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Research article

The beneficial effects of green tea on sleep deprivation-induced cognitive deficits in rats: the involvement of hippocampal antioxidant defense

Fatemeh Forouzanfar [a], Jamileh Gholami [a], Maryam Foroughnia [a], Bahareh Payvar [b], Saeideh Nemati [a], Mohammad Amin Khodadadegan [a], Mahsa Saheb [a], Vahid Hajali [a,b,*]

[a] Department of Neuroscience, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Quchan School of Nursing, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Background: The weight of evidence suggests that sleep is essential for the processes of memory consolidation and sleep deprivation (SD) impairs the retention of long-term memory in both humans and experimental animals, which is associated with oxidative stress damage within the brain. Green tea polyphenols have revealed carcinogenic, antioxidant, anti-, and anti-mutagenic properties. We aimed to investigate the possible protective effect of green tea extract (GTE) and its main active catechin, epigallocatechin-3-gallate (EGCG), on post-training total sleep deprivation (TSD) -induced spatial memory deficits and oxidative stress profile in the hippocampus of the rat.

Methods: Male rats were treated with saline, GTE (100 and 200 mg/kg/day), and EGCG (50 mg/kg/day) intraperitoneally for 21 days and then trained in Morris water maze (MWM) in a single day protocol. Immediately after the end of MWM training, animals were sleep deprived for 6 h by the gentle handling method, and then evaluated for spatial memory. Hippocampal levels of malondialdehyde, (MDA), and thiol was assessed as oxidant and antioxidant markers.

Results: Spatial memory was impaired in the TSD group and GTE at the dose of 200 mg/kg/day as well as EGCG at the dose of 50 mg/kg/day could reverse the impairment to the saline-treated levels. Despite the unchanged MDA levels, hippocampal total thiol was significantly decreased after TSD and EGCG increased it to the basal levels.

Conclusion: In conclusion, green tea and its main catechin, EGCG, could prevent memory impairments during 6 h of TSD; probably through normalizing the antioxidant thiol defense system which was impaired during TSD.

1. Introduction

Sleep plays a critical and complex role in multiple physiological processes that maintain and promote optimal functioning across many aspects of health and wellbeing. Prolonged sleep loss is a rising problem in modern societies and is a risk factor for a broad range of disorders, from psychological (Okun et al., 2018), neurological (Phua et al., 2017), and neurodegenerative diseases (Olsson et al., 2018) to metabolic and cardiovascular disorders (Joukar et al., 2013; Reutrakul and Van Cauter, 2018). The increased risk of car accidents, as well as increased damage risk among the shift workers, could be attributed to the cognitive deficits resulting from insufficient sleep (Geiger-Brown et al., 2012; Komada et al., 2013).

The weight of evidence suggests that sleep is essential for the processes of memory consolidation and sufficient sleep enhances retention of long-term memory in both humans and rodents (Klinzing et al., 2019). Preliminary experimental studies on sleep function hypothesized that sleep after training (post-training sleep) contributes to the consolidation of newly acquired information into long-term memory (Walker and Stickgold, 2004). This theory is more supported by the findings that the neuronal activity patterns displayed in waking are replayed, analyzed, and integrated into memory networks during subsequent sleep (Lee and Wilson, 2002). Consistent with this idea, a selective increase in rapid eye movement (REM) sleep has been detected following successful task acquisition (Datta, 2000). In addition, sleep deprivation (SD) at certain post-training time windows causes subsequent memory loss in both rodents (Havekes et al., 2012) and humans (Stickgold et al., 2000).

A variety of the cellular and molecular correlates of hippocampal synaptic plasticity are influenced by sleep deprivation (SD) (Kreutzmann et al., 2017). Growing evidence has confirmed that cognitive

* Corresponding author.
E-mail address: hajaliv@mums.ac.ir (V. Hajali).

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impairments resulting from SD are in part due to oxidative stress damages in the body (Atrooz and Salim, 2020). Particularly, the hippocampus is more susceptible to oxidative-induced damage than other parts in the brain (Wang and Michaelis, 2010).

