Tea polyphenols protect learning and memory in sleep-deprived mice by promoting AMPA receptor internalization

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Chronic sleep loss caused lots of health problems, also including cognition impairment. Tea is one of the most popular drinks when people stay up late. Nevertheless, the effects of tea on sleep deprivation-induced cognition impairment are still unclear. In the present study, we found 24-h sleep deprivation (S-DEP) increased membrane \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxa-zole-propionate (AMPA) receptor level through a tumor necrosis factor \(\alpha\) (TNF\(\alpha\))-dependent pathway in hippocampi. Blocking elevated TNF\(\alpha\) level can protect S-DEP mice from impaired learning ability according to behavioral test. Tea polyphenols, major active compounds in green tea, suppressed TNF\(\alpha\) production through downregulating TNF\(\alpha\) converting enzyme (TACE) level. Meanwhile, tea polyphenols treatment could ameliorate recognition impairment and anxiety-like behaviors in S-DEP mice. The aforementioned results demonstrate cognition protective effects of tea polyphenols in S-DEP mice model, which provide a theoretical basis for the treatments of S-DEP-induced cognition impairment by targeting the TACE/TNF\(\alpha\)/AMPA pathway. 

NeuroReport 2020, 31:857–864

Keywords: cognition, sleep deprivation, tumor necrosis factor \(\alpha\), tea polyphenols

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Received 4 February 2020 Accepted 8 April 2020

Introduction

Chronic sleep loss is a widespread problem in human society [1]. Insufficient sleep is associated with chronic problems such as heart disease, kidney disease, high blood pressure, diabetes, obesity, and mental illness [2]. As sleep is critical for learning and memory, sleep deprivation (S-DEP) is detrimental to learning, brain maturation, and waking consciousness [3,4]. The association between S-DEP and memory impairment remains unclear. Inflammation may play a crucial role in the relationship between sleep and cognition [5]. S-DEP impairs physiological and behavioral development through the upregulation of some inflammatory cytokines, such as tumor necrosis factor \(\alpha\) (TNF\(\alpha\)) [6,7]. S-DEP increases TNF\(\alpha\) mRNA in the somatosensory cortex, frontal cortex, and basal forebrain [8]. However, the role of TNF\(\alpha\) upregulation in S-DEP-induced cognitive impairment remains unclarified.

During sleep, synapses undergo widespread alterations in composition as well as signaling capacity, including weakening via the removal and dephosphorylation of synaptic \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxa-zole-propionate (AMPA) receptors [9]. The axon–spine interface decreased ~18% following sleep, compared with that during wake [10]. Homeostatic scaling-down of synaptic activities, which prepares synapses for new learning tasks, is a physiological function of sleep that relates to learning and memory. TNF\(\alpha\), a member of the type II transmembrane protein superfamily, is expressed in its full-length membrane-bound form (mTNF\(\alpha\)), which is cleaved by the TNF\(\alpha\) converting enzyme (TACE) to release the soluble peptide form of TNF\(\alpha\) (sTNF\(\alpha\)) [11]. TNFRI may bind to either soluble TNF\(\alpha\) or transmembrane TNF\(\alpha\) but preferably binds to soluble TNF\(\alpha\), where activated TNFRI triggers a complex apoptotic pathway [12]. In contrast, TNFR2 is preferentially activated by transmembrane TNF\(\alpha\) and protects neurons against excitotoxicity [13]. In central nervous system (CNS), TNFR1 activation is associated with AMPA receptor trafficking, excitability, and seizure susceptibility. TNF\(\alpha\) also plays a role in synaptic scaling up and cognitive development [14]. Numerous studies have indicated that S-DEP elevates TNF\(\alpha\) levels in mice. However, the association between elevated TNF\(\alpha\) levels and cognitive impairment remains unclear.
Reportedly, TNFα induces synapse scaling by promoting the insertion of AMPA into the membrane. Thus, the current study investigated whether elevated TNFα levels in S-DEP brain contributed to cognitive impairment by interfering AMPA phosphorylation.

Green tea, produced from the leaves of the plant *Camellia sinensis*, is one of the most widely consumed beverages in the world [15]. Tea polyphenols are natural products in green tea, which exhibit anti-oxidative, and anti-apoptotic effects. It has been shown that glutamate excitotoxicity induced oxidative stress is linked to neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease. Tea polyphenols have also been reported to suppress the production of TNFα in the peripheral system [16,17]. Above all, dietary polyphenols promote resilience against sleep deprivation-induced cognitive impairment by activating protein translation [18]. Therefore, we wonder if tea polyphenols could ameliorate S-DEP induced cognition impairments.

