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Swimming exercise protective effect on waterpipe tobacco smoking-induced impairment of memory and oxidative stress

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ABSTRACT

Waterpipe tobacco smoking (WP) is associated with a vast range of detrimental health effects, including memory impairment and anti-oxidative scavenging dysfunction. Forced swimming exercise (FSE) is known to improve cognitive function and general wellbeing. In this study, we evaluated the neuroprotective effect of FSE on memory impairment induced by exposure to WP in the rat model. Wistar male rats were divided into four groups: fresh air (control), WP exposure, FSE, and WP/FSE. Animals were exposed to WP for 1 h/day, 5 days/ week for 4 weeks. At the same time, animals were forced to swim 1 h/day as 5 min swimming followed by 5 min rest, 5 days/ week for 4 weeks. Spatial learning and memory was assessed using Radial Arm Water Maze (RAWM). Additionally, hippocampal oxidative stress biomarkers including reduced glutathione (GSH), oxidized glutathione (GSSG), GSH/GSSG ratio, glutathione peroxidase (GPx), Catalase, and TBARS were analyzed. Key findings: this study showed that WP exposure impaired both short- and long-term memory ($P < 0.05$). On the other hand, FSE prevented memory impairment induced by WP exposure ($P < 0.05$). Moreover, WP exposure reduced activity of catalase, GPx, and GSH/GSSG ratio ($P < 0.05$) in the hippocampus, which were also normalized by FSE. However, no changes were detected in GSH and TBARS levels in WP exposure and/or FSE groups. In conclusion, WP exposure induced both short- and long- term memory impairments, which was prevented by FSE. This improvement in memory function might be attributed to oxidative stress biomarkers pathways.

1. Introduction

Waterpipe tobacco smoking (WP) is an ancient method of tobacco consumption rooted in the Eastern Mediterranean regions and the Indian subcontinent [1]. It has rapidly spread to western countries, especially among youth [2]. Many factors contributed to its worldwide popularity, including misperception about safety [3], socially acceptable behavior [4], and attractive flavorings of the tobacco [5].

There has been a shift of tobacco smoking as indicated by several studies showed that waterpipe smoking, and nowadays, vaping using electronic cigarettes [6], have replaced cigarette smoking as a method of tobacco smoking [7]. It is estimated that 100 million people worldwide smoke waterpipe every day [8]. Additionally, the popularity of waterpipe smoking has also increased among pregnant women [9]. Several studies showed that exposure to WTS resulted in several detrimental health effects, including respiratory [10], cardiovascular [11], renal [12], and neuronal damage and memory impairment [13]. Additionally, it has been revealed that tobacco smoking negatively affected infant sleeping pattern [14] as well as induced brain damage in breastfed child [15].

Extensive studies on human and animal suggested that physical exercise could have benefits for general health and cognitive function, especially later in life (Reveiwed in [16]). Physical exercise was also reported to improve learning ability and memory function [17]. Exercise might be voluntary as part of our lifestyle or forced during weight loss or therapeutic regimen; both types of exercise improve spatial learning and memory and this improvement parallel a reduction in the accumulation of oxidative damage [18]. The beneficial role of regular exercise is due to increase antioxidant capacity, repair enzymes activity, resistance to oxidative stress and lower oxidative damages

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compared to sedentary lifestyle [19]. The interaction effect of exercise and antioxidant-rich diet on the brain function has been demonstrated. This interaction maximally improve spatial learning in both male and female ApoE4 mice [20]. Additionally, evidence from meta-analysis revealed that exercise may help to improve memory performance among adult patients with mild cognitive impairment [21]. It also might improve or at least slow down the decline in cognitive performance among patients with Alzheimer's disease [22].

Recent studies showed that exercise counteracted memory impairment induced by high fat diet [23], stress [24], arsenic exposure [25], vascular dementia [26], and sleep deprivation [27]. However, the neuroprotective effect of forced swimming exercise on waterpipe-induced memory impairment was not evaluated. Herein, we studied this effect for the first time. Moreover, the effect of forced swimming exercise and waterpipe smoking exposure on the hippocampal oxidative stress biomarkers was evaluated in adult male rats.