Due to low cost, ease of administration, and low adverse effects, natural dietary components with potential antioxidant activity and other health benefits have received particular attention in various chronic conditions. The tea plant, *Camellia sinesis*, belongs to the Theaceae family, and green, black, and oolong teas as the popular beverage are produced from its leaves. Worldwide interest in green tea has grown because it is natural, non-toxic, and has putative preventive and therapeutic benefits for a wide range of health conditions (Farkhondeh et al., 2018; Saeed et al., 2017). Catechins, also referred to as flavanols are the main polyphenols found in tea. The major tea catechins are epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate (EGCG), with the last being highest in concentration and primarily responsible for the green tea effects (Bonoli et al., 2003). Green tea polyphenols have established significant anti-carcinogenic, anti--mutagenic and antioxidant properties in several human, animal, and *in vitro* studies (Saeed et al., 2017). The antioxidant capacity of EGCG, the major polyphenol in green tea, has been well established in a variety of experimental models (Saffar et al., 2020). It exerts both short and long-term antioxidant activity through various mechanisms (Biasibetti et al., 2013).

following simply drinking green tea, polyphenols can easily cross the blood-brain barrier and exhibit neuroprotective effects (Grabska-Kobylecka et al., 2020). Experimental and epidemiological evidence suggests that polyphenols, especially those derived from green tea, can ameliorate age-related cognitive decline, and show neuroprotective effects to Parkinson's disease, Alzheimer's disease, and cerebral ischemia-reperfusion (Farkhondeh et al., 2018). A prior epidemiological study suggested that green tea, both not caffeine or black tea drinking were associated with better cognitive performances (Noguchi-Shinohara et al., 2014). In the present study, we aimed to investigate the possible protective effect of green tea extract (GTE) and its main active catechin (EGCG) on post-training SD-induced spatial memory deficits and oxidative stress profile in the hippocampus of the rat.

2. Methods

2.1. Animals

All experimental processes and handling procedures on animals were based on the guidelines for the care and handling of laboratory animals and were approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.561). The number of animals, as well as their suffering, was minimized as much as possible. The experimental design is depicted in Figure 1. Male Wistar rats at the age of 7 weeks were obtained from the colony maintained by Mashhad Medical Collage Animal Facility. The animals were randomly allocated to one of the 6 experimental groups (n = 8 in each group): i) Saline: Rats treated with normal saline (4 ml) intraperitoneally (IP) for 3 weeks. ii) SD: Rats sleep deprived for 6 h using gentle handling method. iii) Green tea 200 (GT200): Rats received GTE (200 mg/kg/day) for 3 weeks IP. iv) Green tea 100 + SD (GT100 + SD): Rats received GTE (100 mg/kg/day) for 3 weeks IP and then sleep-deprived for 6 h after training in MWM. v) Green tea 200 + SD (GT200 + SD): Rats received GTE (200 mg/kg/day) for 3 weeks IP and then sleep-deprived for 6 h after training in MWM. vi) EGCG 50 + SD (EGCG50 + SD): Rats treated with EGCG (50 mg/kg/day) for 3 weeks IP and then sleep-deprived for 6 h after training in MWM. In all groups, behavioral tests were carried out at the age of 10 weeks. Once the end of the behavioral tests, rats were euthanized for hippocampal tissue dissection and further analysis (Figure 1). Animals were kept in groups of four in standard conditions. In all conditions, food and water were freely accessed and the animals were housed in a climate-controlled room (23 °C ± 1 °C) on a 12-h light-dark cycle (lights-on 06:00–18:00 h). All cages were cleaned once a week.