**Materials and methods**

**Animals**
The protocols for experiments conducted using animals during this study were approved by the national legislation of China and local guidelines. Eight- to ten-week-old C57BL/6J male mice from Jackson laboratory were used in the experiments. Mice were obtained from the Laboratory Animal Center of the Fourth Military Medical University. The animals were housed in groups of four in plastic boxes containing food and water, in a colony room under the following controlled conditions: temperature, 24 ± 2°C; humidity, 50–60%; luminous intensity, 100 lx; and light cycle, 8:00 a.m. to 8:00 p.m. Mice were allowed to adapt to laboratory conditions for at least 1 week before the procedure. All behavioral tests were performed between 9 and 12 a.m. on the designated day of the experiment.

**Drug treatments**
Thalidomide (Selleck Chemicals, Houston, TX, USA catalog S1193, 25 mg/kg), TAPI-0 (TNF-α Protease Inhibitor-0, Santa Cruz Biotechnology, Santa Cruz, CA, USA catalog sc-203410, 1 mg/kg) or tea polyphenols (Abcam, Cambridge, UK, catalog ab141940, 25 mg/kg) were intraperitoneally injected two times, once 24 h before S-DEP and once 30 min before S-DEP. Equal volume of saline was injected as control. Purity of tea polyphenols, determined by high-performance liquid chromatography, was over 95%. Tea polyphenols comprise four major epicatechin derivatives; epicatechin [8], epigallocatechin, epicatechin gallate, and epigallocatechin gallate.

**Induction of S-DEP**
S-DEP was induced as described previously [19]. Briefly, mice were placed on platforms (2.5 cm in diameter), hovering 1 cm above the water surface, in a water-filled tank with 12 platforms. The platforms were spaced at a distance of 5 cm from each other so that mice could move freely from one platform to another. The mice had free access to water and food. When animals entered the rapid eye movement (REM) phase of sleep, they fell into the water due to muscle atony and the small platform size and were forced to awaken. The duration of REM deprivation (24 h) was determined on the basis of previous studies, in which mice deprived of REM for this period of time exhibited memory deficits in shuttle box tasks. During the sleep deprivation period (24 h), the temperature (23 ± 1°C) and light/dark cycle were both maintained under controlled conditions. This method resulted in a 95% deprivation of REM sleep and effectively decreased the time spent in slow-wave sleep by 31% [20]. Control group mice were not subjected to S-DEP and were housed in their home cages.

**Western blot analysis**
Western blot analysis was performed as described previously [21]. Following sleep deprivation, mice were exposed to isoflurane vapors for <1 min and rapidly decapitated. Each brain was carefully removed and immediately placed on ice (<2 min relative to initial handling). The hippocampi were removed with micro scissors, frozen in liquid nitrogen, and stored at −80°C until further analysis. These frozen hippocampi were homogenized via ultrasonication in ice-cold radio-immunoprecipitation assay (RIPA) lysis buffer. The homogenate was separated via centrifugation at 14 000g for 15 min, and the supernatant containing total cellular proteins was collected. The protein concentration was determined using a microplate BCA protein assay kit (Pierce Biotechnology, Rockford, IL, USA), following which the samples were subjected to western blotting analysis. Equal amounts of protein (50 μg) from hippocampi were separated and electrophoretic transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, Massachusetts, USA), and probed with antibodies against GluA1 (dilution ratio, 1:1000, Abcam), p-GluA1ser845 (dilution ratio, 1:1000, Cell Signaling Technology, USA), p-GluA1ser831 (dilution ratio, 1:1000, Abcam), p-β-actin (dilution ratio, 1:1000, Cell Signaling Technology), TNFα (dilution ratio, 1:1000, Cell Signaling Technology), and TACE (dilution ratio, 1:1000, Cell Signaling Technology) and β-actin (dilution ratio, 1:10000, Sigma, St. Louis, Missouri, USA) as the loading control. For data quantification purposes, the band intensity of each blot was calculated as a ratio, relative to that of β-actin. The intensity ratio of the control group was set at 100%, and the intensities of other treatment groups were expressed as percentages of those of the control group. The membranes were incubated with horseradish peroxidase-conjugated secondary antibodies (anti-rabbit/anti-mouse IgG for the primary antibodies), and blots were developed using either standard or enhanced chemiluminescence detection (Millipore or Genshare Biological, Xi’an, Shaanxi, China) and imaged using a Tanon imaging system (Tanon 4200, Shanghai, China).
Surface biotinylation assay