2. Methods

2.1. Animals

Adult male Wistar rats (weight 180-250 g and aged 10–12 weeks) were purchased from Animal House of Jordan University of Science and Technology. Animals were kept as six rats in a metal cage (cage size: LXWXH in cm: 55X45X25) under controlled temperature (25 ± 1 °C) with free access to water and standard rodent food. They were identified by tail labeling and maintained at 12 h dark/light cycle. All experiments were carried out during the light cycle. Wood shaving was used as bedding and replaced regularly for hygienic purposes. This study was approved by Institutional Animal Care and Use Committee at Jordan University of Science and Technology. Rats were allowed to acclimatize for two weeks prior to the experiment.

Animals were assigned randomly into four groups (n = 12rats/group): fresh air (control), waterpipe smoke (WP) exposure, forced swimming exercise (FSE), and WP/FSE. Throughout the experiment, the control group was exposed to room air and had free access to water and food. The WP and WP/FSE groups were exposed to waterpipe smoke for 60 min session/day for 5 days/week for 4 weeks using a whole body exposure apparatus. The apparatus was programmed to simulate Beirut Method (171 puffs of 2.5 s and 17 s inter-puff duration). Ten grams of tobacco (Double Apple Moassel (0.5% nicotine), Nakhla Shisha Flavour Co., Cairo, Egypt, which is commercially available in Jordan) were used in each waterpipe session. Level of carbon monoxide (CO) was regularly monitored using CO analyzer (Monoxor II, Bacharach Inc.) as previously described [10,28]. The average CO levels during WP exposure sessions was 1050 ± 100 ppm (mean ± SD), levels of CO ranged from 805 to 1237, noting that the previously reported LD50 for 60 min exposure to CO in rat were in the range of 3954 to 4670 ppm [29]. The levels of O2 and CO2 were not measured in the exposure chamber.

2.2. Forced swimming exercise

The rats in the FSE and WP/FSE groups were forced to swim for 1 h per day (alternating between 5 min swimming followed by 5 min rest) as described previously [17,18,30]. The swimming protocol was carried out using three identical swimming cylindrical tanks where the dimensions for each tank were 50 cm height, 35 cm diameter, and 35 cm depth. The tanks were filled with water with a depth of 32 cm. The procedure was carried out 5 days/week for one month. After each 5 min swimming, each rat was dried using a towel and returned to home cage to take 5 min rest. The FSE was done first thing in the morning (at 9:00 am) followed by the WP exposure session.

2.3. The radial arm water maze

All animal groups were tested for learning and memory using a radial arm water maze (RAWM) as described previously [31,32]. Briefly, the RAWM is a circular black-colored tub filled with water with a diameter of 167 cm, a height of 55 cm, and a depth of 43 cm. It has stainless steel V-shaped plates (number of plates is six, height: 49 cm, length: 55 cm) arranged around an open central area and six arms with a hidden platform located on the goal arm. The water temperature was maintained at 25 ± 1 °C during the experiment. Two pictures were placed on the wall of the experimental room, serving as visual cues to help rats in determining directions. Learning phase was accomplished by having the rats undergo 12 consecutive trials, the first six successive trials followed by 5 min rest then another six trials. Short-term memory performance was tested at 30 min while long term memory performance was tested at 5 h and 24 h from the last learning trial. In each trial, the rat was allowed to swim freely for 1 min to find a hidden platform (2 cm under water). Once the rat is on the platform, it was allowed to stay for 15 s in order to observe visual cues before the next trial. Once a rat was unable to find the hidden platform within the allowed time (1 min period), it was guided by the technician toward the platform for the 15 s stay. In each trial, the animal was placed in water at a different arm except the goal arm. During the allowed swimming period, an error was counted if a rat entered an arm other than the goal arm. Entry occurred when the whole body of the rat was inside the arm. The RAWM training was carried out immediately after 4 weeks of treatment. Memory test was conducted in a similar manner to learning phase. However, in memory test, rat was neither guided to the hidden platform, nor given the 15 s stay on the hidden platform. Instead, once a rat on the platform, it was immediately picked up and returned to home cage.