2.2. Plant and extract

Green tea contains polyphenols (~90%), amino acids (~7%), caffeine, theanine, and proanthocyanidins (~3%). Among the main polyphenols, catechins and flavonols are the major constituents. EGC, EGCG, and ECG, constitute 80% of the total catechins (Lee et al., 2014). EGCG is the most abundant catechin, accounting for 50–80% of the total catechins in green tea. It is also counted as the major factor in the various health benefits of green tea (Chu et al., 2017). Fresh tea leaves were collected from a local farm in the north of Iran. The leaves were powdered using a grinding machine. The obtained powder was percolated with ethanol 70% for 72 h. After filtering the extract, the solvent was allowed to evaporate at 40 °C under reduced pressure to acquire the crude extract. EGCG was purchased from Carbosynth Ltd, UK (CAS No: 989-51-5). Plant extract and EGCG were resuspended in sterile distilled water to make the desired concentrations.

2.3. Total sleep deprivation (TSD) by "gentle handling"

At the end of MWM acquisition blocks, rats were transferred to a quiet room and were sleep-deprived in their home cages for 6 h by gentle handling method beginning at about noon or left undisturbed (non-sleep-deprived rat). As the SD period was during the circadian phase of the rest of the animals (eg, 12-6 pm), the maximum sleep pressure was applied. The gentle handling consisted of keeping the animals awake by tapping on or moving the cage, and if necessary, by gently touching them with a soft brush whenever behavioral signs of sleep, such as sleep posture or closed eyes are detected. Food and water were accessible ad libitum throughout the entire period (Heckman et al., 2020).

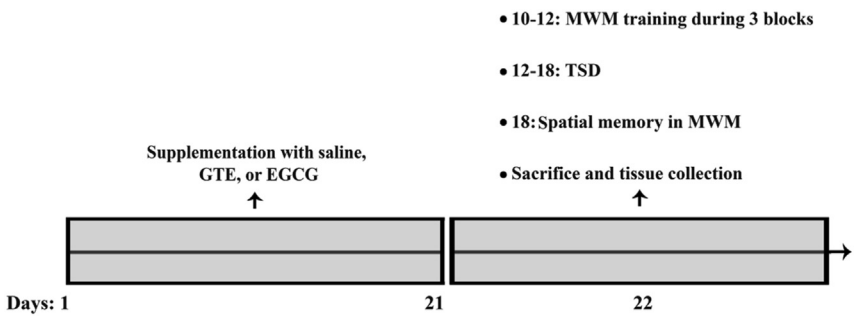

Figure 1. Experimental design. Animals were subjected to different treatments for 21 days. Following treatment, training in MWM, TSD, spatial memory in MWM, and hippocampal extraction were performed. GTE: green tea extract, EGCG: epigallocatechin-3-gallate, MWM: Morris water maze, TSD: total sleep deprivation. For further details see Sections Methods.

2.4. Spatial learning and memory in Morris water maze (MWM)

The MWM was a circular pool (80 cm height and 160 cm diameter) filled with water at 22–24 °C. The pool was theoretically divided into 4 quadrants with equal size and release points were marked in each quadrant as, 1, 2, 3, and 4. An invisible round platform was mounted 2 cm below the water surface at the midpoint of quadrant 3. The task was performed in a dim room in which the fixed geometric pictures (e.g., circles, squares, or triangles) were attached to the walls around the maze. A video tracking system (video tracking Borj Sanat Azma) recorded the animal performance automatically. A single-day version of MWM was used (Figure 1). During the acquisition phase, each subject completed three learning blocks separated by a 30-min rest interval. Each block included 4 sequential trials of 60 s duration and 3 inter-trial intervals (~30 s). In this protocol, animals become perfectly trained in nearly 2 h which is suitable for assessing the effects of some interventions, such as SD (Hajali et al., 2015). The five days version of the MWM task was not applicable for 6 h post-training SD. On each training trial, the animal was immersed into the pool from one of the four release points. The animal was allowed to find the invisible escape platform in 60 s (maximum time). Once the rat found the platform, it was allowed to stay there for 20 s and was then returned to its home cage before the next trial. Those rats that failed to catch the platform within 60 s were directed manually to the platform. The distance and time to find the platform was recorded as spatial learning. A single probe trial was performed 6 h after the last training trial to assess the spatial short-term memory in the MWM. In this trial, the animal was permitted to swim freely for 60 s without any platform. The percentage of distance and time expended in the target quadrant (quadrant 3) was recorded and considered as the spatial memory criteria. The behavioral experiments for all groups were accompanied through the same time of the lights-on phase.