For membrane GluA1 evaluation, after S-DEP, mice were sacrificed immediately and hippocampi were dissected. Surface GluA1 receptors were extracted following the guidelines of the Pierce Cell Surface Protein Isolation Kit (Thermo Fisher, Catalog 89881, Waltham, MA, USA). Briefly, hippocampi were washed with ice-cold PBS and transferred to a 2-mL tissue grinder and cut into small pieces with a pair of scissors. Tissues were reconstituted in 4 mL of biotin solution. The mixture was agitated for 30 min at 4°C, the labeling reaction halted with 200 μL of quenching solution, and the tissues washed two times with tris-buffered saline. The cells were resuspended in 500 μL of lysis buffer and lysed by sonication on ice. The resultant cell lysate was centrifuged at 10,000g for 2 min at 4°C and the clarified supernatant used for the subsequent affinity purification. Neutravidin agarose slurry (500 μL) was added to a snap cap spin column (Thermo Scientific, Rockford, Illinois, USA), washed three times with wash buffer, and incubated with the clarified cell lysate for 60 min at room temperature with end-over-end mixing. After centrifugation at 1000g for 1 min, the flow-through was discarded, and the beads washed three times with wash buffer. Proteins were eluted with 400 μL of SDS-PAGE sample buffer containing 50 mM dithiothreitol to cleave the disulfide bridge in the biotin label. Remove the column’s top cap first and then the bottom cap. Place column in a new collection tube and replace top cap. Centrifuge column for 2 min at 1000g. Add a trace amount of bromophenol blue to eluate and analyze by Western blot. Store sample at −20°C if not used immediately.

Shuttle box avoidance learning

The conditional stimulus in the shuttle-box apparatus was applied in the form of light from an electric bulb, while the unconditional stimulus was applied using an electric shock of 0.2 mA delivered to the paws of the mice through the grid floor of the apparatus. One hundred trials were performed, with a mean inter-trial interval of 60 s. Learning ability was evaluated by recording the frequency of successful avoidance of foot shock, by mice, using a software program (Shanghai Jiliang Software Technology Co LTD, Shanghai, China).

Open-field test

The open-field test was conducted as described previously [22]. The test was carried out in a square arena (30 cm × 30 cm × 30 cm) made of clear plexiglass walls and flooring, which was placed inside an isolation chamber with dim illumination and a fan. Mice were placed in the center of the box and allowed to freely explore the surroundings for 15 min. Mice were videotaped using a camera fixed above the floor and analyzed via a video-tracking system (Shanghai Jiliang Software Technology Co LTD).

Elevated plus maze

The elevated plus maze (EPM) was constructed as described previously [23]. The apparatus (Dig Behv-EPMG, Shanghai Jiliang, China) comprised of two open arms (25 cm × 8 cm × 0.5 cm) and two closed arms (25 cm × 8 cm × 12 cm) that extended from a common central platform (8 cm × 8 cm). The apparatus was elevated to a height of 50 cm above floor level. For each test, an individual animal was placed in the center square, facing an open arm, and allowed to move freely for 5 min. Mice were videotaped using a camera fixed above the maze and analyzed via a video-tracking system. Entry was defined as all four paws placed inside an arm. The number of entries and time spent in each arm were recorded.

Statistical analysis

Statistical analysis was conducted by GraphPad Prism version 7.0 (GraphPad Software, Inc., La Jolla, California, USA). Data were gathered from at least three independent experiments and were presented as mean ± SEM. Statistical analysis was carried out by one-way ANOVA followed by the Student–Newman–Keuls test. Two-tailed Student’s t-tests were used to compare differences between the two groups when indicated. The values were considered significantly different when the P value was <0.05. The P values in the figures represent the results of the one-way ANOVA or Student’s t-test. P < 0.05 was considered significant.

Results

S-DEP induced a tumor necrosis factor α dependent AMPA receptors translation onto membrane