2.4. Hippocampus dissection

At the end of the experiment, animals were killed using a guillotine, the brain of rats were removed from their skull immediately and placed on filter paper soaked with normal saline. The filter paper was placed over crushed ice in plate of glass. The hippocampus was dissected out and placed in an Eppendorf tube and then immersed immediately in a container filled with liquid nitrogen. All Eppendorf tubes were stored in refrigerator at −30 °C until the time of tissues processing [31].

2.5. Molecular assays

The tissues of the hippocampus were homogenized in phosphate buffer (200 μL). using a plastic pestle, the homogenization buffer was prepared by the 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) in distilled water (200 mL). Then, mixture of homogenized tissues and buffer were centrifuged at 15000 ×g for 10 min (4C°) in order to eliminate tissues that failed to dissolve in the buffer and thus remained insoluble. The supernatant from the previous step was recovered and stored for further analysis. Total protein concentration in the recovered supernatant was measured using a commercially available kit purchased from Bio-rad (Bio-Rad, USA). For oxidative stress biomarkers, total glutathione, oxidized glutathione (GSSG), Glutathione peroxidase (GPx), catalase and Thiobarbituric acid reactive substance (TBARs), commercially available kits were utilized as per kit's manufacturer's instructions (total glutathione and GSSG: Glutathione assay kit, CS0260, Sigma-Aldrich, MI, USA, GPx: Glutathione Peroxidase Cellular Activity Assay Kit, catalog number: CGP1, Sigma-Aldrich, MI, USA, Catalase: catalase assay kit, Cayman Chem, Ann Arbor, MI, USA, TBARs: Cayman Chem, item № 10009055, Ann arbor, MI. USA). In the total glutathione/GSSG assay, samples were subjected to deproteinized with the 5% 5-Sulfosalicylic acid solution and centrifugation to remove the precipitated protein as

indicated in the CS0260 kit. Absorbance for each assay was measured spectrophotometrically using a Epoch Microplate Spectrophotometer at specified wavelength in each of the after-mentioned kits (Bio-tek instruments, Highland Park, Winooski, USA).

2.6. Statistical analysis

Data were represented as mean ± standard error of means (SEM). GraphPad Prism (version 4.0, GraphPad software, LA Jolle, CA) was used to carry out all statistics. Three-way ANOVA was used to compare number of errors in the RAWM learning trials, with multiple comparison posttest. Time (repeated measures factor) and interaction with WTS/no WTS and FSE/no FSE were used as independent group dimensions. Comparisons of number of errors in RAWM memory tests and biochemical assays results were carried out using two-way ANOVA; followed by Bonferroni's posttest. Moreover, Pearson's correlations between memory tests and oxidative stress biomarkers levels were also carried out. $P < 0.05$ was considered statistically significant.

3. Results

3.1. The effect of WP and/or FSE on learning and memory

During the learning phase, the four animal groups were able to learn the location of the submersed platform as shown by the remarkable decrease in the numbers of errors with subsequent learning trial. There was no observed significant interaction among treatment groups ($P > 0.05$) in trials 1 through 12. This demonstrates that neither WP nor FSE influenced learning (Fig. 1).

During the short-term memory, and 5 h and 24 h long-term memory tests, significant differences were detected between FSE treated and non-FSE treated groups, and/or WP versus non-WP groups. Additionally, the presence of both factors, FSE and WP, resulted in significant interactions at all memory tests (short-term memory test: $F(1, 56) = 11.50$, $P < 0.01$, Fig. 2A, long-term 5 h memory test: $F(1, 56) = 4.40$, $P < 0.05$, Fig. 2B, long-term 24 h memory test: $F(1, 56) = 10.95$, $P < 0.01$, Fig. 2C). In conclusion, WP resulted in increased number of errors in short- and long- term memory tests, whereas FSE prevented WP induced short- and long- term memory impairments.

