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Effect of waterpipe tobacco smoke exposure during lactation on learning and memory of offspring rats: Role of oxidative stress

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ABSTRACT

Aims: The prevalence of waterpipe tobacco smoking is increasing among breastfeeding women. Herein, the effect of maternal waterpipe tobacco smoke (WTS) exposure during lactation on learning and memory of adult offspring rats was examined.

Main methods: Lactating rats received either fresh air or mainstream WTS (1 h twice daily) from day 4 to day 21. Learning and memory was examined by the radial arm water maze and the levels of brain derived neurotrophic factor (BDNF) and oxidative stress biomarkers superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase and thiobarbituric acid reactive substances (TBARS) were assessed in the hippocampus of adult male offspring rats.

Key findings: Maternal exposure to WTS during lactation impaired the long-term memory and reduced levels of BDNF ($P < 0.05$) in hippocampus in adult male offspring rats. The activity of SOD, GPx and catalase were reduced ($P < 0.05$) while level of TBARS was increased ($P < 0.05$).

Significance: Maternal WTS exposure during lactation impaired the long-term memory of adult male offspring that was associated with low levels of BDNF and altered oxidative stress balance. Therefore, careful measures should be taken to enhance waterpipe smoking cessation during breastfeeding.

1. Introduction

The number of smokers has increased worldwide. It reached 1.1 billion smokers, most of them in low- and middle- income countries as shown by WHO statistics [1]. The increased prevalence of smoking was also observed in women during pregnancy, as the estimated global prevalence of smoking during pregnancy was 1.7% [2]. The prevalence of smoking during pregnancy varies between countries and regions of the world [2]. Maternal exposure to tobacco smoke during pregnancy negatively influences the intellectual abilities in the adult offspring [3] and causes neurobehavioral and cognitive abnormalities [4]. For these reasons, several women quit tobacco smoking during pregnancy [5]. However, women who quit smoking during pregnancy usually relapses during the breastfeeding period [6,7].

Currently, there is a shift in the popularity of cigarette smoking as the several epidemiological studies revealed that waterpipe tobacco smoke (WTS) has already replaced cigarettes as a common form of tobacco use [8]. The prevalence of WTS consumption exceeded cigarette smoking in many countries. It was estimated that around 100 million people smoke WTS daily all around the world [9]. The popularity of WTS has been increased dramatically over the last years in several countries, especially among the youth population [10,11] and pregnant women [12,13].

Smoking during the breastfeeding period is very critical as the breastfed child is exposed to the harmful components of the cigarettes. Nicotine exposure during lactation reduced the level of the released prolactin [14] and hence the amount of milk produced by the mother is expected to be reduced [15]. Moreover, nicotine exposure induced brain damage of the breastfed child [16] as well as an altered infant sleep pattern [17]. Postnatal exposure to nicotine during lactation via breast milk upregulated the nicotinic receptors in the brain, similar to those found in adult smokers [18]. This exposure negatively affected the neuronal development and resulted in several detrimental long-term learning and memory deficits [18]. Further, nicotine exposure before breeding, during gestation and during lactation impaired working memory as well as attention in male mice [19]. However, the effect of maternal WTS exposure during lactation on learning and memory of offspring was not examined. Herein, we examined this effect

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for the first time. Moreover, the effect of maternal WTS exposure during lactation on oxidative stress major biomarkers and brain derived neurotrophic factor levels were investigated in the hippocampus of adult male offspring rats.