2.5. Hippocampal oxidant, malondialdehyde, (MDA), and, antioxidant, (Thiol) assessment

Analysis of MDA, the most plentiful product originating from lipid peroxidation has been extensively considered as an index of oxidative stress. Thiol groups are the major members of the antioxidant network because they eliminate reactive oxygen species (ROS) and other free radicals through enzymatic and non-enzymatic machinery. Immediately after the end of the MWM task, the rats were euthanized under deep anesthesia by injecting ketamine and xylazine (100 mg/kg and 10 mg/kg) intraperitoneally. The animals' brain was rapidly removed and the hippocampus was dissected and stored at -80° until processed. The hippocampal MDA and total thiol contents were measured according to the previous methods (Rakhshandeh et al., 2021). Briefly, for the measurement of MDA, samples react with thiobarbituric acid (TBA) and provide a pink material that was indicated using a spectrophotometer. Total thiol content in the brain tissues was measured by the Ellman method. In this assay, DTNB (2,2′-dinitro-5,5′-dithiodibenzoic acid) reacts with the thiol groups to produce a yellow complex that has a peak absorbance at 412 nm.

2.6. Statistical analysis

All analysis of data collected in the oxidative stress measures, probe trials, and swimming speed were accomplished with one-way ANOVA monitored by Tukey's post hoc multiple comparison test. The distance and time to find the escape platform was analyzed using a two-way ANOVA with repeated measures (group and blocks as the factors) to test the differences in the learning ability between the groups. The values are stated as Means ± standard error of the mean (SEM), and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Spatial learning and memory in MWM

In the acquisition trials, all groups successfully were trained to find the platform as revealed by a gradual decrease in escape latency (Figure 2A) and distance moved (Figure 2B) within the successive blocks of training. There was no significant difference in distance traveled or escape latency among the four groups as analyzed by two-way repeated-measures analysis of ANOVA. Figure 2C shows the spatial memory performance in the single probe trial. One-way ANOVA revealed a significant difference in the percentage of the time, distance, or crossing in the

