidative stress biomarkers were measured in the hippocampus: glutathione (GSH), oxidized glutathione (GSSG), GSH/GSSG, glutathione peroxidase (GPx), catalase, superoxide dismutase (SOD), and thiobarbituric acid reactive substance (TBARS).

Key findings: Animals in the SD group committed significantly more errors in both short- and long- term memory tests of the RAWM compared to other groups. On the other hand, animals that were sleep deprived and treated with omega-3 fatty acids committed similar number of errors compared to the control group. This indicates that SD impaired both short- and long- term memories, and that chronic omega-3 fatty acids administration prevented these effects. Omega-3 fatty acids also prevented the decreases in hippocampal GPx, catalase and GSH/GSSG ratio and normalized the increases in GSSG levels, which were impaired by SD model. No changes were observed on hippocampal TBARS levels, or activity of SOD among experimental groups.

Significance: In conclusion, a protective effect of omega-3 fatty acids administration has been observed against chronic SD-induced memory impairment probably via improving hippocampus antioxidant effects.

1. Introduction

One of the important elements of human welfare and general health is memory that requires enough and comfortable sleep. Sleep is a protective mechanism that maintains homeostasis of autonomic, neuroendocrine and immune system [1–5]. Sleep is divided into two major categories: the rapid eye movement (REM) and the non-rapid eye movement (NREM) [6]. An essential cognitive benefit of sleep is to set newly acquired memory for long-term durations [7]. In fact, REM sleep duration is increased after active learning processes [8,9].

Sleep deprivation (SD) is increasingly spreading through modern lifestyles [10,11]. As a result, studying the relationship between sleep deprivations and cognitive function mainly memory and learning is of increased importance. The hippocampus region of the brain is affected by sleep deprivation resulting in memory impairment [12,13]. This memory impairment is related to increased oxidative stress in the brain, in particular, the hippocampus [14–18].

Long chain omega-3 polyunsaturated fatty acids (ω-3 PUFA) that consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have anti-inflammatory and anti-oxidative properties [19–21]. They also augment beta-oxidation of free fatty acids [22–25], which reduces the accumulation of toxic free fatty acids derivatives [26,27]. Existing evidence shows that the consumption of ω-3 PUFA plays a protective role in age-related cognitive decline [28] and Alzheimer's disease [29]. The effect of Omega-3 fatty acids on memory impairment is not fully characterized. In this study, the possible preventive effect Omega-3 fatty acids on chronic sleep deprivation-induced impairment of hippocampal memory was investigated.

2. Methods

Adult male Wistar rats weighing 200–250 g (8–10 weeks old) were obtained from Jordan University of Science and Technology (JUST) animal care facility. Animals were kept in plastic cages (around 6 rats

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per cage) under suitable hygienic conditions and were left one week to acclimate before experimental manipulations started. The animals were kept at room temperature (24 ± 1 °C) with free access to water and food. Rats were tagged by labeling their tails and they were housed in 12 h light/dark cycle (light at 7:00 am). The whole experimental work was done in the light cycle following the Animal Care and Use Committee (ACUC) approval at JUST.

2.1. Animal groups and treatments

Sixty-five rats were randomly distributed into five categories (13/group): control, Omeg-3 fatty acids (Omega-3), Sleep deprivation (SD), Wide platform (WPF), and sleep deprivation with Omega-3 Fatty Acids (Omega-3/SD). The control, WPF and SD groups received the vehicle (corn oil: 4 μl/g of body weight (BWT). The Omega-3 and Omega-3/SD groups received Menhaden fish oil (24.3% EPA and DHA, Sigma-Aldrich Co., St. Louis, MI, USA) as 4 μl/g BWT, which is equal to 100 mg omega-3/100 g BWT as previously described in [30]. The fish oil was diluted as needed using corn oil. The SD and Omega-3/SD groups were sleep deprived for 8 h per day from 8:30 AM-4:30 PM for 8 weeks.

2.2. Procedure time course

For a particular animal, sleep deprivation and/or Omega-3 fatty acids administration were concurrently started at day 1 of the experiments, and continued for 8 weeks. These manipulations continued throughout the RAWM experimental days, and until animals' sacrifice day.

2.3. Induction of sleep deprivation model

The REM sleep deprivation was instituted using the modified multiple platforms model, as previously described [31–34]. Rats were placed in a large glass aquarium that contains 20 columns (platforms) coordinated in two rows. The columns were elevated above the water level by two cm. Each platform was 5 cm in diameter, and the distance between the two columns (edge to edge) was 7 cm in order to permit the rats freely move among the columns. When a rat reached REM phase of sleep, muscle atonia set in and animals fell into the water and woke up, and it immediately climbed up to the platform and sat on it. For the WPF group, wide platforms with 12 cm diameter, which permitted animals to sleep without falling into the water, were used with the aim of assessing possible stresses of the aquarium environment.

2.4. Radial arm water maze (RAWM)

The RAWM was used to test spatial learning and memory, as explained in details elsewhere [35–38]. Briefly, the RAWM consisted of six arms radiating out to an open central area to form six swimming paths with escape platform located at the end of a goal arm that is kept constant for each particular rat during all trials/tests with different starting arm at each trial/test. All four groups were tested using the RAWM for spatial learning ability and memory performance after completing twenty-one day treatment period. All experiments were carried out in a dimly lit room with visual cues fixed on the walls of the room during the experiment. Water temperature was maintained at 23 ± 1 °C. Each animal had to find the submerged platform (2 cm beneath water level) located at the end of the one swimming arm (goal arm) in one minute. There were two phases, the learning phase and the testing phase. The learning phase consisted of two sessions, each session had six trials one minute/trial, and 5 min rest between the two sessions. During each trial, the animal was allowed to freely swim to find the submerged platform. However, it was guided to the platform after spending one minute of swimming without finding hidden platform. Once on the platform, the animal was left there for 15 s to observe visual cues on the walls before the next trial was started. In memory tests, the animal was neither guided to the platform nor given 15 s on the platform. Each rat had to undergo 12 learning trials followed by three memory tests. The short-term memory test, which was done 30 min, and the long-term memory test, which was done 5 h after the last learning trial. In memory tests, each rat was given one minute to locate the hidden platform. An error was recorded when the rat entered to any arm other than the goal arm.