3.2. The effect of chronic WP exposure and FSE on hippocampus oxidative stress biomarkers

3.2.1. Hippocampus catalase, GPx, and TBARS levels

The WP exposure significantly reduced catalase and GPx activities as compared to control, FSE, and WP/FSE groups ($F(1, 56) = 4.10$, $P < 0.05$; $F(1, 56) = 4.13$, $P < 0.05$, Fig. 3A and B). Moreover, catalase and GPx activities in the WP/FSE group were comparable to that in the FSE and control groups. No changes were observed in TBARS levels among all study groups, thus, FSE did not change the level of TBARS during WP exposure ($F(1, 56) = 0.17$, $P > 0.05$, Fig. 3C).

3.2.2. Levels of the hippocampus GSH, GSSG and GSH/GSSG ratio

Whereas no significant changes were observed in the GSH levels among all study groups ($F(1, 56) = 0.16$, $P > 0.05$; Fig. 4A), exposure to WP resulted in a significant increase in GSSG, and a significant decrease in the GSH/GSSG ratio compared with control, FSE, and WP/FSE groups ($F(1, 56) = 4.32$, $P < 0.05$; $F(1, 56) = 4.23$, $P < 0.05$; Fig. 4B and C). Interestingly, FSE prevented the changes in the GSSG and GSH/GSSG ratio during WP exposure (Fig. 4B and C) where there were no significant changes in the GSSG and GSH/GSSG ratio in WP/FSE compared with control, and FSE groups.

3.2.3. Correlation of RAWM memory tests performance and hippocampus levels/activities of oxidative stress biomarkers and enzymes

Pearson's correlation showed between number of errors committed by each animal in short- and long- term memory tests with levels of oxidative stress biomarkers and activities of oxidative stress enzymes. Whereas GSSG levels showed moderate to strong positive correlations (r: 0.52–0.71), GSH/GSSG ratio, and GPx and catalase activities showed moderate to strong negative correlations (r: −0.58–0.72), with the number of errors committed by each animal in the memory tests. The levels of GSH and TBARs showed very weak correlations (r: −0.05–0.09) with the number of errors committed by each animal in the memory tests.

4. Discussion

In this study, we evaluated the neuroprotective effect of FSE on short and long- term memory impairment induced by WP exposure in rat model. The findings of this study indicated that WP exposure impaired memory but not learning and FSE prevented WP-induced short- and long- term memory impairment as indicated by remarkable reduction in the numbers of errors during RAWM memory test done at 30 min, 5- and 24- h. Moreover, WP exposure increased hippocampal oxidative stress as indicated by increase in GSSG levels and decrease in GSH/GSSG ratio and decrease in antioxidant enzymes activities, including catalase and GPx. The increase in hippocampal oxidative stress levels induced by WP were prevented by FSE.

Current findings are in parallel with previous studies that showed the potential effect of WP exposure on short- and long- term memory impairment in animals without effect the ability to learn. For example, it has been revealed that exposing rats to waterpipe smoke impaired

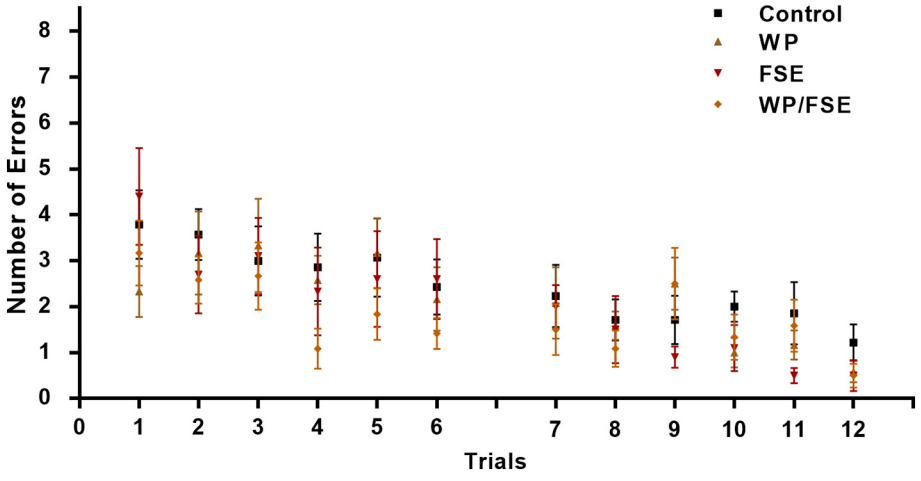

Fig. 1. Animal learning performance using radial arm water maze (RAWM). Comparison of fresh air (control), waterpipe (WP), forced swimming exercise (FSE), and WP/FSE groups. Each rat was trained for 12 trials; each 6 trials were separated by 5 min. Rat performance was recorded as average number of errors in each trial. Each value is the mean ± SEM (n = 12 rats/group).