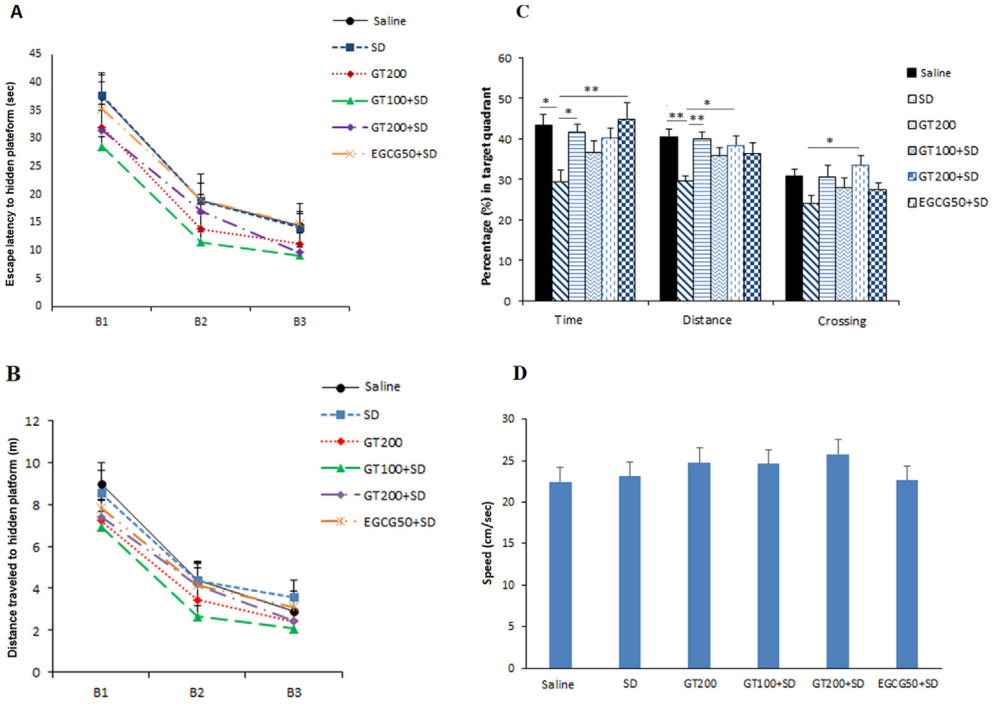

Figure 2. A, B, C, and D. (A and B) The spatial learning in the Morris water maze (MWM) test in saline, SD, GT200, GT100 + SD, GT200 + SD, and EGCG50 groups. Each block shows the mean latency (A) and distance traveled (B) of four consecutive trials to find the hidden platform. There were no significant differences in spatial learning ability among the groups. Data are shown as mean ± S.E.M. (two-way repeated measure ANOVA). (C) The spatial memory in MWM as shown by the percentage of the time, distance, and crossing over the target quadrant. *P < 0.05 and **P < 0.01. (D) The swimming speed in MWM. Data are shown as mean ± S.E.M. (one-way ANOVA followed by Tukey test). GT: green tea extract, SD: sleep deprivation, EGCG: epigallocatechin-3-gallate. 50, 100, and 200 mg/kg.

target quadrant (Q3) between the groups ($F_{(5,41)} = 4.226$, $P = 0.003$ for the time, $F_{(5,41)} = 4.287$, $P = 0.003$, for distance, and $F_{(5,41)} = 2.321$, $P = 0.060$ for the crossing). Pairwise comparisons showed that SD animals had lower time ($P < 0.05$, 0.05, and 0.01 vs saline, GT200, and EGCG50 + SD respectively), distance ($P < 0.01$, 0.01, and 0.05 vs saline, GT200, and GT200 + SD respectively), and crossing ($P < 0.05$ vs GT200 + SD) in the target quadrant. No significant difference was found in swimming speed among the six experimental groups (Figure 2D).

3.2. Hippocampal MDA and Thiol analysis

The results of the MDA and Thiol levels in hippocampal tissue are depicted in Figure 3 A and B. The MDA levels showed no significant differences between the groups ($F_{(5,30)} = 1.049$, $P = 0.408$, Figure 3 A). One-way ANOVA revealed a significant difference in hippocampal Thiol concentration between the groups ($F_{(5,28)} = 4.808$, $P = 0.003$, Figure 3 B). Multiple comparisons showed that Thiol levels were significantly decreased in the SD ($P < 0.05$ vs saline and EGCG50 + SD) and GT100 + SD ($P < 0.05$ vs EGCG50 + SD) groups.

4. Discussion

Based on previous evidence reporting the benefits of green tea catechins in cognitive deficit situations in humans and a variety of experimental models, we aimed to investigate the possible protective effect of different doses of GTE and EGCG, its main active catechin, on post-training SD-induced spatial memory alterations and oxidative stress status in the hippocampus of the rat. We found that 6-h SD significantly impaired spatial memory performance in MWM and both a high dose (200 mg/kg) of mixed GTE as well as its pure compound, EGCG, were effective to reverse the impairments. Analysis of oxidant and antioxidant biomarkers within the hippocampus (eg, MDA and thiol, respectively) revealed that while MDA changes were not significant in SD untreated or SD treated groups, thiol levels were significantly decreased in SD animals and EGCG administration could revers it to the control levels.

The adverse consequences of sleep loss on cognitive performance in experimental models have been recorded regardless of the method used for SD. It has been hypothesized that both stages of sleep (eg, REM and non-REM) are necessary for memory processing, with non-REM sleep being more important for the early processing, and REM sleep being more critical to the last stages of consolidation (Ambrosini and Giuditta, 2001). Additionally, as SD in humans does not occur selectively in either stage, TSD is a more translatable model to the human condition to evaluate the behavioral and biochemical alterations during SD situations. Therefore, we aimed our study at the prevention of total sleep and the application of a method to produce TSD.