2.5. Animals' brain dissection

Animals were sacrificed by decapitation. “Immediately after, the brains were removed from the skull and placed over a filter paper saturated with normal saline, which is placed on a cold glass dish filled with crushed ice. The isolated hippocampus was then, placed in a prelabeled Eppendorf tube, then transported in a box filled with liquid nitrogen. Tissue samples were frozen at −80C° until the analysis [36].

Biochemical tests for oxidative stress biomarkers.

The hippocampus tissue were homogenized manually using a plastic pestle, and a homogenization buffer that was prepared by the reconstitution of two protease inhibitor tablets (Sigma Chemical CO., Saint Louis, MO), and one tablet of phosphate buffered saline (Sigma Chemical CO., Saint Louis, MO) in distilled water (200 ml). The homogenized buffer was centrifuged (10,000 ×*g*, 15 min at 4C°) to remove insoluble materials. The supernatant was, then, stored at −20C° for further analysis. The concentration of total proteins was measured in the supernatant using a commercial kit (Bio-Rad, Hercules, CA, USA).

For total glutathione measurement, homogenates of hippocampus tissues were deproteinized using 5% of 5-sulfosalicylic acid (SSA). To remove the precipitated protein, the homogenates were centrifuged at 10,000 ×*g* for 10 min at 4 °C. Then, they were assayed photometrically for glutathione as per instructed in the kit's manual (Glutathione assay kit, Sigma-Aldrich, MI, USA). The GSSG was quantified by adding 10 μl of 1 M 2-vinylpyridine (Sigma-Aldrich, MI, USA) per 1 ml of supernatant from the sample. Thereafter, the kit's procedure was carried out as described above for total glutathione. The levels of GSH were then derived by subtracting GSSG value from total glutathione. The GPx activity was measured spectrophotometrically using cellular activity assay kit (CGP1, Sigma-Aldrich, MI, USA). Catalase and superoxide dismutase (SOD) activities were determined using commercially available kits as per the instructions of the kit's manufacturer (SOD: Sigma-Aldrich Corp; Catalase: Cayman Chem, Ann Arbor, MI, USA). The levels of TBARS were determined via the TBARS assay kit (Cayman Chem.Com. Ann arbor, MI. USA).The kit's specified wavelengths were used to read the microplates via an automated reader” (Epoch Microplate Spectrophotometer, Bio-tek instruments, Highland Park, Winooski, USA).

2.6. Statistical analysis

Statistics were done using GraphPad Prism software version 6.0 (GraphPad Software, La Jolla, CA). For the RAWM experimental data, comparisons of the number of errors were done via two-way ANOVA; followed by Bonferroni posttest. The independent variables were time (repeated measures factors) and treatment (between-subjects factor). For biochemical assays data, one-way ANOVA; followed by Bonferroni posttest were used. Significant differences were considered at $P < 0.05$. All values were presented as mean ± SEM.

3. Results

3.1. The effect of chronic sleep deprivation and omega-3 fatty acids on learning and memory

In the learning phase, a high number of errors were initially observed for rats from all groups. As the learning trials continued, the

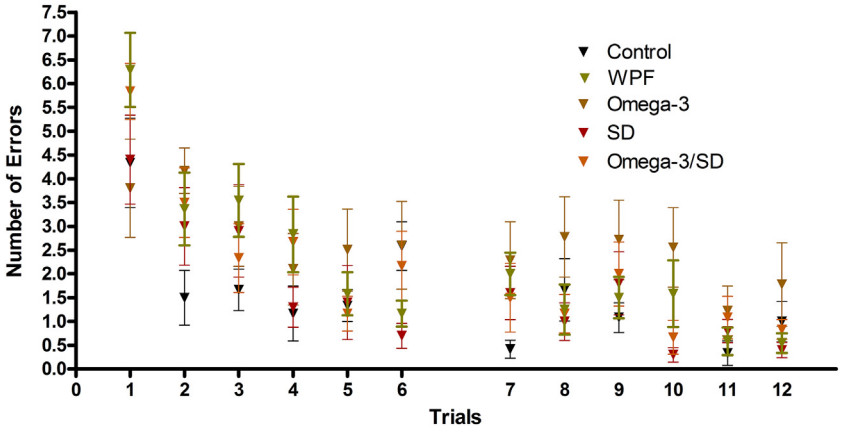

Fig. 1. Animal learning performance in the radial arm water maze. Learning performance among control (control), wide platform (WPF), Omega-3 fatty acids, chronic sleep deprivation (SD), and chronic sleep deprivation with Omega-3 fatty acids (Omega-3/SD) groups. Each rat had to undergo twelve learning trials that were divided into two sessions, six trials for each session with five min rest between the two sessions. No difference was observed in learning ability among experimental groups. Each point is the Mean ± SEM, N = 13 animals/group.

errors slowly started to decrease with no differences among the experimental groups ($p > 0.05$, Fig. 1).

In terms of memory testing, the number of errors observed for the SD group was higher than other groups for both short and long term memory tests ($P < 0.05$, Fig. 2). Moreover, the Omega-3/SD group exhibited a similar number of errors as compared to those made by the control, WPF and Omega-3 groups.