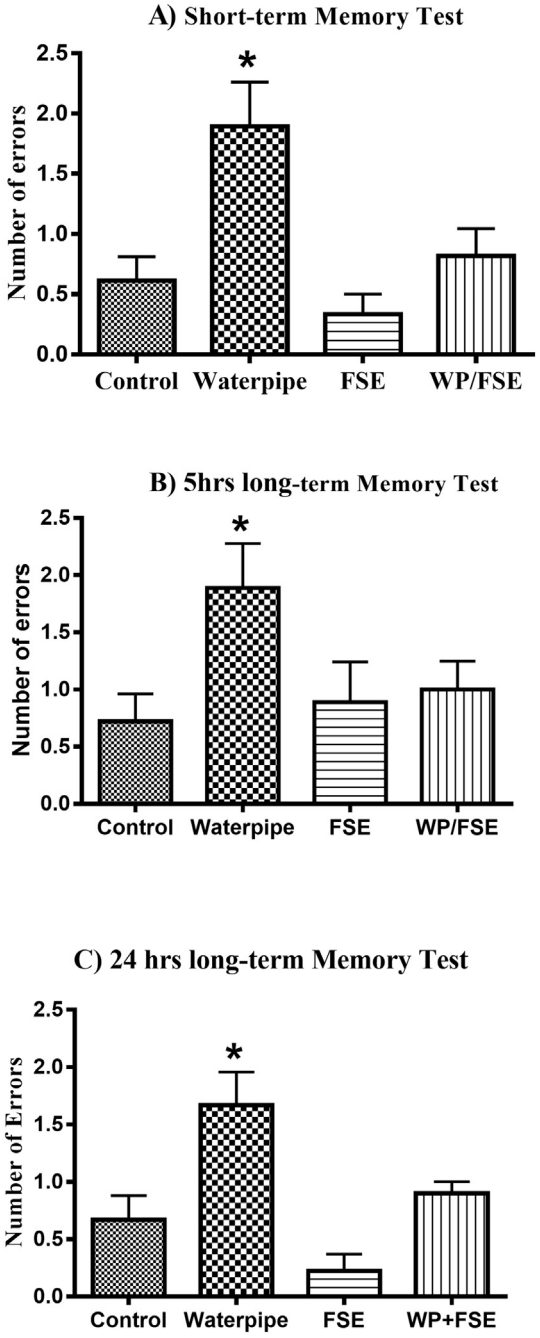

Fig. 2. Forced swimming exercise (FSE) prevents waterpipe smoking-induced memory impairment. (A): short-term memory test, (B): long-term memory test after 5 h, (C): long term memory test after 12 h. Chronic exposure to waterpipe smoke impaired short-term and long-term memory which was prevented by FSE. Each point is the mean ± SEM of numbers of errors during memory test. *Indicates significant difference from control, FSE, and WP/FSE ($P < 0.05$, $n = 12$ rats/group).