2. Materials and methods

2.1. Animals

Twenty-four adult male and female rats (9–10 weeks old) were purchased from the animal house of Jordan University of Science and Technology. The animals were kept at controlled temperature (25 ± 1 °C), 12 h light/dark cycle and free access to water and food. Mating was performed by placing one male and one female rat in the same cage overnight and pregnancy was checked by the presence of vaginal plug the next morning [20]. Once the vaginal plug was detected, it was considered as day zero of pregnancy. Females were monitored until delivery. After delivery, female rats were randomly assigned to receive either fresh air (control) or mainstream WTS (WTS). The exposure to WTS started on lactation day 4 and continued until day 21 since it is essentially important to keep the dams with the litters immediatley after birth [21]. Lactating rats were separated from the letters during the exposure period and the litters were kept in their cages under controlled temperature. All experimental approaches were approved by the Animal Care and Use Committee at Jordan University of Science and Technology. Further, all animal procedures were in accordance to the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

2.2. Mainstream waterpipe tobacco smoke (WTS) exposure

Female rats in the WTS group were exposed to mainstream waterpipe smoke for 1 h twice daily using whole body exposure system [20,22]. The system is composed of an exposure chamber, diaphragm pump to draw the smoke into the exposure chamber and a WTS apparatus. The apparatus is programmed to perform in accordance with Beirut Method where there were around 171 puffs of 2.6 s duration and 17 s inter-puffs duration. 10 g of Nakhla Double Apple tobacco were used in each exposure session. The level of carbon monoxide (CO) was monitored throughout the exposure period via CO analyzer (Monoxor II, Bacharach Inc.) to ensure that all animals were exposed to the same level of CO (1050 ± 100 ppm, mean ± SD).

2.3. The radial arm water maze (RAWM)

Due to the advantage of male rats in spatial memory, male offspring rats were used in RAWM [23]. Short- and long- term memory of adult male offspring rats (12 male rats from each group, 1 rat from each dam, 20 weeks old) were tested by RAWM as described previously [20,24]. In brief, one male adult offspring rats from each dam was used. The RAWM consisted of 6 stainless steel arms and a central black circular water-filled tube with a hidden platform located on the goal arm. The animals were allowed to swim in the water that was maintained at 24 ± 1 °C. Two pictures were kept on the walls of the experimental room that served as a cue for the animal. The animals must find the hidden platform in the goal arm that was not changed for a particular rat. The RAWM procedure was composed of a learning phase where animals were given six successive trials followed by 5 min rest then another six trials. Short-term memory was tested at 30 min while long-term memory was tested at 5 and 24 h after the end of the last trial of the learning phase. During the RAWM test, an error was counted for each animal if the rat entered an arm other than the goal arm during a 1-minute period.

2.4. Hippocampus dissection

The adult offspring rats were sacrificed by rapid decapitation [20,25]. The hippocampus was dissected and immersed immediately in liquid nitrogen until further analysis.

2.5. Measuring oxidative stress biomarkers and brain derived neurotrophic factor

The hippocampus was homogenized using Tissue Master-125 homogenizer (Omni International, Kennesaw, GA, USA) in lysis buffer that contained a protease inhibitor cocktail (Sigma–Aldrich Corp., MI, USA) [25]. The levels of thiobarbituric acid reactive substances (TBARS) (Cayman Chemical, MI, USA) and brain derived neurotrophic factor (BDNF) (R&D Systems, MN, USA) were measured following the kit's manufacturers' instructions. Moreover, the activity of anti-oxidant enzymes; superoxide dismutase (SOD) (Sigma–Aldrich Corp., MI, USA), glutathione peroxidase (GPX) (Sigma–Aldrich Corp., MI, USA) and catalase (Cayman Chemical, MI, USA) were measured accordingly. The TBARS, and BDNF levels, and oxidative stress enzyme activities were normalized to total protein in each sample. Total protein concentration was measured using a commercially available kit (BioRAD, Hercules, CA, USA). The used microplates were read at the specified wavelengths as per manufacturer instructions using an Epoch Biotek microplate reader (BioTek, Winooski, VT, USA).

2.6. Statistics

Data were presented as mean ± standard error means (SEM). Comparisons of the errors' numbers were analyzed utilizing repeated ANOVA; followed by Bonferroni post-test. Unpaired Student's t-test was used for two group comparisons. The analysis was performed using GraphPad Prism 5® software. $p < 0.05$ was considered statistically significant.