3.2. The effect of sleep deprivation and/or omega-3 fatty acids on the hippocampal oxidative stress biomarkers

Both Glutathione Peroxidase (GPx) and catalase activities were significantly lowered by SD compared to control group ($P < 0.05$, Fig. 3A and B). On the other hand, catalase and GPx activities in Omega-3/SD group were similar to control, WPF, and Omega-3 groups. No significant difference in SOD activity was noticed in the SD group as

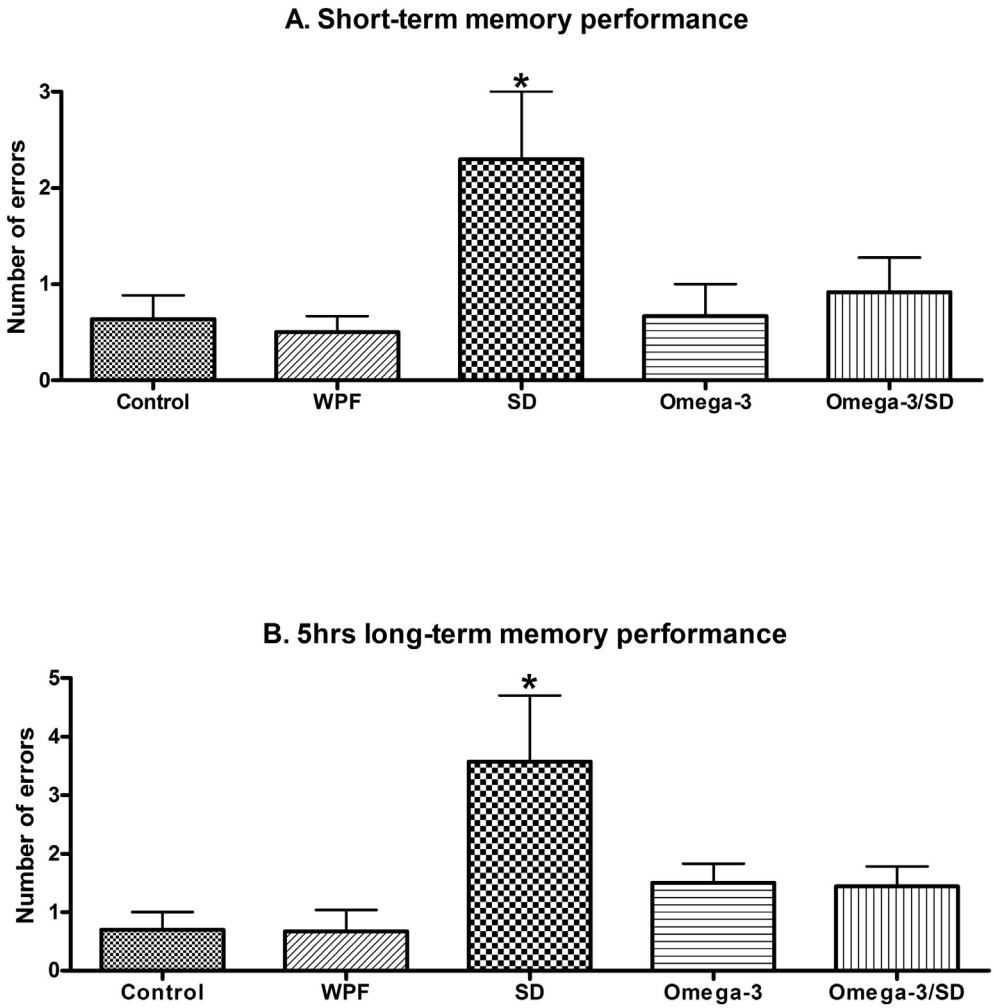

Fig. 2. Omega-3 fatty acids prevented hippocampal memory impairment induced by chronic sleep deprivation. Short-term memory (A) and long-term memory performance (B) among control, wide plates form (WPF), Omega-3 fatty acids (Omega-3), chronic sleep deprivation (SD), and chronic sleep deprivation with Omega-3 fatty acids (Omega-3/SD). Each column is the Mean ± SEM, N = 13 animals/group. * Indicates significant difference from other groups ($P < 0.05$).