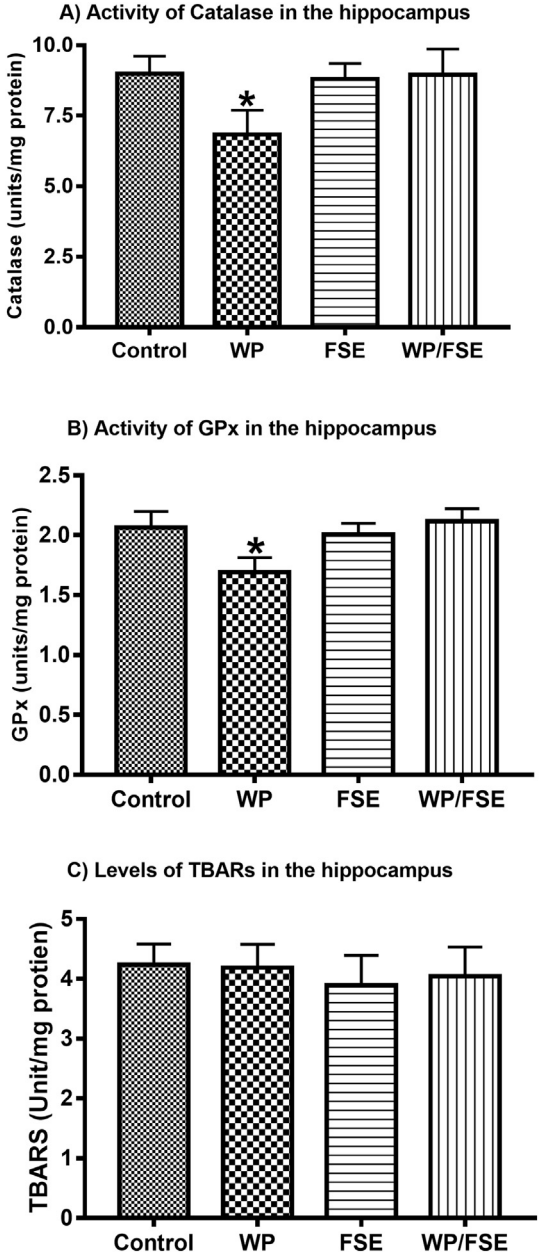

Fig. 3. Effect of waterpipe exposure on hippocampal oxidative stress biomarkers. Chronic exposure to waterpipe smoking reduced the activity of catalase (A) and GPx (B), but not TBARS (C) in the hippocampus which was prevented by forced swimming exercise (FSE). Each point is the mean ± SEM of 12 rats/group. *Indicates significant difference from control, FSE, and WP/FSE ($P < 0.05$, $n = 12$ rats/group).

memory functions without an effect on learning [13,33]. Moreover, previous studies demonstrated that exposing animals during prenatal or maternal phases of life to WP can impair memory, but not learning, in adult offspring rats [34]. Additionally, it has been shown that prenatal exposure to cigarette smoke and during lactation impaired in spatial and reference memories of offspring mice [35,36].

The mechanism by which WP induced memory impairment might be attributed to induction of oxidative stress in the hippocampus. It has been shown that induction of oxidative stress could predispose hippocampal neurons to damage and lead to subsequent memory impairment, while antioxidants that preserved oxidative stress were essential in memory retention [33,37]. In fact, removal of reactive oxygen species that play potential role in oxidative stress state, which is maintained by enzymatic (catalase, SOD, GPx) and non-enzymatic (GSH) pathways [38]. Interestingly, it was found that memory impairment induced by WP exposure was associated with remarkable reduction in the hippocampal oxidative stress biomarkers and enzymes, such as catalase, GPx, GSH, and GSH/GSSG ratio [13]. These findings suggested that depletion of hippocampal oxidative stress biomarkers could be attributed to the production of free radicals, elevation of heavy metals, or exposure to other toxic chemicals during WP [39]. For these reasons, shifting the balance toward increasing antioxidants levels or