3. Results

3.1. The effects of WTS during lactation on learning and memory

Adult offspring rats for dams that were exposed to WTS during lactation were tested for learning as well as short- and long- term memories. All rats in both groups, control and WTS, learned the location of the hidden platform and there was no significant difference between the two groups ($P > 0.05$) in trials 1–12 as shown in Fig. 1.

The short-term memory that was tested at 30 min (0.25 ± 0.13 errors in the control group versus 1.33 ± 0.70 errors in WTS group, $P = 0.14$), and the long-term memory that was tested 5 h (0.33 ± 0.19 errors in the control group versus 0.58 ± 0.23 errors in WTS group, $p = 0.41$) after the last learning trial, did not show any alteration by WTS during lactation (Fig. 2A and B). However, offspring rats for dams that were exposed to WTS during lactation showed the significant higher number of errors tested at 24 h after the last learning trial as compared to unexposed ones (0.17 ± 0.11 errors in control group versus 1.25 ± 0.51 errors in WTS group, $p = 0.049$) (Fig. 2C).

3.2. The effect of WTS during lactation on BDNF levels in hippocampus tissues

The measured levels of BDNF in hippocampus tissues of offspring rats for dams that were exposed to WTS during lactation were significantly lower compared to unexposed rats (288.6 ± 38.33 ng/mg protein in the control group versus 145.7 ± 17.12 ng/mg protein in WTS group, $P < 0.05$) (Fig. 3).

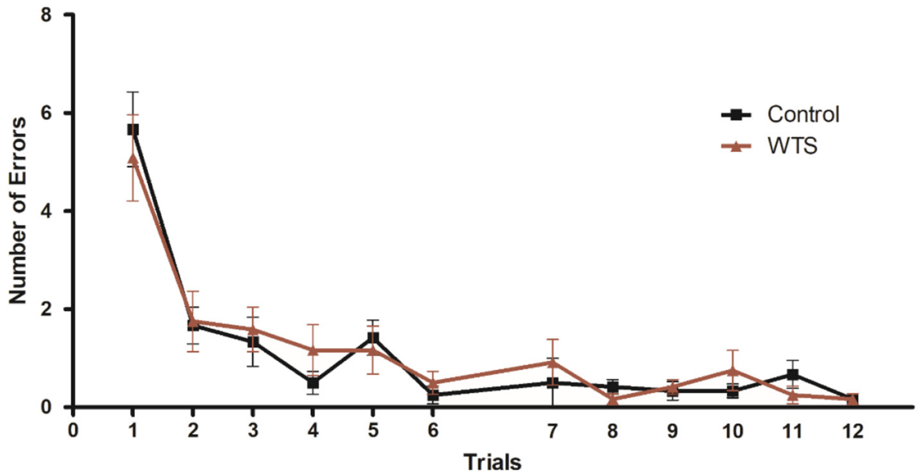

Fig. 1. Performance of adult offspring rats during learning phase of radial arm water maze. Offspring rats for dams that were exposed to fresh air (control) or WTS for 2 h per day (WTS) during lactation were tested for learning (n = 10–12). Each offspring rat was trained for 12 trials, each 6 was separated by 5 min rest phase. Performance of animals was recorded as the average number of errors in each trial. Values were expressed as mean ± SEM. $P < 0.05$ was considered significant.

3.3. The effects of WTS during lactation on oxidative stress biomarkers

The activity of antioxidant enzymes was analyzed in the hippocampus tissues. Exposure to WTS during lactation significantly reduced the activity of SOD (0.17 ± 0.02 units/mg protein in control group versus 0.10 ± 0.01 units/mg protein in WTS group, P < 0.05), catalase (2.35 ± 0.37 units/mg protein in control group versus 1.36 ± 0.18 units/mg protein in WTS group, P < 0.05), and GPx (21.03 ± 1.78 units/mg protein in the control group versus 7.10 ± 1.13 units/mg protein in WTS group, P < 0.05) compared to unexposed groups (Fig. 4A, B and C). Furthermore, the levels of TBARS were significantly higher in rats that were exposed to WTS during lactation compared to control (0.31 ± 0.04 μM/mg protein in control group versus 0.71 ± 0.19 μM/mg protein in WTS group, P < 0.05) (Fig. 4D).