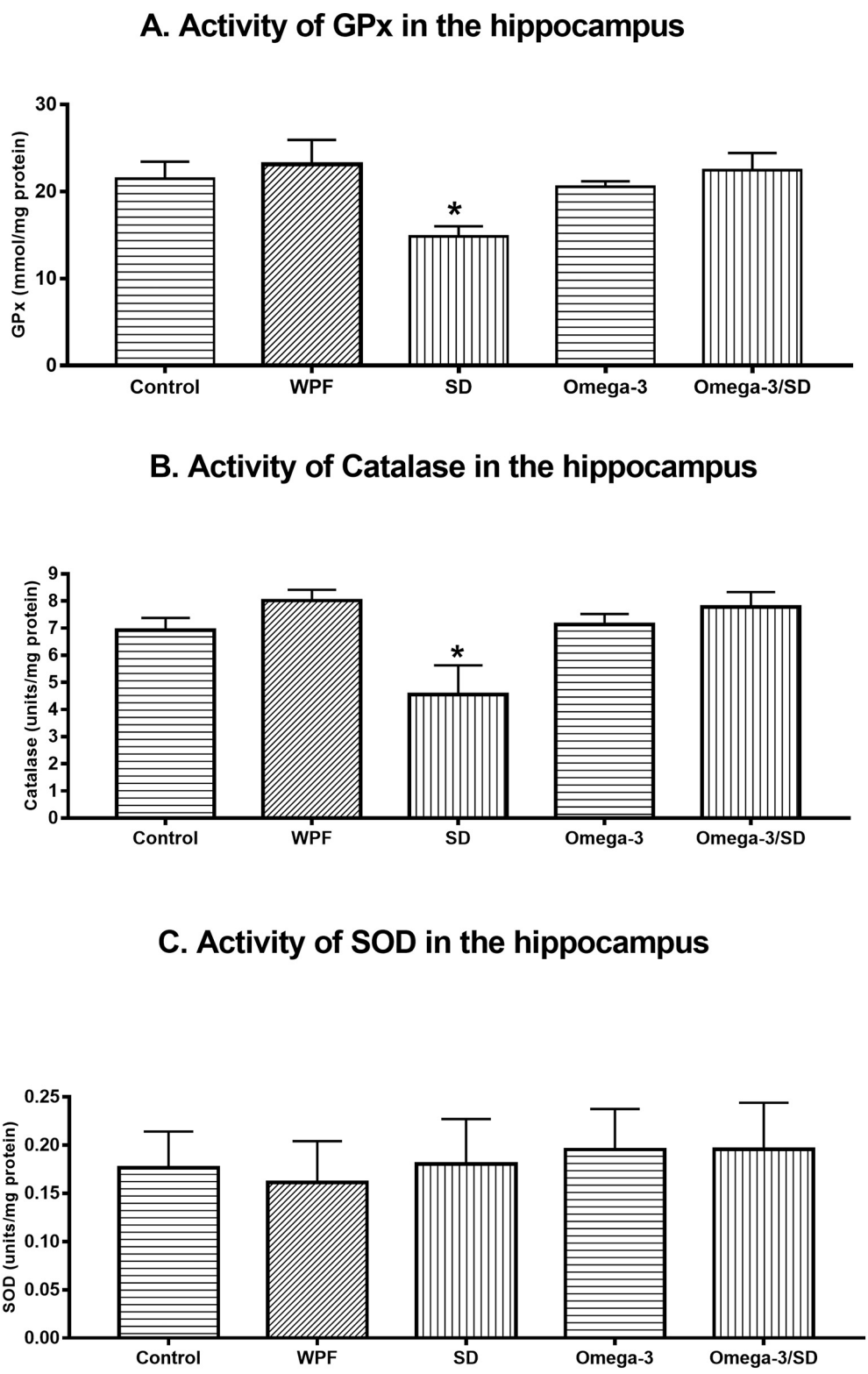

Fig. 3. Effect of chronic Omega-3 fatty acids treatment on activities of antioxidant enzymes in the hippocampus of chronically sleep-deprived rats. (A) Activity of glutathione peroxidase (GPx), and (B) activity of catalase, and (C) activity of superoxide dismutase (SOD) among experimental groups. While no change was observed in the activity of SOD, Omega-3 fatty acids treatment prevented chronic sleep deprivation-induced reduction in the enzymatic activities of GPx and catalase. Each column is the Mean ± SEM, N = 13 animals/group. * Indicates significant difference from other groups ($P < 0.05$).

compared to other experimental groups ($P > 0.05$, Fig. 3C).

Levels of GSH were not significantly changed among experimental groups. The SD group showed increased GSSG levels, and GSH/GSSG ratio compared to other groups. On the other hand, no significant change was noted in GSSG level, and the ratio of GSH/GSSG among the Omega-3/SD, control, WPF and Omega-3 groups (Fig. 4). No changes in the levels of TBARs among all experimental groups (Fig. 5, $P > 0.05$).

