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The neuroprotective effect of vitamin E on waterpipe tobacco smoking-induced memory impairment: The antioxidative role

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ABSTRACT

Aims: Tobacco smoking is associated with a vast range of adverse health effects, including diminished cognitive and anti-oxidative capabilities. Conversely, vitamin E (VitE) is known to enhance data acquisition and retention and hippocampal oxidative defense. No studies, however, examined the protective effect of VitE with tobacco administration. Therefore, this study examined the protective effect of VitE on the cognitive and oxidative debilitating effects induced by waterpipe smoking.

Materials and methods: Wistar male rats were divided into four groups: waterpipe smoking, VitE, waterpipe combined with VitE, and control group. The exposure to waterpipe and VitE was for one month and then spatial learning and memory were assesses using Radial Arms Water Maze. Additionally, oxidative stress biomarkers (Catalase, GPx, and TBARS, GSH, GSSG, and GSH/GSSG ratio) were assessed in the hippocampus.

Key findings: The results revealed that waterpipe smoking impaired short-term and long-term memory ($P < 0.05$). Waterpipe smoking reduced activity of catalase ($P < 0.05$), GPx ($P < 0.05$) and GSH/GSSG ratio ($P < 0.05$) in the hippocampus. Administration of VitE prevented memory impairment and alterations in oxidative stress biomarkers.

Significance: waterpipe smoking induces short-term and long-term memory impairments, which were prevented by administration of VitE via its anti-oxidative properties.

1. Introduction

Waterpipe tobacco smoking also known as (Hookah) is a method of tobacco use that is thought to be less harmful than cigarette smoking. Though it is originated and most popular in the Middle East, [1], waterpipe smoking has spread to many parts of the world [2]. In in fact, smoking waterpipe has exceeded smoking cigarettes, especially among youngsters, mainly due to health misconceptions, social and cultural acceptance, and accessibility [3,4].

One in 10 deaths around the word is attributed to tobacco use [5]. In 20th century, tobacco use has killed 100 million people world-wide [6]. Available evidence support an association between waterpipe smoking and many detrimental health effects, including cardiovascular [7], respiratory [8–12], renal [13], reflux disorder [14], and pregnancy complications [15–17]. Additionally, prenatal maternal or adult waterpipe smoking exposure in animals was shown to impair short-term and long-term memory performance [15–17]. Interestingly, this impairment was accopmained by marked changes in hippocamus oxidative stress markers an such as glutathione (GSH), GSH/GSSG ratio, superoxide dismutase (SOD), peroxidase (GPx), and catalase [18].

In addition to it is dietry importance, vitanmin E (VitE) is a well known antioxidant substance. Due to its anitoxidative capacity, VitE is associated with improvement in memory impairment-related disorders, such as age related neuronal damage [19–21], hypothyroidism [22], stroke [23], early model of Parkinson's disease [24]. Moreover, VitE has been shown to amileorate memory deficit induced by high-fat diet [25] and chronic sleeping deprivation-induced learning and memory impairments [26]. Furthermore, it has been revealed that VitE confers protection againist learning and memory impairments as a result of lead exposure [27]. Moreover, VitE has been shown to protect against several devastating effects of tobacco smoking, such as tubal damage [28], lung tumor [29], and coronary heart disease [30]. However, no study

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has evaluated the effect of VitE on memory impairment due to waterpipe smoke. In this study, we explored the hypothesis that chronic VitE supplementation prevents chronic waterpipe tobacco exposure-induced impairment of hippocampal learning and memory via its antioxidant properties. Both behavioral approaches using radial arm water maze and the molecular enzymatic assay approach were used to test this hypothesis.

2. Methods

2.1. Animals and treatments

Adult Wistar male rats weighing between 180-250g were obtained from Animal House at Jordan University of Science and Technology, Irbid, Jordan. This study was approved by Animal Care and Use Committee (ACUC) at Jordan University of Science and Technology. Animals were housed as five rats in a metal cage under a temperature controlled room (24 ± 1 °C) with free access to water and food and maintained at 12h dark/light cycle. They were identified by tail labeling and weighted on weekly bases. All experiments carried out during the light cycle. Wood shaving was used as bedding; these conditions were maintained constant throughout the experiments. Before starting the experiment, rats were allowed to stay in their cages for two weeks for establishing social hierarchy for each group.