4. Discussion

This study showed that maternal exposure to WTS during lactation resulted in impaired long-term memory that was associated with

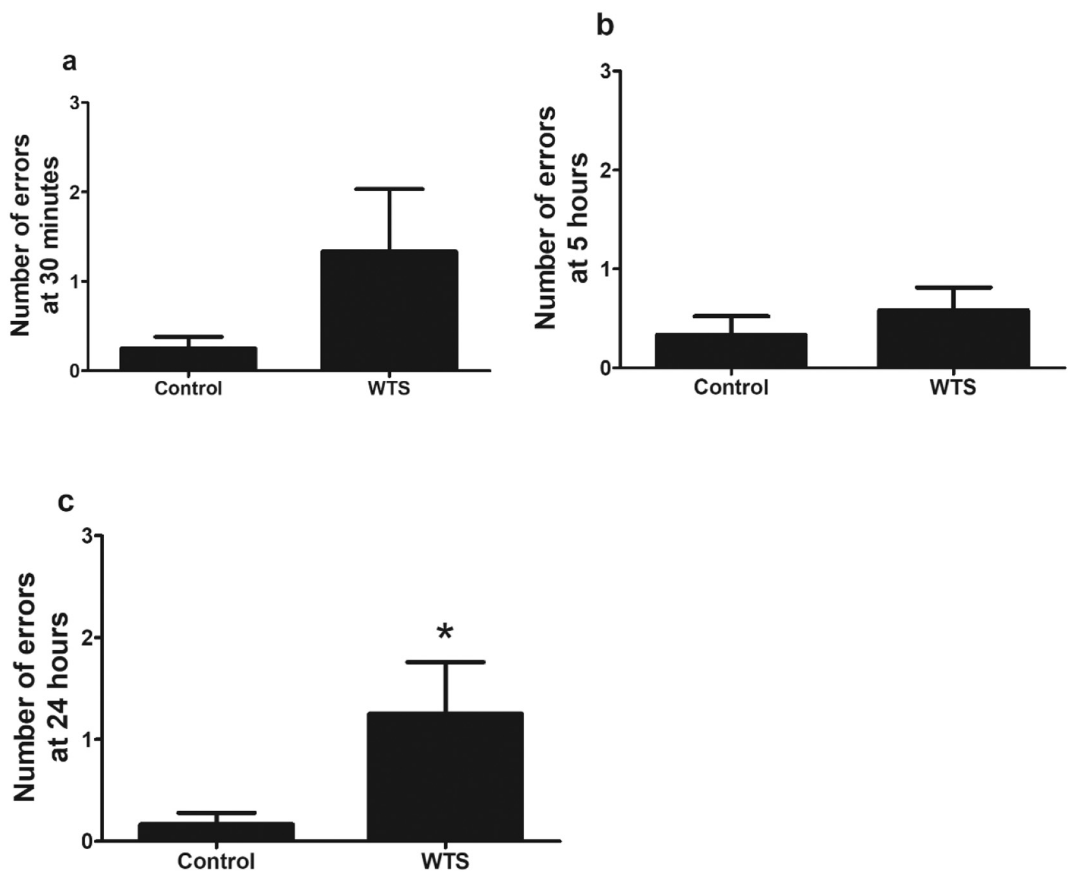

Fig. 2. Effect of WTS exposure during lactation on offspring's memory. Short-term memory test at 30 min (a), long-term memory tests at 5 h (b) and at 24 h (c), after the last trial of the learning trials. Offspring rats for dams that were exposed to fresh air (control) or WTS for 2 h per day (WTS) during lactation were tested for memory (n = 10–12). Performance of animals was recorded as the average number of errors in each memory test. * indicates significant difference from the control group. Values were expressed as mean ± SEM. P < 0.05 was considered significant.

