Sodium tanshinone IIA sulfonate improves cognitive impairment via regulating Aβ transportation in AD transgenic mouse model

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Abstract
Alzheimer’s disease (AD) is a most common neurodegenerative disease. Sodium Tanshinone IIA Sulfonate (STS) has been reported to ameliorate AD pathology. However, the underlying mechanism is still unclear. In this study, AD transgenic mouse model (APP/PS1) was used to explore the potential mechanism of STS against AD. Morris water maze and Y-maze tests showed that administration of STS improved learning and memory abilities of APP/PS1 mice. STS reduced the levels of reactive oxygen species and malondialdehyde, while improved the activity of superoxide dismutase in both hippocampus and cortex in APP/PS1 mice. STS inhibited the activity of acetylcholinesterase, while improved the activity of choline acetyltransferase in APP/PS1 mice. In addition, STS elevated the protein expressions of neurotrophic factors and synapse-related proteins in both the hippocampus and cortex in APP/PS1 mice. At last, STS improved the protein expressions of glucose transporter 1 (GLUT1) and low-density lipoprotein receptor-related protein 1 (LRP1). These results indicated that the potential mechanism of STS on AD might be related to Aβ transportation function via GLUT1/LRP1 pathway.

Highlights
STS improves cognitive impairment of APP/PS1 mice.
STS ameliorates the oxidative stress damage and improves the cholinergic system.
STS protects against neuronal dysfunction and enhances the synaptic plasticity.
STS mediates the Aβ transportation of BMECs.

Keywords  Alzheimer’s disease · Cognitive impairment · Sodium Tanshinone IIA Sulfonate · GLUT1 · LRP1

Introduction
Alzheimer’s disease (AD), a common neurodegenerative disorder, is the main cause of dementia and characterized by progressive cognitive impairment and memory loss (Selkoe 2001). As reported by European Journal of Neurology, there was 44 million people suffered from dementia in 2018, and the number will reach to more than triple in 2050 (Lane et al. 2018). However, there is yet no suitable treatment for AD. Almost all phase III clinical trials targeting Aβ have failed (Kryscio et al. 2017; Schott et al. 2019; Sevigny et al. 2016). Therefore, it is urgent to find new drugs for AD treatment.

Numerous studies have confirmed the central role of Aβ and its oligomers in the pathogenesis of AD (Barage and Sonawane 2015). The blood–brain barrier (BBB) protects neurons from neurotoxic factors, BBB breakdown and dysfunction have been shown in early stages during AD
pathophysiological progression. The BBB is responsible for 80–85% of the clearance of AD related forms of Aβ from the brain by transvascular transport (Sweeney et al. 2018). Low-density lipoprotein receptor-related protein 1 (LRP1) and receptor for advanced glycation end products (RAGE), expressed at BBB, have been proved to play a vital role in the transportation of Aβ, eventually leading to the Aβ clearance (Cai et al. 2016; Horwood and Davies 1994; Moradian et al. 1997). RAGE regulates influx of circulating Aβ into brain, whereas LRP1 mediates the efflux of Aβ into the circulation via BBB. The glucose transporter isoform 1 (GLUT1), expressed at BBB, mediates glucose transport into the brain, which is necessary for the maintenance of BBB integrity. Several studies reported that low GLUT1 level was associated with microvascular impairment and BBB dysfunction in AD patients (Kalaria and Harik 1989), and the reductions in BBB transport may be explained by the fact that the reduced expression of GLUT1 was found in the brain capillaries of AD patients in postmortem studies (Simpson et al. 1994).

*Salvia miltiorrhiza* Bge (Danshen), a traditional Chinese medicine, has been widely used to treat a variety of diseases with few side effects, especially cardiovascular diseases (Li et al. 2018; Liu and Liu 2013). Sodium Tanshinone IIA Sulfonate (STS) is a water-soluble substance obtained by sulfonation of tanshinone IIA (Tan IIA) which is main component of Danshen (Fig. 1) (Zhou et al. 2018). STS has been proved with multiple pharmacological activities, including anti-inflammation, anti-oxidative, anti-apoptosis and interaction with iron channels, and has a broad prospect for the development of neuro-protective drugs (Shang et al. 2012). In previous studies, we have reported that STS could decrease the levels of Aβ via modulating Aβ degradation and generation in vitro model and attenuates cognitive dysfunctions via improving cholinergic system in vivo model of AD (Liu et al., 2020; Xu et al. 2016; Zhang et al. 2020). Nevertheless, whether the STS against cognitive impairment through the transportation of Aβ remained to be unclear.

In the present study, two different doses (10 or 20 mg/kg) of STS were used to treat AD transgenic mouse models which overexpressed amyloid precursor protein and presenilin 1 (APP/PS1) gene. The results elucidated that STS may improve learning and memory dysfunction by relieving oxidative stress, regulating cholinergic system, preventing neuron dysfunction, enhancing the synaptic plasticity, and regulating the transportation of Aβ.