Animals were randomly assigned into four groups (n = 12–13 rats/group). Fresh air or control (n = 13), Waterpipe tobacco smoke exposure (Waterpipe, n = 12), VitE (VitE, n = 12), and WS/VitE (n = 12). The control group had free access to water and food and exposed to room air throughout the experiment. Waterpipe and WS/VitE groups were exposed to waterpipe smoke for one hour session/day for five days/week for one month, using whole body exposure apparatus as previously described [31–33]. Concurrently, the VitE and WS with VitE groups were treated with VitE (α-tocopherol, Sigma, St. Louis, MO) at a dose of 100mg/kg once a day (from Saturday to Thursday) by oral gavage, administered freshly after preparation for one month and during the behavioral testing period. The dose, rout of administration, and treatment duration were previously used by others [26,34–36]. The control and Waterpipe groups were administered vehicle by oral gavage throughout the experiment period.

3. The radial arm water maze (RAWM)

The RAWM was used to test spatial learning and memory for all groups. This paradigm is previously described by [15,31,37–39]. Briefly, RAWM is black round water filled stainless steel tank (dimension: 167 cm diameter; 55 cm height; 43 cm depth) with six V-shape stainless steel plate (55 cm length; 49 cm height) are wedge to the internal wall of the tank to form six swimming paths with opened central area. All experiments were carried out in a dimly lit room with spatial visual cues fixed at the wall of the room during experiment. Water temperature was maintained at 24 ± 1C°. The animal had to find a submerged platform (2cm beneath water level) located at the end of the one swimming arm (goal arm) in 1 min. There are two phases, the acquisition phase (learning phase) and the memory test. The acquisition phase consists of 12 trials separated by 5 minutes rest after trials six then another six trials. Each trial started from different arm (except the goal arm). Each particular rat was allowed to find the hidden platform in one minute period and stay there for 15 s to observe spatial visual cues on the wall before the next trial. When a rat was unable to locate the hidden platform, it was guided to the platform and award 15 second stay. In memory test, a rat neither guided to platform nor given 15 s to see the visual cues. Instead of that, once the rat on the platform, it was taken and dried well then returned to its cage. Short memory test was done 30 min after the last trial of the acquisition phase, and long memory tests were done after 5 and 24 h from the last trial of the acquisition phase. Each time the rat entered to the wrong arm, an error was recorded. Entry defined as an access of whole body of the rat inside the swimming arm regardless of its tail. The goal arm was fixed for each particular rat during the acquisition phase and memory test. In each time, we changed the goal arm for each particular rat; amount of fresh water was added after withdrawing almost the same amount from the tank in order to get rid of scent of path.

4. Hippocampus dissection

Animals were killed by decapitation. The brain was dissected from the skull immediately after killing and placed over filter paper soaked with normal saline on petri dish filled with crushed ice. The brain was divided into two halves, the right and left hippocampus were removed and placed in Eppendorf tubes, then placed in a container filled with liquid nitrogen. Finally, Eppendorf tubes were frozen at −30C° until required for tissue analysis [40–43].

5. Calorimetric assays

The obtained hippocampus tissues were homogenized manually by plastic pestle in 200 mL phosphate buffer. The buffer was prepared by dissolving 8 g NaCl, 0.2 KCL, 0.24 KH2PO4, and 1.44 g Na2HPO4, 5 mM EDTA as preservative, and protease inhibitor cocktail, all were dissolved in 1 L distilled water (Sigma-Aldrich Corp, MI, USA) as described by [44,45]. The homogenized tissues were centrifuged (15,000 ×*g* for 10 min at 4 °C) in order to remove insoluble materials. Concentration of total proteins in homogenate was estimated using available commercial kit (BioRad, Hercules, CA, USA). To quantify the reduced GSH, tissue homogenates were treated with 5-Sulfosalicylic acid, then centrifuged (10,000 ×*g*, 10 min, and 4 °C) then supernatant was assay according to kit instructions (GSH Assay Kit, Sigma-Aldrich Corp). For GSSG analysis, the same procedures of GSH were used except that tissues homogenates were treated by 2-vinylpyridine in 1:10 ratio (1 mL sample: 10 μL of 4vinylpyridine). GPx activity was determined spectrophotometrically using cellular activity assay kit (CGP1, Sigma-Aldrich, MI, USA). Catalase enzyme level was determined in the hippocampal homogenized tissue using catalase assay kit according to manufacturer instructions (Cayman Chem, Ann Arbor, MI, USA). TBARS activity in hippocampal homogenized tissue was measured using TBARS assay kit (Cayman Chem). The reaction was carried out under high temperature and acidic condition then measured colorimetrically at 540 nm using automated plate reader (ELx800, Bio-tek instrument, plate's Reader Highland Park, Winooski, USA).