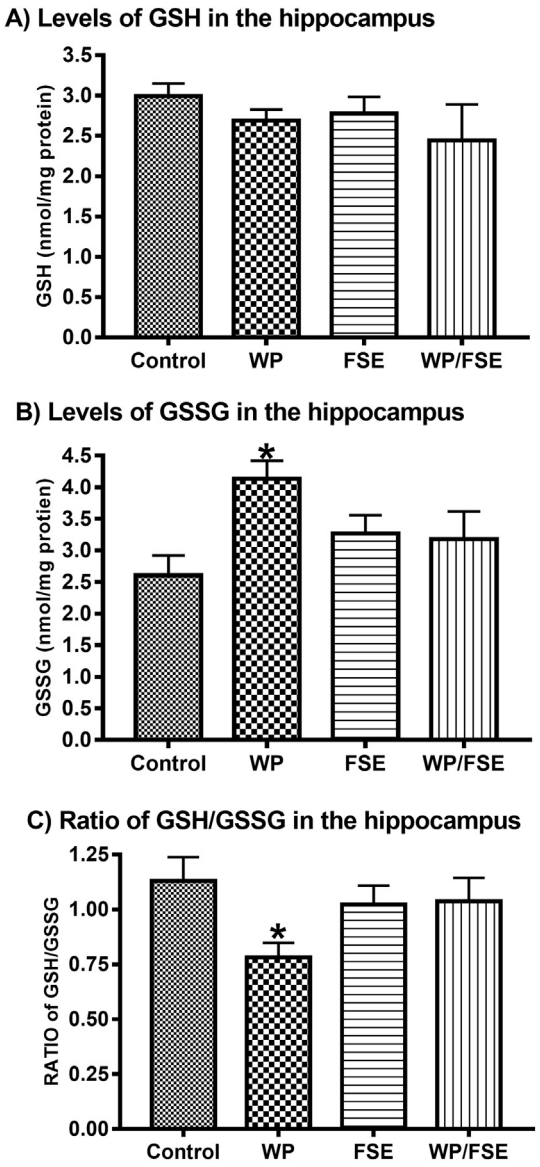

Fig. 4. Changes of GSH, GSSG, and GSH/GSSG ratio in the hippocampus. Chronic waterpipe exposure did not change the levels of GSH (A), while it increased the levels of GSSG (B), and decreased the GSH/GSSG ratio (C). Each point is the mean ± SEM. *Indicates significant difference from control, FSE, and WP/FSE ($P < 0.05$; n = 12 rats/group).

preventing its depletion might help preventing memory impairment induced by WP exposure.

In this study, it has been shown that forcing rats to swim, as non-voluntary exercise training, prevented short- and long- term memory impairment induced by WP exposure in rats. The findings of the current study were in agreement with previous studies that showed the neuroprotective role of exercise on other learning and memory impairment. For example, exercise improved learning and memory impairment induced by sleep deprivation [40], nicotine [41], aging [42], tramadol-treatment [43], stress [24]. Alongside, this study also demonstrated that FSE prevented memory impairment induced by WP via normalizing oxidative stress biomarkers.

We demonstrate that WP triggered oxidative stress in hippocampus of rats by producing reactive oxygen species subsequently attenuating antioxidant scavenging system. Oxidative stress biomarkers/enzymes that played a major role in cognitive activity were catalase, GPx, GSSG, and GSH/GSSG ratio, and theses biomarkers/enzymes were normalized by FSE during WP exposure. The findings of this study were similar to previous studies that demonstrated the ability of exercise to normalize oxidative stress biomarkers not only in the hippocampus [44] but also in the liver [45], lungs [46] and heart [47]. However, no changes have been detected in the TBARS levels among all experimental groups, indicating that TBARS and lipid peroxidation were not involved in memory impairment induced by WP exposure. This finding is consistent with previous studies that revealed chronic exposure to WP not to change TBARS levels in the hippocampus [28], and cardiac tissues [48]. However, lipid peroxidation was reported to be significantly elevated in kidney tissues of mice after chronic exposure to WP [12].

Current study may suffer some limitations. For example, the FSE and WP procedures were carried out every day including the behavioral testing day. This raises the possibility of stress interferences or acute effect for FSE and/or WP during the learning and memory behaviors. However, current results and previous studies using the same procedures have shown that FSE preserves memory functions [17,30], which suggests against a significant interference for acute stress due to FSE on memory functions. Yet, a future study to test the contributions of acute FSE and/or WP (if any) into the currently observed results could be warranted.

In conclusion, chronic exposure to waterpipe smoking impaired short- and long- term memory in rats, and this impairment was associated with reduction in the levels and activity of hippocampal oxidative stress biomarkers and enzymes. Forced swimming training has neuroprotective effect against memory deficit induced by waterpipe smoking possibly through preserving endogenous antioxidant defense system in the hippocampus.

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