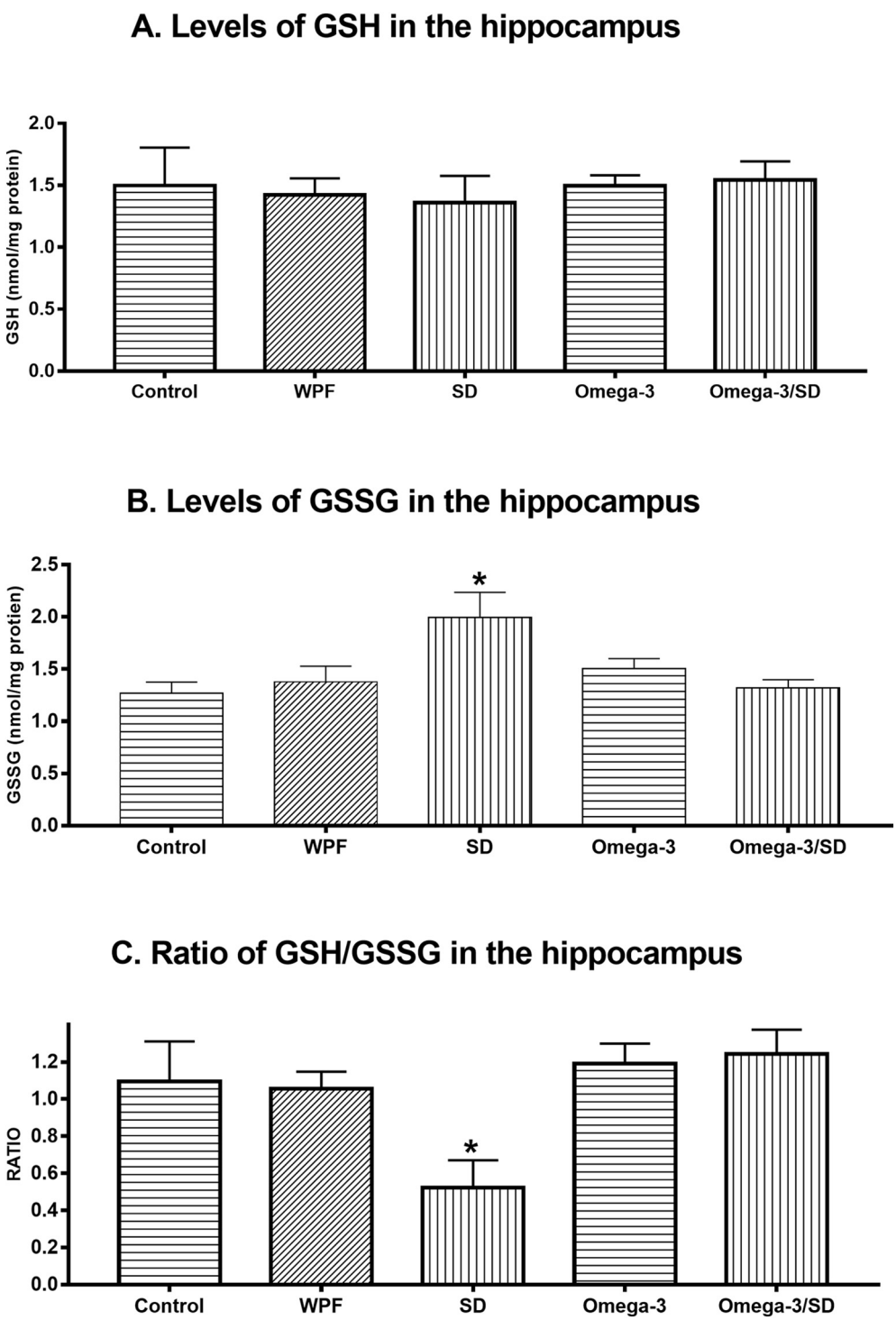

Fig. 4. Chronic omega-3 fatty acids treatment prevented alteration in the GSSG and GSH/GSSG ratio in the hippocampus during chronic sleep deprivation. Levels of (A) reduced glutathione (GSH), (B) oxidized glutathione (GSSG) and (C) ratio of GSH/GSSG in SD group compared to control, WPF, omega-3 fatty acids (Omega-3), and Omega-3/SD groups. Each column is the Mean ± SEM, N = 13 animals/group. * Indicates significant difference from other groups ($P < 0.05$).

4. Discussion

The goal of the present study was to evaluate the possible protective effect of chronic Omega-3 administration on SD-induced memory impairment. The REM sleep dysfunction is a major manifestation of sleep deprivation [31,39–41]. Current results revealed that SD impaired both short- and long- term memory probably by promoting oxidative stress in the hippocampus. Previously, it has been shown that twenty-four hours of sleep deprivation using the modified multiple platform model resulted in short-term memory impairment as displayed in the RAWM [31,42]. Results from this laboratory revealed spatial memory in rats was negatively affected by chronic SD using the RAWM [14,37,40], which is in correlation with the results of the current study.

Oxidative stress has also been correlated to cognitive function defects in numerous health conditions such as aging [43,44] and Alzheimer's disease [45], high fat diet ingestion [37,46], hyperhomocytienemia [47], post-traumatic stress disorder [48–51], and Parkinson's disease [52]. It was previously shown that SD increases hippocampal

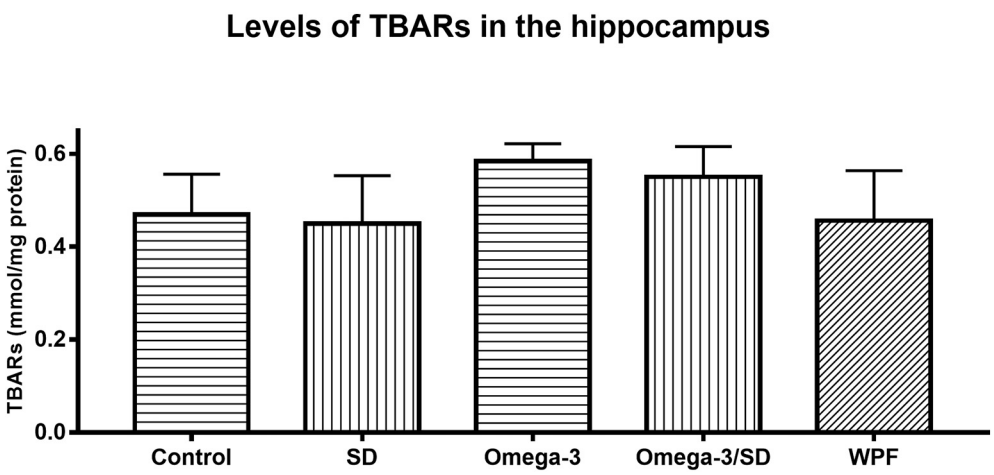

Fig. 5. Hippocampal Levels of thiobarbituric acid reactive substances (TBARS). No change was observed in the levels of TBARS among control, wide plate form (WPF), Omega-3 fatty acids, chronic sleep deprivation (SD), and chronic sleep deprivation with Omega-3 fatty acids (Omega-3/SD). Each column is the Mean ± SEM, N = 13 animals/group.

oxidative stress through reducing reduced glutathione levels and elevating GSSG/GSH ratio [40,53,37]. The SD was also shown to reduce brain GSH, which was associated with increased brain inflammation and dysfunction in brain activity during [43,44]. In addition, SD reduced both hippocampus and brainstem activity of catalase [40,54,37].

The protective effect of Omega-3 fatty acids on SD-induced memory impairment has not been previously studied. The current study revealed that administration of Omega-3 fatty acids prevented short- and long-term memory impairment induced by chronic SD. Treatment with Omega-3 fatty acids prevented changes in oxidative stress biomarkers levels and antioxidant enzymes in the hippocampus including GPx, catalase, and GSH/GSSG ratio. Interestingly, it has been found that Omega-3 fatty acids have a protective effect on oxidative stress-induced apoptosis [55]. Omega-3 fatty acids were also reported to ameliorate cognitive impairment and increased oxidative stress induced by seizure animal models [56]. Additionally, omega-3 fatty acids were shown to possess beneficial effects on oxidative stress induced by streptozotocin induced diabetes in rats ([57], in scopolamine-induced amnesia {Ajami, 2012 #25}), and aging process [58,59].