Considerable evidence has reached the consensus that there is a fundamental relationship between sleep and cognitive processing. While both pre-and post-training sleep is believed to be essential for memory consolidation, early studies designed to examine the effect of post-learning sleep within the specific time windows on learning and memory. Overall, old and new studies suggest that sleep from 3 to 6 h immediately after a training task is critical for the consolidation of hippocampal-dependent new memories to long-term memories (Graves et al., 2003; Karabulut et al., 2019; Prince et al., 2014). Smith and Rose (1997) reported an increase in the REM sleep after the training in the MWM task and they noticed that postponing the REM sleep for the first 4-h following training impairs memory. These observations are further supported by the demonstration that the patterns of activity-related neuronal discharge are repeated during subsequent sleep, confirming the notion that memory track reactivation and consolidation may happen during sleep (Lee and Wilson, 2002). Accordingly, the present study showed that 6 h SD immediately after training disrupted the spatial memory as showed by a decrease in time and distance spent in the target quadrant in MWM. The learning trials were achieved successfully, but equally by all groups in the acquisition blocks. Given this, and since the swimming speed was not different among the groups, it could be postulated that the observed impairments in memory function may not be due to confounding factors such as individual differences in sensorimotor integration or motivation of the animals.

Along with the well-established findings of responsible mechanisms for SD-induced cognitive impairments such as alterations in cellular and molecular signaling correlated to the hippocampal synaptic plasticity (Eide et al., 2021), oxidative stress contribution has also attracted attention. The oxidant-antioxidant balance is a critical mechanism for maintaining homeostasis in an organism. Reactive oxygen and nitrogen species (RONS, eg, O_2^-, H_2O_2, and, NO) are highly reactive molecules with unpaired electrons, developed as a result of several metabolic and physiological processes. Oxidative stress occurs once the weight of pro-oxidants exceeds the antioxidant capacity of the body, leading to deleterious effects on lipids, proteins, DNA, and RNA (Betteridge, 2000). These changes could, in turn, result in the peroxidation of unsaturated fatty acids of plasma membranes, enzyme inactivation, and oxidation of sulfhydryl groups, as seen in aged conditions and neurodegenerative diseases (Singh et al., 2019).

Oxidative stress has been attributed to cognitive defects in several health conditions such as aging (Liguori et al., 2018), Alzheimer's disease (Singh et al., 2019), and post-traumatic stress disorder (Alzoubi et al., 2018a). Sleep is believed to limit metabolic demands. Thus, SD can lead to increased metabolic rate and, consequently, increased oxidative stress production (Atrooz and Salim, 2020). SD in rats has elevated oxidative stress by diminishing the levels of antioxidant enzymes, superoxide dismutase (SOD), and glutathione peroxidase (GPx), and increasing the content of oxidant marker, MDA, in the hippocampus (Alzoubi et al., 2018b; Wang et al., 2018). Elevations in hippocampal oxidative stress through enhancing glutathione disulfide (GSSG) and MDA levels, increasing glutathione disulfide/glutathione (GSSG/GSH) ratio, decreasing GSH/GSSG ratio, and diminishing catalase and glutathione