6. Statistical analysis

Statistical analysis was carried out using the GraphPad Prism (version 4.0, GraphPad software, LA Jolle, CA). Comparisons of the number of errors during the RAWM were made using two-way ANOVA; followed by Bonferroni posttest. Time (repeated measures factor) and treatment (between-subjects factor) groups were the independent variables. Comparisons of biomarkers were made using one-way ANOVA; followed by Bonferroni posttest. All values are represented as mean ± SEM. $P < 0.05$ was considered significant.

7. Results

7.1. The effect of waterpipe smoking and VitE on learning and memory

In the acquisition phase of the behavioral test, all animal groups were able to learn the location of the submerged platform as determined by the obvious reduction of errors during subsequent learning trials, without significant differences among these groups ($P > 0.05$) (trial 1 to 12) as shown in Fig. 1.

In the short-term memory test, which was carried out 30 min after the last trial of the acquisition phase, waterpipe smoke exposure

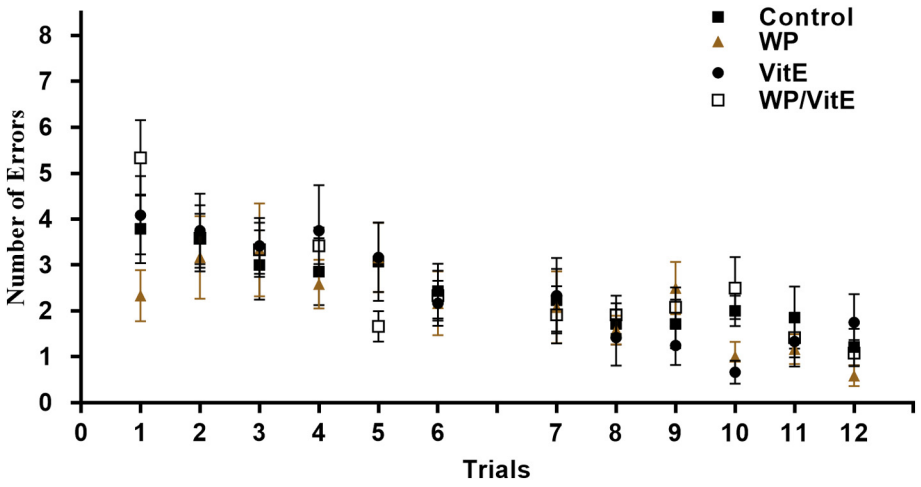


Fig. 1. Animal learning performance in the radial arm water maze (RAWM). Comparison of control group, which was exposed to fresh air, waterpipe group, which exposed for 1 h/day, 5-days/week for one month to watepipe smoke, Vitamin E (VitE, 100 mg/kg by oral gavage) group, and waterpipe and vitamin E (WP/VitE) group. Each point is the mean ± SEM of 12–13 animals/group.

impaired short-term memory, as indicated by the significantly higher number of errors ($P < 0.05$) that were committed by the waterpipe group compared to that of the control group. On the other hand, VitE administration prevented waterpipe smoking induced short-term memory impairment, as indicated by fewer numbers of errors to find the submerged platform than untreated waterpipe smoke exposed rats. In addition, VitE administration in normal rats had no significant effect on short-term memory performance during the RAWM testing. Furthermore, no significant difference was found among the control, VitE, and WP/VitE groups (Fig. 2A).