The levels of TBARs, a marker of lipid peroxidation, were unaltered among the experimental groups. This indicates that lipid peroxidation is not affected by chronic sleep deprivation. In contrast, previous studies using acute, but not chronic, sleep deprivation models showed increased TBARS or lipid peroxidation levels in the hippocampus, hypothalamus, thalamus, and cortex during acute SD [14,60–62].

Collectively, current findings suggest that Omega-3 fatty acids may protect against SD induced memory by preventing changes in GPx and catalase activities and ratio of GSH/GSSG in the SD rat's hippocampus. Further studies are needed to understand the exact mechanisms of Omega-3 fatty acids effects on memory functions in the hippocampus.

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References

[1] T. Abel, R. Havekes, J.M. Saletin, M.P. Walker, Sleep, plasticity and memory from molecules to whole-brain networks, Curr. Biol. 23 (2013) R774–R788.
[2] R. Havekes, C.G. Vecsey, T. Abel, The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity, Cell. Signal. 24 (2012) 1251–1260.
[3] J.C. Kreutzmann, R. Havekes, T. Abel, P. Meerlo, Sleep deprivation and hippocampal vulnerability: changes in neuronal plasticity, neurogenesis and cognitive function, Neuroscience 309 (2015) 173–190.
[4] C. Moreira, M.H. Tsuhako, M.T. de Franco, M. Modolell, C.A. Pereira, Arginine metabolism during macrophage autocrine activation and infection with mouse hepatitis virus 3, Immunobiology 209 (2004) 585–598.
[5] G. Tononi, C. Cirelli, Sleep function and synaptic homeostasis, Sleep Med. Rev. 10 (2006) 49–62.
[6] M.H. Silber, S. Ancoli-Israel, M.H. Bonnet, S. Chokroverty, M.M. Grigg-Damberger, M. Hirshkowitz, S. Kapen, S.A. Keenan, M.H. Kryger, T. Penzel, M.R. Pressman, C. Iber, The visual scoring of sleep in adults, J. Clin. Sleep Med. 3 (2007) 121–131.
[7] U. Wagner, J. Born, Memory consolidation during sleep: interactive effects of sleep stages and HPA regulation, Stress 11 (2008) 28–41.
[8] O.P. Hornung, F. Regen, H. Danker-Hopfe, M. Schredl, I. Heuser, The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication, Biol. Psychiatry 61 (2007) 750–757.
[9] J.M. Siegel, The REM sleep-memory consolidation hypothesis, Science 294 (2001) 1058–1063.
[10] M. Basner, K.M. Fomberstein, F.M. Razavi, S. Banks, J.H. William, R.R. Rosa, D.F. Dinges, American time use survey: sleep time and its relationship to waking activities, Sleep 30 (2007) 1085–1095.
[11] F.P. Dubiela, C.M. Queiroz, K.D. Moreira, J.N. Nobrega, L.V. Sita, S. Tufik, D.C. Hipolide, AMPA receptors mediate passive avoidance deficits induced by sleep deprivation, Behav. Brain Res. 257 (2013) 189–196.
[12] M.W. Chee, L.Y. Chuah, Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition, Curr. Opin. Neurol. 21 (2008) 417–423.
[13] N. Goel, H. Rao, J.S. Durmer, D.F. Dinges, Neurocognitive consequences of sleep deprivation, Semin. Neurol. 29 (2009) 320–339.
[14] K.H. Alzoubi, A.M. Rababa'h, A. Owaisi, Khabour OF, L-carnitine prevents memory impairment induced by chronic REM-sleep deprivation, Brain Res. Bull. 131 (2017) 176–182.
[15] K.H. Alzoubi, B.S. Malkawi, Khabour OF, T. El-Elimat, F.Q. Alali, Arbutus andrachne L. reverses sleep deprivation-induced memory impairments in rats, Mol. Neurobiol. 55 (2018) 1150–1156.
[16] K.H. Alzoubi, F.A. Mayyas, Khabour OF, F.M. Bani Salama, F.H. Alhashimi, N.M. Mhaidat, Chronic melatonin treatment prevents memory impairment induced by chronic sleep deprivation, Mol. Neurobiol. 53 (2016) 3439–3447.
[17] N.M. Mhaidat, K.H. Alzoubi, Khabour OF, N.H. Tashtoush, S.A. Banihani, K.K. Abdul-razzak, Exploring the effect of vitamin C on sleep deprivation induced memory impairment, Brain Res. Bull. 113 (2015) 41–47.
[18] J. Noguti, M.L. Andersen, C. Cirelli, D.A. Ribeiro, Oxidative stress, cancer, and sleep deprivation: is there a logical link in this association? Sleep Breath. 17 (2013) 905–910.
[19] D.Y. Oh, S. Talukdar, E.J. Bae, T. Imamura, H. Morinaga, W. Fan, P. Li, W.J. Lu, S.M. Watkins, J.M. Olefsky, GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects, Cell 142 (2010) 687–698.
[20] S.M. Weldon, A.C. Mullen, C.E. Loscher, L.A. Hurley, H.M. Roche, Docosahexaenoic acid induces an anti-inflammatory profile in lipopolysaccharide-stimulated human THP-1 macrophages more effectively than eicosapentaenoic acid, J. Nutr. Biochem. 18 (2007) 250–258.
[21] B. Xue, Z. Yang, X. Wang, H. Shi, Omega-3 polyunsaturated fatty acids antagonize macrophage inflammation via activation of AMPK/SIRT1 pathway, PLoS One 7 (2012) e45990.
[22] M. Figueras, M. Olivan, S. Busquets, F.J. Lopez-Soriano, J.M. Argiles, Effects of eicosapentaenoic acid (EPA) treatment on insulin sensitivity in an animal model of diabetes: improvement of the inflammatory status. Obesity (silver spring, Md), 19 (2011) 362–369.
[23] P. Flachs, R. Ruhl, M. Hensler, P. Janovska, P. Zouhar, V. Kus, Z. Macek Jilkova, E. Papp, O. Kuda, M. Svobodova, M. Rossmeisl, G. Tsenov, V. Mohamed-Ali, J. Kopecky, Synergistic induction of lipid catabolism and anti-inflammatory lipids in white fat of dietary obese mice in response to calorie restriction and n-3 fatty acids, Diabetologia 54 (2011) 2626–2638.
[24] J. Kopecky, M. Rossmeisl, P. Flachs, O. Kuda, P. Brauner, Z. Jilkova, B. Stankova, E. Tvrzicka, M. Bryhn, n-3 PUFA: bioavailability and modulation of adipose tissue function, Proc. Nutr. Soc. 68 (2009) 361–369.
[25] S. Lorente-Cebrian, M. Bustos, A. Marti, J.A. Martinez, M.J. Moreno-Aliaga, Eicosapentaenoic acid stimulates AMP-activated protein kinase and increases visfatin secretion in cultured murine adipocytes, Clinical science (London, England:

1979) (117) (2009) 243–249.
[26] A.M. Lottenberg, S. Afonso Mda, M.S. Lavrador, R.M. Machado, E.R. Nakandakare, The role of dietary fatty acids in the pathology of metabolic syndrome, J. Nutr. Biochem. 23 (2012) 1027–1040.
[27] Y. Yao, F. Chen, M. Wang, J. Wang, G. Ren, Antidiabetic activity of mung bean extracts in diabetic KK-Ay mice, J. Agric. Food Chem. 56 (2008) 8869–8873.
[28] M.C. Morris, D.A. Evans, C.C. Tangney, J.L. Bienias, R.S. Wilson, Fish consumption and cognitive decline with age in a large community study, Arch. Neurol. 62 (2005) 1849–1853.
[29] M.C. Morris, D.A. Evans, J.L. Bienias, C.C. Tangney, D.A. Bennett, R.S. Wilson, N. Aggarwal, J. Schneider, Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease, Arch. Neurol. 60 (2003) 940–946.
[30] F. Mayyas, R. Jaradat, K.H. Alzoubi, Cardiac effects of fish oil in a rat model of streptozotocin-induced diabetes, Nutr. Metab. Cardiovasc. Dis. 28 (2018) 592–599.
[31] A.M. Aleisa, K.H. Alzoubi, K.A. Alkadhi, Post-learning REM sleep deprivation impairs long-term memory: reversal by acute nicotine treatment, Neurosci. Lett. 499 (2011) 28–31.
[32] I.A. Alhaider, A.M. Aleisa, T.T. Tran, K.A. Alkadhi, Caffeine prevents sleep loss-induced deficits in long-term potentiation and related signaling molecules in the dentate gyrus, Eur. J. Neurosci. 31 (2010) 1368–1376.
[33] K.H. Alzoubi, M. Srivareerat, T.T. Tran, K.A. Alkadhi, Role of alpha7- and alpha4beta2-nAChRs in the neuroprotective effect of nicotine in stress-induced impairment of hippocampus-dependent memory, Int. J. Neuropsychopharmacol. 16 (2013) 1105–1113.
[34] M. Zagaar, I. Alhaider, A. Dao, A. Levine, A. Alkarawi, M. Alzubaidy, K. Alkadhi, The beneficial effects of regular exercise on cognition in REM sleep deprivation: behavioral, electrophysiological and molecular evidence, Neurobiol. Dis. 45 (2012) 1153–1162.
[35] H. Alzoubi, F. Khabour, S. I Al-azzam, M. H Tashtoush, N. M Mhaidat, Metformin eased cognitive impairment induced by chronic L-methionine administration: potential role of oxidative stress, Curr. Neuropharmacol. 12 (2014) 186–192.
[36] K. Alzoubi, O. Khabour, N.H. Tashtoush, S.I. Al-azzam, N.M. Mhaidat, Evaluation of the effect of pentoxifylline on sleep-deprivation induced memory impairment, Hippocampus 23 (2013) 812–819.
[37] K.H. Alzoubi, Khabour OF, H.A. Salah, B.E. Abu Rashid, The combined effect of sleep deprivation and Western diet on spatial learning and memory: role of BDNF and oxidative stress, J. Mol. Neurosci. 50 (2013) 124–133.
[38] K.H. Alzoubi, Khabour OF, A.S. Albawaana, F.H. Alhashimi, R.Y. Athamneh, Tempol prevents chronic sleep-deprivation induced memory impairment, Brain Res. Bull. 120 (2016) 144–150.
[39] A.M. Aleisa, G. Helal, I.A. Alhaider, K.H. Alzoubi, M. Srivareerat, T.T. Tran, S.S. Al-Rejaie, K.A. Alkadhi, Acute nicotine treatment prevents REM sleep deprivation-induced learning and memory impairment in rat, Hippocampus 21 (2011) 899–909.
[40] K.H. Alzoubi, Khabour OF, B.A. Rashid, I.M. Damaj, H.A. Salah, The neuroprotective effect of vitamin E on chronic sleep deprivation-induced memory impairment: the role of oxidative stress, Behav. Brain Res. 226 (2012) 205–210.
[41] Y. Harrison, J.A. Horne, The impact of sleep deprivation on decision making: a review, J. Exp. Psychol. Appl. 6 (2000) 236–249.
[42] M. Nasehi, S.M. Mosavi-Nezhad, F. Khakpai, M.R. Zarrindast, The role of omega-3 on modulation of cognitive deficiency induced by REM sleep deprivation in rats, Behav. Brain Res. 351 (2018) 152–160.
[43] A. Currais, P. Maher, Functional consequences of age-dependent changes in glutathione status in the brain, Antioxid. Redox Signal. 19 (2013) 813–822.
[44] C.A. Everson, C.D. Laatsch, N. Hogg, Antioxidant defense responses to sleep loss and sleep recovery, Am. J. Physiol. Regul. Integr. Comp. Physiol. 288 (2005) R374–R383.