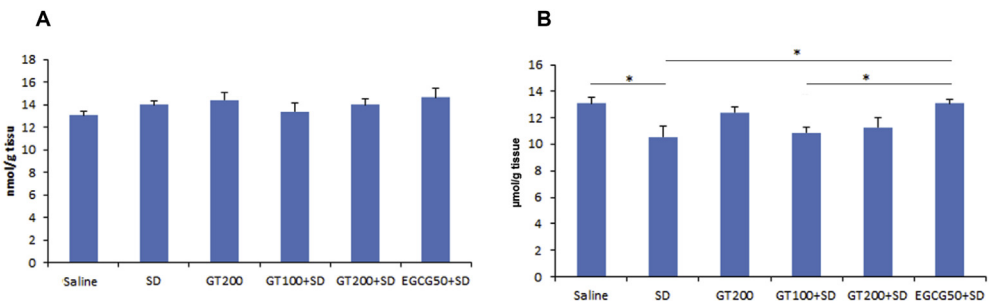

Figure 3. A and B. The hippocampal levels of malondialdehyde (MDA) (A) and thiol (B) in saline, SD, GT200, GT100 + SD, GT200 + SD, and EGCG50 groups. MDA levels were not different, but thiol levels were decreased in the SD group and EGCG 50 reversed it to the normal levels. *$P < 0.05$. Data are shown as mean ± S.E.M. (one-way ANOVA followed by Tukey test). GT: green tea extract, SD: sleep deprivation, EGCG: epigallocatechin-3-gallate. 50, 100, and 200 mg/kg.

peroxidase (GPx) activity have also been reported after SD (Alzoubi et al., 2012, 2013; Silva et al., 2004).

Our data, however, failed to detect a significant elevation in hippocampal MDA levels following 6 h SD. In accordance, few studies reported that SD may not cause oxidative damage for the brain or peripheral tissues. Gopalakrishnan et al. (2004), found no sign of oxidative damage at the protein or lipid levels in SD animals, neither in the brain nor in the peripheral tissues, suggesting that continuous periods of wakefulness do not lead to an additional oxidative challenge. The results from another study also suggest that SD per se is not connected to the oxidative damage within the brain (D'Almeida et al., 1997). The discrepancy of results might be due to the variation in methods applied for SD, the duration of SD, the animal strains used, or the region of the brain assessed for the effect of SD on oxidative stress status. The difference in duration of SD and the brain region explored seems to be more pronounced. Indeed, some studies suggest that while prolonged SD can elevate the oxidative stress markers or diminish the antioxidant capacity in the brain or peripheral tissues, acute or short-term (6 or 24 h) SD in rats seems to enhance the antioxidant capacity of the brain by reducing the lipid peroxidation in the hippocampus or increasing the GPx activity, GSH, glyoxalase (GLO-1), and glutathione reductase (GSR-1) levels within the various areas of the brain (Melgarejo-Gutiérrez et al., 2013; Ramanathan et al., 2010; Vollert et al., 2011).

Despite the insignificant increase in MDA levels, hippocampal total thiol was significantly decreased after SD in the present study. The term“thiol’’ is used for compounds containing sulfur. Thiol groups are the main members of the antioxidant network because they eliminate ROS and other free radicals by enzymatic and non-enzymatic machinery. The level of total thiol is considered as an index of excess free radical generation in both physiological and pathological contexts (Cadenas, 1989). The decreased thiol/disulfide levels for example have recently attracted attention as a biomarker of obstructive sleep apnea which leads to the oxidative stress imbalance and formation of reactive oxygen species in patients (Sengoren Dikis et al., 2021).

As mentioned above, oxidative stress occurs whenever oxidant production is increased or antioxidant defenses are decreased, or both. Therefore, impaired antioxidant defense as revealed by diminished hippocampal total thiol in our study can be a reasonable explanation for the memory impairment in sleep-deprived rats. Both clinical and preclinical studies have strongly shown that memory impairments are associated with an oxidant-antioxidant imbalance in many situations (Liguori et al., 2018; Singh et al., 2019). Human studies have shown that subjects with low-antioxidant conditions are more vulnerable to cognitive loss and dementia than cases with higher-antioxidant conditions (Zheng et al., 2018).