In the long-term memory tests, which were performed 5 h and 24 h after the last trial of the acquisition phase, the waterpipe group committed significantly more errors ($P < 0.05$) to locate the submerged platform than the control group. Chronic administration of VitE prevented waterpipe smoking induced long-term memory impairment as indicated by fewer errors made during the long-term memory performance. Moreover, comparable numbers of errors were made in the control, VitE, and WP/VitE groups (Fig. 2B and C). These results revealed that chronic administration of VitE prevented long-term memory impairment induced by waterpipe smoke exposure.

7.2. The effect of chronic waterpipe smoking exposure and VitE on hippocampus oxidative stress biomarkers

7.2.1. Hippocampus catalase, GPx, and TBARS levels

In the waterpipe group, the activity of the catalase enzyme and *GPx* was significantly reduced compared with the control group ($P < 0.05$; Fig. 3A and B). Moreover, no significant difference was found among the other groups compared with the control group; this finding indicated that chronic administration of VitE prevented reductions catalase and GPx activities induced by waterpipe smoke exposure. For the levels of TBARS, no significant differences were found among all experimental groups (Fig. 3C).

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

GSH levels were not changed among the different experimental groups (Fig. 4A). On the other hand, the level of GSSG was significantly increased in the waterpipe group compared to the control (Fig. 4B). Additionally, the ratio of GSH/GSSG was significantly reduced in the waterpipe group compared to the control (Fig. 4C). Moreover, no change was observed in the GSSG level and the ration of GSH/GSSG between control, VitE, and VitE/waterpipe groups. These findings indicate that chronic administration of VitE prevented the GSSG level and GSH/GSSG ratio reductions induced by waterpipe smoke exposure.

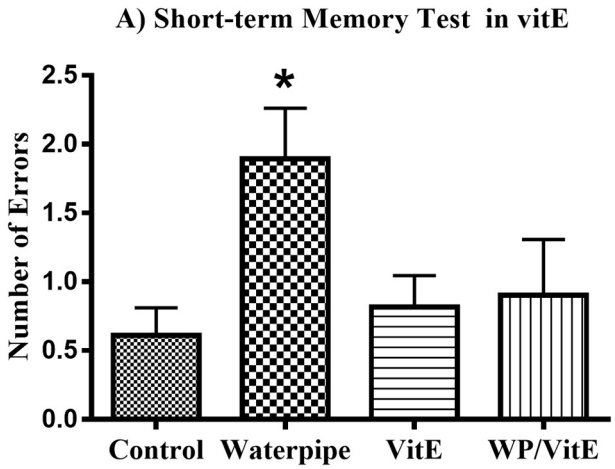
8. Discussion

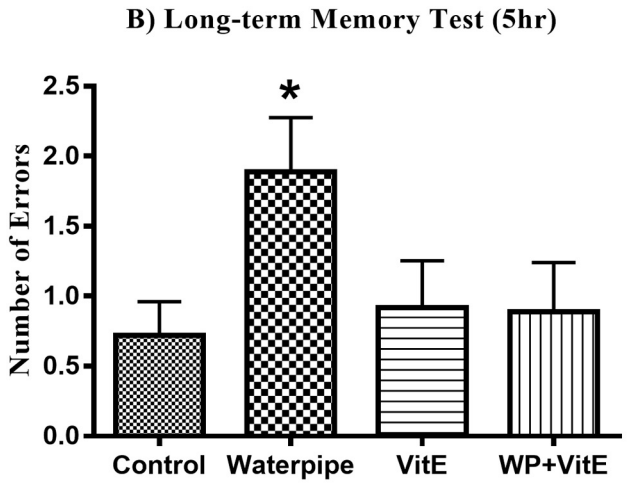
In this study, the neuroprotective effect of VitE on short- and long-term memory impairment induced by waterpipe smoking exposure was evaluated in rats. Exposure to waterpipe smoke resulted in impaired short- and long- term memory and elevated oxidative stress status. Interestingly, altered memory and oxidative stress were prevented by VitE administration. The results indicate that reducing oxidative stress by VitE administration might have prevented waterpipe-induced memory impairment. The findings are unique and confirm the harmful effect of waterpipe exposure and the protective benefits of VitE administration on cognitive function in rats.