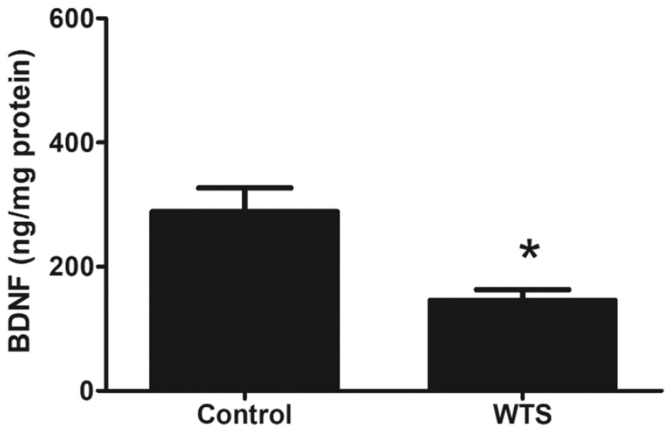

Fig. 3. Effect of WTS exposure during lactation on BDNF levels. Levels of BDNF were measured in offspring rats for dams that were exposed to fresh air (control) or WTS for 2 h per day (WTS) during lactation (n = 10–12). * indicates significant difference from the control group. Values were expressed as mean ± SEM. P < 0.05 was considered significant.

reduced levels of BDNF in hippocampus of adult male offspring rats. Moreover, it altered major oxidative stress capacity enzymes and increased the lipid peroxidation biomarker, TBARS, in adult male offspring rats.

The waterpipe was invented by Hakim AbulFath, an Indian physician, who adopted and promoted the misconception that the harmful effect of waterpipe is reduced as the tobacco smoke passed through the water [26]. The prevalence of WTS increased dramatically, even among pregnant and breastfeeding women. The exposure to WTS during pregnancy negatively affected the health status of offspring, as increased their susceptibility to develop asthma [27] and negatively influenced memory [20]. Waterpipe tobacco smoke contains several harmful components beside nicotine, such as heavy metals, tar [28], polycyclic aromatic hydrocarbons [29] and carbon monoxide [30].

This study revealed that exclusive exposure to WTS of mothers during lactation did not affect the hippocampus-dependent learning in adult offspring rats. This is consistent with active chronic WTS exposure [31] and prenatal WTS exposure during pregnancy [25] in rats. A previous study reported that maternal exposure to nicotine in the first 15 days of lactation resulted in impairment of long-term spatial memory in adolescent mice [32]. Consistent finding was observed in the current study where maternal WTS exposure during lactation, reduced long-term memory tested after 24 h. Short-term memory showed some increase in the number of errors as compared to unexposed animals but this increase was not significant. The majority of long-term memories require gene transcription and translation mediated by neuronal growth factors to synthesize new proteins, whereas short-term memories involve changes at the level of synapses [33]. For example, targeted mutations to cAMP-responsive element-binding protein (CREB), a transcription factor, impaired long-term memory in mice without affecting short-term memory [34]. In addition, changes in growth factors such as the prototype NGF and brain-derived neurotrophic factor (BDNF) have been implicated in long-term but not short-term cognitive functions [35,36].The differences observed in the findings of the current study could be exaplained by the different molecules and signaling pathways that are involved in short- versus long-term memories [37]. Therefore, examining different candidate signaling molecules by WTS will be of interest in future studies. The CNS develops during pregnancy and postnatal life. The hypothalamus, that plays a role in the higher functions of the brain as well as spatial memory, is developed during the first two weeks of postnatal life in