Current data indicated that pretreatment with a high dose of GTE as well as with EGCG could protect the animals from impairing effects of SD on memory function. Green tea is a potent antioxidant that prevents the propagation of free radical reactions and inhibits oxidative stress (Lambert and Elias, 2010). As the EGCG could normalize the hippocampal thiol levels that were reduced during SD, it seems that the antioxidant potency of green tea may have a role. The same conclusion has been drawn by other studies. Supplementation with whole GTE has restored cognitive impairments in a variety of experimental models including aged (Li et al., 2009), maternal deprived (Menezes et al., 2017), and stroke (Altermann et al., 2017) animals as well as, scopolamine (Bae et al., 2020), ethanol (Zhang et al., 2018), and beta-amyloid (Haque et al., 2008) -treated models. Among the different polyphenolic ingredients of green tea, EGCG has appealed the most attention. In reserpine-induced cognitive impairment in rats, treatment with EGCG at the dose of 100 mg/kg for one week significantly improved memory impairment (Chen et al., 2016). In the experimentally induced Parkinson's disease, animals that received EGCG (10 mg/kg) for 2 weeks exhibited better memory and locomotors function in comparison to the vehicle-treated group (Bitu Pinto et al., 2015). Biasibetti et al. sowed that orally administered EGCG for 4 weeks was able to completely reverse the cognitive deficit in MWM, acetylcholinesterase activity, glutathione peroxidase activity ROS, and, NO metabolites in a streptozotocin-induced model of dementia confirming the neuroprotective capacity of this compound (Biasibetti et al., 2013). In the case of beta-amyloid pathology, two other studies have also confirmed the beneficial effect of orally or intraperitoneal injection of EGCG on memory deficits and hippocampal beta-amyloid deposition in the mutant mice (Rezai-Zadeh et al., 2005, 2008).

Human studies have also addressed the benefits of green tea consumption for cognitive functions (Ide and Yamada, 2015). A follow-up survey in Japanese residents aged >60 years concluded that consumption of green tea every day is associated with a reduced risk of cognitive decline (Noguchi-Shinohara et al., 2014). Of interest, no association was revealed between black tea or coffee consumption and the incidence of overall cognitive decline in this study (Noguchi-Shinohara et al., 2014). Administration of a milk-based soft drink containing GTE (13.75 or 27.5 g) enhanced parieto-frontal connectivity during working memory which was apparent from functional magnetic resonance imaging (fMRI) (Schmidt et al., 2014). The majority of these studies have associated the neuroprotective effects of GTE or EGCG with the antioxidant potency of this beverage (Altermann et al., 2017; Bitu Pinto et al., 2015; Haque et al., 2008; Menezes et al., 2017).

To our knowledge, there is only one recent study devoted to evaluate the effect of green tea administration on memory deficits in sleep-deprived rats (Nayak et al., 2019). In this study, 20 mg/kg of GTE was given orally one hour (acute) and 8 weeks (chronic) before the memory test in 96 h REM-sleep-deprived rats. Acute dosing of GTE post-SD failed to positively affect memory impairment, but chronic uptake before SD could modulate cognitive impairments as well as oxidative stress in SD animals. The data of chronic dosing is consistent with our findings, confirming the involvement of oxidative stress status for benefits of green tea in memory deficits in sleep loss conditions. Results of our study show that since green tea preserved memory and anti-oxidant profile during SD, it was not effective in the normal sleep group. This is in agreement with previous studies, suggesting that green tea seems to be a memory protective, but not enhancing element.

Assumed mechanisms that link oxidative stress with cognitive impairment induced by SD are not well understood. Some oxidative stress-responsive signaling molecules such as CAMKIV and CREB could be the case. It has been reported that oxidative stress is associated with reduced levels of phosphorylated CREB and CAMKIV (Salim et al., 2011), which are the core signaling molecules for memory formation (Asok et al., 2019). The central nervous system is particularly susceptible to oxidative stress because of relatively low levels of antioxidants and high levels of transition metals in the brain (Wang and Michaelis, 2010). Therefore, the detrimental effects of increased oxidative stress on memory functions during SD may be mediated by suppression of signaling molecules essential for memory possessing such as CREB and CaMKIV. Green tea polyphenols with antioxidant properties could protect memory performance by preventing this sequence of events during SD.

In conclusion, green tea and its main catechin, EGCG, could prevent memory impairments during 6 h of TSD; probably through normalizing the antioxidant thiol defense system which was impaired during SD.

Declarations

Author contribution statement

Fatemeh Forouzanfar: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Jamileh Gholami, Maryam Foroughnia, Saeideh Nemati, Mohammad Amin Khodadadegan, Mahsa Saheb: Performed the experiments.

Bahareh Payvar: Analyzed and interpreted the data.

Vahid Hajali: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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