This study is in accordance with other studies that showed the negative effect of waterpipe tobacco smoking on memory but not learning in adult rats [18,46]. In accordance, prenatal maternal exposure to waterpipe tobacco smoke impaired short- and long- term memory of offspring rats without effect on learning [15]. Another study revealed that exposing mice to tobacco smoke during pregnancy has been shown to induce learning and memory impairment of their offspring [47]. Similarly, gestational exposure to cigarette smoke impaired spatial learning and reference memory of offspring mice [48].

The positive impact of VitE on cognitive impairments has been widely studied. In a couple of studies, it was shown that administration of VitE via oral gavage has prevented short- and long-term memory impairment induced by chronic sleep deprivation [26] and by high-fat diet [34]. In another study, VitE supplementation to aged rats has resulted in marked improvement in cognitive function [21]. Moreover, it has been shown that combined administration of VitE and vitamin C improved passive avoidance learning and memory in diabetic rats [35,49]. Diet supplementation of VitE counteracted memory and learning deficits induced by mild traumatic brain injury in rats [50]. Furthermore, another study showed that impairment of learning and memory as a result of chronic exposure to lead in rats was ameliorated by VitE administration [27]. In juvenile hypothyroid rats, administration of VitE improved learning and memory deficits [51]. The findings of the current study are consistent with these previous studies in revealing that VitE prevents both short- and long- term memory impairments induced by watepipe tobacco smoking.

Similar to the current findings, previous studies have demonstrated impaired memory with waterpipe smoke exposure. Alzoubi, Alqudah, Al-Sawalha, and their colleagues reported that the potential mechanism of memory impairment associated with waterpipe could be induction of oxidative stress and alteration in the hippocampus antioxidant enzymes [15,18,46]. Previous studies showed that waterpipe smoke contains similar profile of toxicants to that of tobacco cigarette smoke but with relatively greater magnitude. For example, exposure to carbon monoxide, poly aromatic hydrocarbons, formaldehyde, and heavy metals





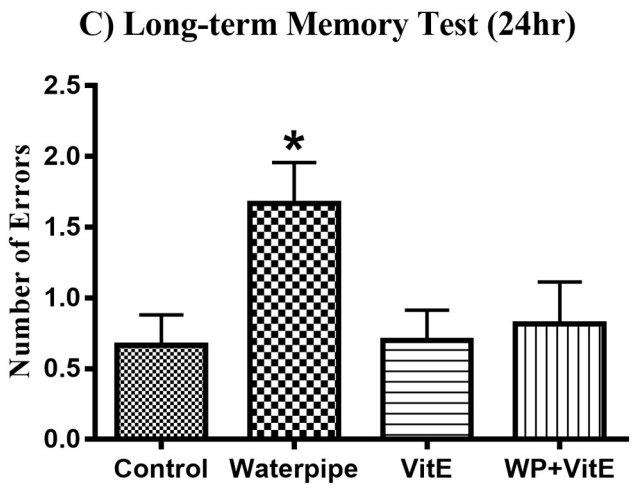
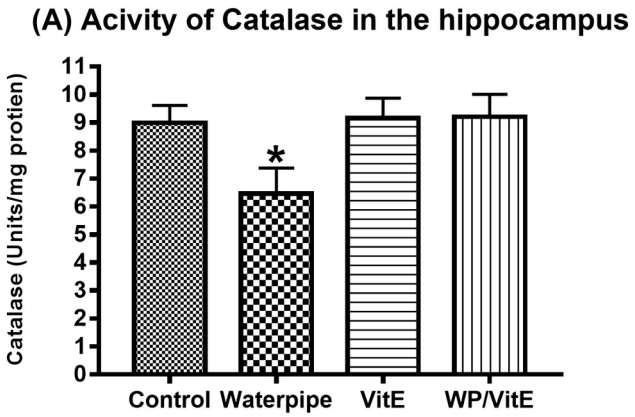
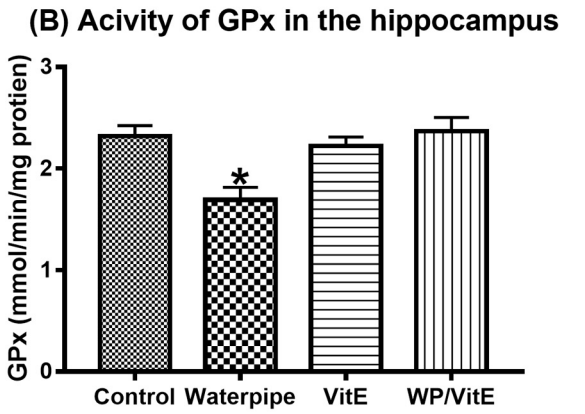