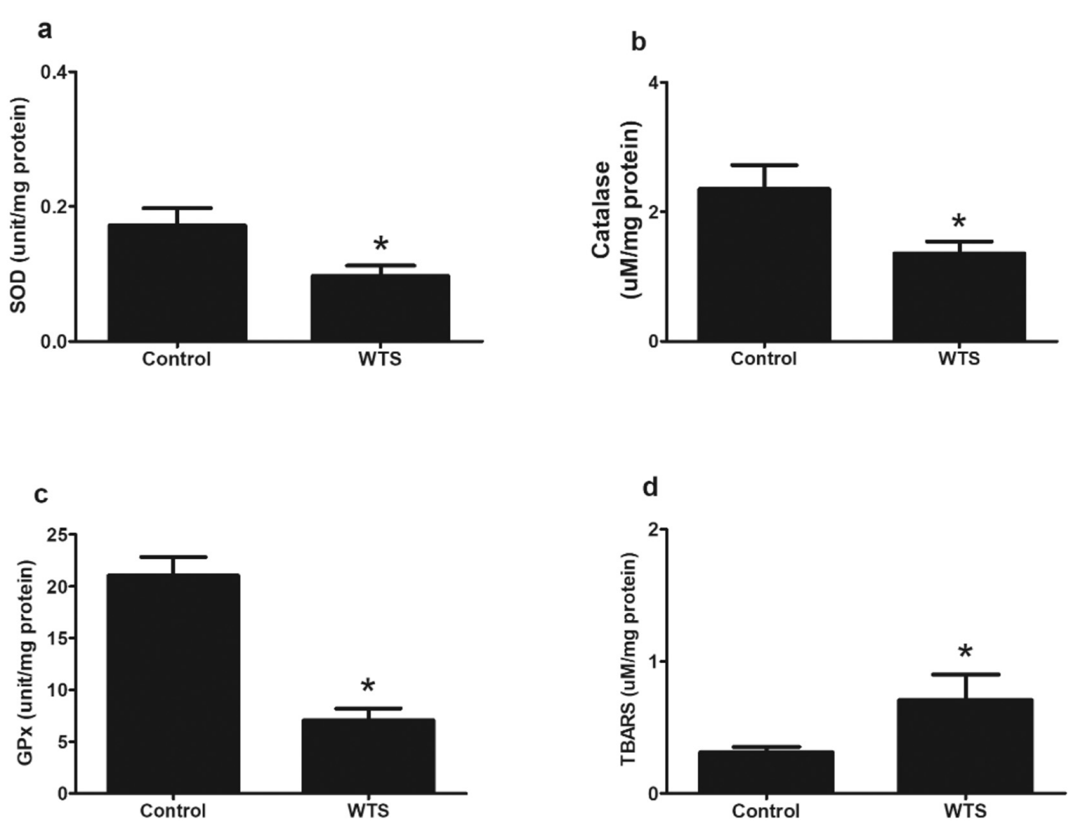

Fig. 4. Effect of WTS exposure during lactation on oxidative stress in hippocampus. The activity of (a) superoxide dismutase (SOD), (b) catalase, (c) glutathione peroxidase (GPx) and (d) level of TBARS was measured in offspring rats for dams that were exposed to fresh air (control) or WTS for 2 h per day (WTS) during lactation were tested for memory (n = 10–12). * indicates significant difference from the control group. Values were expressed as mean ± SEM. P < 0.05 was considered significant.

laboratory animals and during the first few years of life in human infant [38]. This could explain the negative effect of WTS on memory during this critical period as the dams were exposed to WTS from day 4 to day 21 of lactation. Acetylcholine plays an important role in memory [39]. Therefore, future works need to elucidate the involvement of acetylcholine in the determintal effects of WTS exposure. It has been shown that CO exposure to newborn impaired learning and memory [40]. Therefore, the noticed effect in the current study could be due to CO. Further studies are needed to examine the exact composition of WTS that resulted in memory impairment.