Elevated water plates were used by the current study to induce sleep deprivation for 24 h, following which differences in protein levels were determined. Phosphorylated GluA1 (at Ser845 and Ser831) but not total GluA1 was increased in S-DEP mice compared with Control (Con) group (Fig. 1a). This result indicates S-DEP only affects phosphorylation state of GluA1 but not its expression. Reinsertion of GluA1 subunits at post-synaptic densities in the membranes was increased due to phosphorylation of GluA1, raising the question of whether membrane GluA1 is altered following S-DEP. Membrane proteins were separated after being labeled with biotin. Moreover, membrane GluA1 were increased following S-DEP (Fig. 1b). To detect the underlying mechanism, both increased TNFα and TACE, which cleaves membrane TNFα to soluble TNFα, were found (Fig. 1c). Previously, TNFα has been reported to induce synaptic scaling in the mouse brain, therefore, we hypothesized that increased TNFα may induce AMPA trafficking into the membrane. In order to test this hypothesis, TAPI-0, an inhibitor of TACE, and thalidomide, an inhibitor of TNFα, were administrated. Results indicated that both TAPI-0 and thalidomide could block increased phosphorylated GluA1 in S-DEP mice (Fig. 2). These results indicated that S-DEP increased membrane GluA receptors via a TNFα dependent pathway.
Blocking tumor necrosis factor α converting enzyme/tumor necrosis factor α pathway protected S-DEP mice from impaired learning ability

Increased TNFα levels have reportedly induced hippocampi-dependent cognitive impairment in rodents [19]. The current study deprived mice of sleep for 24h, following which behavioral testing was conducted. As indicated by an active avoidance test recorded via the shuttle box, S-DEP significantly decreased the learning curve of S-DEP mice, but this decrease was significantly reversed by TAPI-0 treatment (Fig. 3a). An open-field test and an elevated plus maze were used to test anxiety-like
disturbances. The results showed that TAPI-0 treatment significantly improved anxiety-like behaviors in S-DEP mice. The current study provides evidence for the potential of TNFα/α2A-DEP pathway as a therapeutic target for sleep deprivation-induced cognitive impairment.

Fig. 1
Effects of sleep deprivation on protein levels. (a) Western-blot samples of p-GluA1ser831, p-GluA1ser845, and GluA1. (b) Western-blot samples of membrane GluA1. (c) Western-blot samples of TNFα and TACE. n=5 mice per group; unpaired student t-test, **P<0.01 versus control mice. Band intensities were quantified as a percentage of values from control mice hippocampi. S-DEP, sleep deprivation; TACE, TNFα converting enzyme.

Fig. 2
Effects of blocker, TAPI-0, on p-GluA1ser831, p-GluA1ser845, and GluA1 levels in S-DEP mice. (a) Western-blot samples of p-GluA1ser831, p-GluA1ser845, and GluA1. (b) Densitometric analysis of p-GluA1ser831, p-GluA1ser845, and GluA1 of corresponding bands relative to β-actin bands = 5 mice per group; unpaired student t-test, **P<0.01 versus control mice, ##P<0.01 versus S-DEP mice. Band intensities were quantified as a percentage of values from control mice hippocampi. S-DEP, sleep deprivation.
Sleep deprivation-induced memory impairment and anxiety-like behaviors. (a) Frequency of successful avoidance in 60 trials of the active avoidance test. (b) Sample traces of locomotor activity in the open-field test (Left). S-DEP significantly reduced the total distance traveled and time spent in the center area (Right). (c) Sample traces of locomotor activity in the elevated plus maze test (Left). S-DEP significantly reduced entry into open arms and time spent in open arms (Right). n=5 per group; two-way ANOVA, **P<0.01 versus control mice, ##P<0.01 versus S-DEP mice. S-DEP, sleep deprivation.

behavioral patterns. In the open-field test, both the total distance traveled and time spent in the center area was decreased in S-DEP mice. In the EPM test, no difference in the total number of entries into open and closed arms was found between control and S-DEP mice. However, the number of entries into open arms and the time spent therein were notably decreased in S-DEP mice. These impairments were also protected by TAPI-0 (Figs. 3b, c). These results indicated that S-DEP induces learning and memory deficits and anxiety-like behaviors, which could be ameliorated by blocking the TACE/TNFα signaling pathway.

Tea polyphenols decreased tumor necrosis factor α levels in the hippocampi of S-DEP mice

Pretreatment with tea polyphenols has been reported suppressed TNFα production in LPS induced liver injury [24]. Thus, we questioned whether tea polyphenols
regulate TNFα production in the S-DEP mouse brain. Following S-DEP, the mice were immediately sacrificed and their hippocampi were dissected on ice. Protein levels were evaluated via western blot. As the results indicated, tea polyphenols treatment did not affect either TNFα nor TACE level in Con mice. However, tea polyphenols significantly decreased TNFα in the hippocampi of S-DEP mice (Fig. 4a). On the contrary, tea polyphenols also reduced TACE levels in S-DEP mice, but TAPI-0 did not (Fig. 4a). Furthermore, co-administering of TAPI-0 and tea polyphenols did not decrease TNFα in S-DEP mice any further (Fig. 4b). These results indicated that tea polyphenols suppressed the over-activated TACE/TNFα pathway.