Fig. 2. Vitamin E (VitE) prevented hippocampal memory impairment induced by waterpipe smoke exposure. Short-term memory test performed 30 min (A), long-term memory tests (B) 5 h and (C) 24 h, after the last trial of the acquisition phase. Each column is the mean ± SEM of 12–13 rats. *Significant difference from other groups using two-way ANOVA followed by Bonferroni post hoc test ($P < 0.05$).





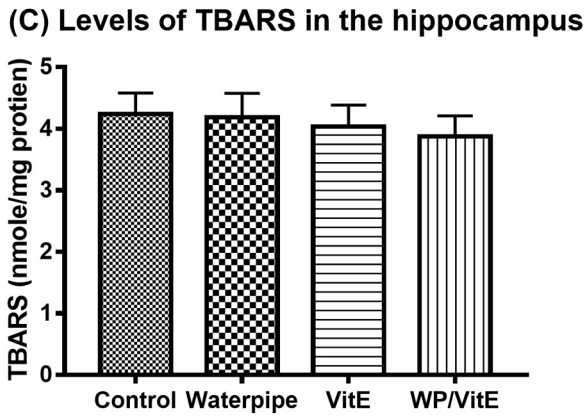


Fig. 3. Activities of (A) Catalase, and (B) GPx, and (C) levels of TBARS in the hippocampus. Each bar represents the mean ± SEM of 10–13 rats. *Indicates significant difference from other groups, ($P < 0.05$).

are several folds higher in WTP [52,53]. These components are known to modulate brain functions via mechanisms that involved induction of oxidative stress [54–57]. However, nicotine, one of the component of waterpipe smoke [53], has cognitive protective effects [58–61]. Thus, according to current results and previous literature, the neurotoxic effects of most components of waterpipe smoke exceed the beneficial effect of nicotine on cognitive function [54]. The current study showed, for the first time, that waterpipe-induced memory impairment was prevented by VitE administration. We believe that VitE plays an