The BDNF, belongs to the neurotrophin family of growth factors, plays an important role in neurogenesis, neuronal regeneration [41], and synaptic plasticity [42]. The maternal exposure to WTS during lactation reduced the level of BDNF in adult male offspring rats. In consistence, prenatal WTS exposure during gestation also reduced hippocampal BDNF levels [20]. Lower levels of BDNF were shown to be involved in the pathogenesis of neurodegenerative disorders such as Huntington's disease [43] and neurodevelopmental and psychiatric conditions as schizophrenia [44]. Hence, it is expected that maternal exposure to WTS during breastfeeding increases the susceptibility of offspring to develop a variety of psychotic and neurodegenerative conditions. It is worth to mention that growth factors other than BDNF (i.e. nerve growth factors: NGF) are implicated in memory formation [45,46]. Changes in the expression of NGF have been reported to be associated with exposure to cigarette smoke [47–50]. Therefore, it is recommended in future studies to examine the involvement of other growth factors and neurotrophic factors such as nerve growth factor.

The exposure to WTS and cigarette smoke results in tissue inflammation and damage due to the release of a large amount of free radicals. Several reports examined the effect of nicotine in disturbing the oxidative balance. Nicotine exposure during lactation induced oxidative stress; it reduced the activity of SOD and catalase while it increased levels of malondialdehyde (MDA) in the liver and lung of lactating male offspring rats [51]. Further, Ozokutan and colleagues reported that lactating dams that were exposed to nicotine during the first 10 days of lactation showed decreased activity of SOD and catalase while MDA levels were increased in the liver of lactating offspring rats at the age of 10 days postnatal [52]. Offspring mice for dams that were exposed to nicotine, from day 12 of gestation to postnatal day 15, showed decreased activity of SOD and GSH as well as increased levels of MDA in the cerebrum [53]. Male offspring mice for dams that were exposed to cigarette smoke prior to mating, during gestation and lactation had lower levels of antioxidants, higher levels of mitochondrial activities and cell damage in the brain as compared to unexposed offspring [54]. Studies on WTS revealed consistent results, where there is an imbalance in the level of anti-oxidant enzymes. Previous studies revealed that chronic exposure to WTS reduced the ratio of GSH/GSSG, the activity of GPx and catalase [31,55] as well as SOD [31] in hippocampus. However, prenatal WTS did not affect the activity of anti-oxidant enzymes in hippocampus of adult male offspring rats [20]. Our results showed that WTS exposure via breast milk reduced the activities of SOD, catalase and GPx in the hippocampus of offspring rats. These reductions in the anti-oxidant capacity enzymes were associated with increased lipid byproduct of lipid peroxidation as manifested by increased TBARS levels in the hippocampus of offspring rats. In addition, it has been shown that early postnatal CO exposure increased oxidative stress in the brain of rats [56]. Future studies are recommended to examine the effect of each constituent of WTS on oxidative stress biomarkers. In addition, future studies are needed to elucidate the effect of WTS during lactation on activity of other antioxidant enzymes such as glutathione S-transferase-alpha as well as other oxidative stress biomarkers such as peroxynitrites and hydroxyl radicals among others.

A notable limitation of this study is the possibility that the effect of WTS on offspring rats could be in part due to licking the fur of dams that were exposed to WTS via whole body exposure system. However, it is well documented from human studies that milk of mother smokers contains smoke toxicants that can be transferred to their infants via breastfeeding. Therefore, contribution of licking the fur to the observed WTS effects is expected to be limited. Another limitation of the current study is the lack of analysis of the leading toxicants that resulted in the negative observed consequences.

5. Conclusions

In conclusion, the current study revealed the harmful consequences of maternal WTS exposure during lactation in impairing the long-term memory, reducing the level of BDNF, inducing oxidative stress in hippocampus of adult male offspring rats. Thus, careful strategies and legislation polices to enhance WTS cessation during breastfeeding are demanding.

Conflict of interests

The Authors declare that there is no conflict of interest.

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