Tea polyphenols protected impaired learning ability in active avoidance test

Because the findings of the current study established that tea polyphenols suppress TNFα levels in S-DEP mice, we questioned whether tea polyphenols ameliorates the impaired learning ability of S-DEP mice. Tea polyphenols were administered as stated above. As indicated by the results, tea polyphenols relieved the impaired learning ability of S-DEP mice (Fig. 5a). The open-field test demonstrated that tea polyphenols increased the time spent in the center area (Fig. 5b), while the elevated plus maze showed that tea polyphenols increased entry into open arms (Fig. 5c). Considered together, these results indicated that tea polyphenols protect the learning ability of S-DEP mice and produce anxiolytic effects.

Discussion

In this study, we found that TNFα increased synaptic scaling by down-regulating Homer1a expression in the hippocampi, resulting in cognitive impairment. Tea polyphenols prevented the elevation of TNFα and inhibited cognitive impairment in S-DEP mice. Furthermore, S-DEP induced phosphorylation of AMPA receptors, via TNFα upregulation, was reduced by tea polyphenols. Considered together, these results demonstrated that tea polyphenols may protect against S-DEP induced impaired learning ability of S-DEP mice. Tea polyphenols suppressed TNFα/TACE pathway activation and elevated membrane GluA1 in S-DEP mice. (a) Western-blot samples of TNFα, TACE, membrane GluA1 and total GluA1 following tea polyphenols treatment in S-DEP mice (left). Tea polyphenols significantly reduced TNFα, TACE and GluA1 levels in S-DEP mice (right). (b) Western-blot samples of tea polyphenols and TAPI-0 co-treatment in S-DEP mice (left). Tea polyphenols and TAPI-0 co-treatment did not further reduce TNFα, TACE and GluA1 levels in S-DEP mice (right). n=5 per group; one-way ANOVA or two-way ANOVA, **P<0.01 versus control mice, ##P<0.01 versus S-DEP mice. S-DEP, sleep deprivation; TACE, TNFα converting enzyme.
Tea polyphenols protect learning and memory in sleep-deprived mice by promoting AMPA receptor internalization.

Yang et al. 863

Sleep is critical for learning and memory consolidation [25]. In regard to declarative memory, slow-wave sleep is known to exert a beneficial effect on the consolidation of memories acquired during sleep that precedes wakefulness. Sleep deprivation-induced sustained high membrane AMPARs levels, thereby impairing the balance between GABA and glutamate receptors on excitatory cortical neurons [9]. Thus, attenuation of membrane AMPARs levels shows promise as a treatment for S-DEP induced memory impairment. Mechanisms underlying the increase in membrane AMPARs following S-DEP, may involve enhanced TNFα levels in the brain. TNFα-TNFR signaling has attracted great attention owing to its role in CNS associated pathologies. TNFα activates the membrane-bound TNF receptors, TNFR1 and TNFR2. Although TNFR1 is able to bind either soluble TNFα or transmembrane TNFα, it preferably binds to soluble TNFα, whereby this receptor is activated, triggering a complex apoptotic pathway. In contrast, TNFR2 is preferentially activated by transmembrane TNFα and protects neurons against excitotoxicity [13]. In the CNS, activation of TNFR1 is associated with AMPA trafficking, enhanced excitability, and seizure susceptibility. TNFα also plays a role in synaptic scaling and cognitive development [26]. Thus, a properly titrated level of TNFα is required for normal brain function. Our results indicated that S-DEP induced higher levels of membrane AMPA receptor in a TNFα dependent manner. Tea polyphenols suppressed higher levels of TNFα caused by S-DEP, thereby protecting learning and memory. This effect was not enhanced by thalidomide, a TNFα blocker.
indicating that they shared the same pathway. However, tea polyphenols regulation of TNFα levels downstream of the pathway requires further study. Therefore, the possibility that tea polyphenols may protect learning and memory via other antioxidant effects cannot be excluded [27]. Long-term tea polyphenols consumption may also induce some epigenetic changes to participate in cognition protection [18]. Despite this poor efficiency of oral absorption (0.1–10%) [28], the high catechin content in tea polyphenols may protect learning and memory via other antioxidant effects cannot be excluded. The possibility that tea polyphenols may protect learning and memory via other antioxidant effects cannot be excluded.

In summary, our research indicates that increased TNFα post-consumption of tea by human subjects.

Natural Science Foundation of China (No. 81771227).

Acknowledgements
This study was supported by grants from the National Natural Science Foundation of China (No. 81771227).  

Conflicts of interest
There are no conflicts of interest.

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