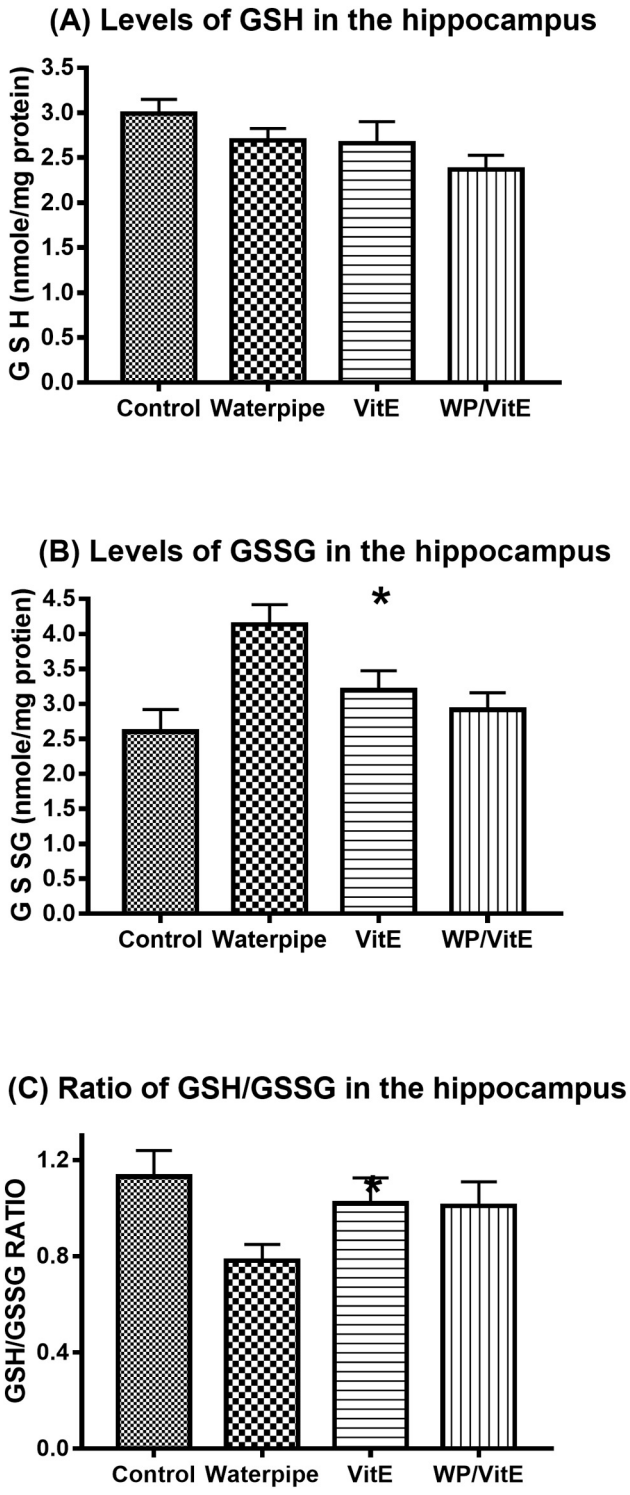


Fig. 4. Changes in glutathione levels in the hippocampus. Comparison of waterpipe smoking (WP), VitE (VitE), and waterpipe smoking with VitE groups (WP with VitE) with control. A: Level of GSH; B: Level of GSSG. C: Level of GSH/GSSG ratio. Each bar is the mean ± SEM. *Indicates significant difference from other groups, ($P < 0.05$; n = 10–12 rats/group).

important role in restoring antioxidant enzymes in the hippocampus of waterpipe smoke exposure groups, thus preventing short- and long-term memory impairment in these animals. Moreover, in the current study, we found that changes in the endogenous antioxidant enzymes and molecules of the hippocampus such as GPx, catalase, and GSSG and GSH/GSSG were prevented by administration of VitE in the waterpipe smoke group. Such effect might be attributed to the antioxidant properties of VitE, which worked as a free radical scavenger; therefore preventing memory impairment during exposure to waterpipe smoke. The findings of this study are consistent with other studies that examined the protective effect of VitE against harmful exposures. For instance, VitE administration prevented memory impairment induced by high-fat high-carbohydrate diet through normalizing antioxidant biomarkers [25]. Another study revealed that administration of VitE restored chronic sleep deprivation-induced memory impairment in rat model via normalizing hippocampus molecules including GSH/GSSG ratio and antioxidant enzymes such as catalase, GPx, and SOD [26]. Furthermore, VitE might improve cognitive and memory impairments in Alzheimer rat model by decreasing oxidative stress markers [62]. The current study showed that VitE did not enhance memory in rats with intact memory function. However, it protected memory during waterpipe smoke exposure. This finding agrees with other studies that emphasis the role of VitE as protecting but not as enhancing agent of memory function [26,63,64].

Previous studies have shown that exposure to tobacco smoke lowers circulatory VitE levels [65,66]. Thus, it is possible that levels of VitE are low in waterpipe group and VitE supplementations restored its normal level and the subsequent protection against memory impairments and prevention of changes in oxidative stress biomarkers. In the current study, hippocampal VitE levels were not evaluated and more investigations are required to test this assumption. In addition, current study showed that TBARS levels were not changed during chronic waterpipe smoking and/or chronic VitE administration. These findings indicated that lipid peroxidation was not affected by chronic smoke exposure. Previous studies revealed similarity to these findings. They showed that chronic waterpipe smoke exposure did not affect hippocampus lipid peroxidation [15,18,46], and lung lipid peroxidation [67]. On the other hand, another study revealed that lipid peroxidation in mice kidney showed significant elevation following chronic exposure to waterpipe smoke [13].

In conclusion, chronic exposure to waterpipe tobacco smoke induces short- and long- term memory impairments in rats. VitE, on the other hand, has protective effect against waterpipe-induced short-and long-term memory impairment memory impairment possibly through normalizing oxidative stress biomarkers and restoring antioxidant defense systems of the hippocampus.

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