[45] Y. Zhou, Z.F. Wang, W. Li, H. Hong, J. Chen, Y. Tian, Z.Y. Liu, Protective effects of microRNA-330 on amyloid beta-protein production, oxidative stress, and mitochondrial dysfunction in Alzheimer's disease by targeting VAV1 via the MAPK signaling pathway, J. Cell. Biochem. 119 (2018) 5437–5448.
[46] K.H. Alzoubi, Khabour OF, H.A. Salah, Z. Hasan, Vitamin E prevents high-fat high-carbohydrates diet-induced memory impairment: the role of oxidative stress, Physiol. Behav. 119 (2013) 72–78.
[47] K.H. Alzoubi, N.M. Mhaidat, E.A. Obaid, Khabour OF, Caffeine prevents memory impairment induced by Hyperhomocysteinemia, J. Mol. Neurosci. 66 (2018) 222–228.
[48] K.H. Alzoubi, A.M. Rababa'h, O.N. Al Yacoub, Tempol prevents post-traumatic stress disorder induced memory impairment, Physiol. Behav. 184 (2018) 189–195.
[49] K.H. Alzoubi, Khabour OF, M. Ahmed, Pentoxifylline prevents post-traumatic stress disorder induced memory impairment, Brain Res. Bull. 139 (2018) 263–268.
[50] K.H. Alzoubi, A.M. Al-Ibbini, K.Q. Nuseir, Prevention of memory impairment induced by post-traumatic stress disorder by cerebrolysin, Psychiatry Res. 270 (2018) 430–437.
[51] T. El-Elimat, K.H. Alzoubi, M.M. AbuAlSamen, Z.Y. Al Subeh, T.N. Graf, N.H. Oberlies, Silymarin prevents memory impairments, anxiety, and depressive-like symptoms in a rat model of post-traumatic stress disorder, Planta Med. 85 (2019) 32–40.
[52] K.H. Alzoubi, E. Mokhemer, A.N. Abuirmeileh, Beneficial effect of etazolate on depression-like behavior and, learning, and memory impairment in a model of Parkinson's disease, Behav. Brain Res. 350 (2018) 109–115.
[53] R.H. Silva, V.C. Abilio, A.L. Takatsu, S.R. Kameda, C. Grassl, A.B. Chehin, W.A. Medrano, M.B. Calzavara, S. Registro, M.L. Andersen, R.B. Machado, R.C. Carvalho, Rde A. Ribeiro, S. Tufik, R. Frussa-Filho, Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice, Neuropharmacology 46 (2004) 895–903.
[54] L. Ramanathan, S. Hu, S.A. Frautschy, J.M. Siegel, Short-term total sleep deprivation in the rat increases antioxidant responses in multiple brain regions without impairing spontaneous alternation behavior, Behav. Brain Res. 207 (2010) 305–309.
[55] A.M. El-Mowafy, M.M. Katary, C. Pye, A.S. Ibrahim, A.A. Elmarakby, Novel molecular triggers underlie valproate-induced liver injury and its alleviation by the omega-3 fatty acid DHA: role of inflammation and apoptosis, Heliyon 2 (2016) e00130.
[56] B.A. Abdel-Wahab, J.M. Al-Qahtani, S.A. El-Safty, Omega-3 polyunsaturated fatty acids in large doses attenuate seizures, cognitive impairment, and hippocampal oxidative DNA damage in young kindled rats, Neurosci. Lett. 584 (2015) 173–177.
[57] S. Yadav, K.V. Mitha, M.T. Shenoy, S. Mayannavar, B. Ganaraja, Beneficial effect of Omega-3 polyunsaturated fatty acids on neurosensorial impairments and oxidative status in Streptozotocin induced diabetic rats, Indian J. Physiol. Pharmacol. 58 (2014) 346–353.
[58] D. Cutuli, P. De Bartolo, P. Caporali, D. Laricchiuta, F. Foti, M. Ronci, C. Rossi, C. Neri, G. Spalletta, C. Caltagirone, S. Farioli-Vecchioli, L. Petrosini, n-3 polyunsaturated fatty acids supplementation enhances hippocampal functionality in aged mice, Front. Aging Neurosci. 6 (2014) 220.
[59] M.M. Zhou, H.X. Che, J.Q. Huang, T.T. Zhang, J. Xu, C.H. Xue, Y.M. Wang, Comparative study of different polar groups of EPA-enriched phospholipids on ameliorating memory loss and cognitive deficiency in aged SAMP8 mice, Mol. Nutr. Food Res. 62 (2018) e1700637.
[60] A.M. Lima, V.M. de Bruin, E.R. Rios, P.F. de Bruin, Differential effects of paradoxical sleep deprivation on memory and oxidative stress, Naunyn Schmiedeberg's Arch. Pharmacol. 387 (2014) 399–406.
[61] R. Singh, J. Kiloung, S. Singh, D. Sharma, Effect of paradoxical sleep deprivation on oxidative stress parameters in brain regions of adult and old rats, Biogerontology 9 (2008) 153–162.
[62] L. Zhang, H.Q. Zhang, X.Y. Liang, H.F. Zhang, T. Zhang, F.E. Liu, Melatonin ameliorates cognitive impairment induced by sleep deprivation in rats: role of oxidative stress, BDNF and CaMKII, Behav. Brain Res. 256 (2013) 72–81.