### Materials and methods

#### Materials

STS (purity > 96%) was purchased from Shanghai NO.1 Biochemical & Pharmaceutical Co. Kits used for detection of choline acetyltransferase (ChAT; cat. no. A079-1–1), acetylcholinesterase (AChE; cat. no. A024-1–1), reactive oxygen species (ROS; cat. no. E004-1–1), malondialdehyde (MDA; cat. no. A003-1–2), and superoxide dismutase (SOD; cat. no. A001–3–2) were purchased from the Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Primary antibodies including anti-postsynaptic density 95 (PSD95; cat. no. 3409), anti-postsynaptic density 93 (PSD93; cat. no. 19046), anti-synaptophysin (SYP; cat. no. 36406), anti-nerve growth factor (NGF; cat. no. 2046), anti-brain-derived neurotrophic factor (BDNF; cat. no. 47808) and anti-Aβ (cat. no. 15126 s) were purchased from Cell Signaling Technology, Inc. Anti-glucose transporter isoform 1 (GLUT1; cat. no. 19046), anti-low-density lipoprotein receptor-related protein 1 (LRP1; cat. no. ab92544), anti-receptor for advanced glycation end products (RAGE; cat. no. ab37647), anti-CD31 (cat. no. ab9498) and anti-β-actin (cat. no. ab8227) were purchased from Abcam. All secondary antibodies horseradish peroxidase conjugated anti-rabbit IgG (cat. no. 14708) and anti-mouse IgG (cat. no. 14709) were purchased from Cell Signaling Technology, Inc. Liberase Blendzyme 2 was purchased from Roche, Dulbecco’s PBS (D-PBS) was purchased from EuroClone. Penicillin–streptomycin was purchased from Gibco.

#### Animal and treatment

APP/PS1 (APPswe/PSEN1dE9) double transgenic male mice and wild-type male mice (non-transgenic mice) were purchased from the Model Research Centre of Nanjing University with the same background and age. Animals were housed at a standard temperature (22–25 °C) with automatic light cycles (12-h light/dark) and a relative humidity of 50—60%. The animals were kept in accordance with the Guiding Principles for the Care and Use of Laboratory Animals adopted and promulgated by United States National
Institutes of Health. Twelve-month-old mice were randomly divided into 5 groups (n = 10 each group): WT group (wild-type, 0.9% saline), WT + STS-H group (wild-type, STS 20 mg/kg/day), APP/PS1 group (APP/PS1, 0.9% saline), STS-L group (APP/PS1, STS 10 mg/kg/day), and STS-H group (APP/PS1, STS 20 mg/kg/day). Mice were treated with saline or STS by intraperitoneal injection once a day for 8 weeks. All mice were anesthetized and decapitated after behavioral experiments immediately. The hippocampus and cortex were carefully dissected from brains for examination. All the processes were performed on ice-cold plate. Tissues were rapidly stored at – 80 °C.

**Morris water maze test**

Using Morris water maze test to evaluate the spatial learning and memory ability was mentioned in previous study (Xu et al. 2019). The Morris Water Maze Animal Behavioral Analysis System (Guangzhou Feidi Biology Technology Co., Ltd., Guangzhou, China) consisted of a black circular tank filled with water at 22–26 °C, a hidden platform, and a recording system. The pool (120 cm in diameter, 40 cm in height) was spatially divided into 4 imaginary quadrants (NE, SE, SW, NW) by a computerized tracking/image analyzer system. A circular transparent escape platform (10 cm diameter) was positioned 1–2 cm below the opaque water surface in the middle of the target quadrant of the pool. The learning and memory abilities of mice were assessed by the Morris water maze test in a dark room. Mice were given orientation navigation tests for 6 consecutive days. Before the measurement, mice were trained once to find the platform. For each daily trial, there were 4 sequential training trials beginning with placement of the animal in the water facing the wall of the pool with the drop location changing for each trial randomly; the recording system then started to record the time. The escape latency and the swim path tracking until the mice landed on the platform were recorded on video tape. If the mouse failed to locate the platform within 60 s, it was guided to the platform and kept there for 10 s. For the probe trials, the mice were allowed to swim freely in the pool for 60 s with platform removal. The time required to cross to the original platform position, the time spent in the target quadrant, and the escape latency were measured.

**Y-maze test**

Y-maze tests were used to assess cognitive changes, short-term spatial working memory (by spontaneous alternation), and exploratory activity (by total number of arm choices) of mice. The method was mentioned in previous study (Wang et al. 2018). The Y-maze is a three-arm horizontal maze (30 cm long and 8 cm wide with 15 cm high walls) in which the arms are symmetrically disposed at 120° from each other. The maze of floors and walls are made of opaque polyethylene plastic in a black environment. The test consisted of two phases with 1-h intervals. During the training, the new arm was separated with a baffle and the mice were placed into the starting arm for 10 min, during which they had free access to the starting arm and the other arm. The test was performed 1-h after the training. For this, the baffle in the new arm was removed and the mice were placed into the starting arm. The number of mice access into the three arms within 5 min was recorded. An alternation was recorded when mice made consecutive visits to the three different arms. The Y-maze spontaneous alternation was calculated as follows: Alternation behavior (%) = number of alternations / (total arm entries-2) × 100%. At the end of the experiment, arms were cleaned with alcohol so as to remove the scent of previous mice.

**Measurement of ChAT and AChE activity**

The hippocampus and cortex tissues were homogenized with ice-cold saline. The homogenate was centrifuged at 12,000×g for 15 min at 4 °C. The supernatant was collected for the assay of the ChAT and AChE activities according to the manufacturer’s instructions.

**ROS, MDA, and SOD assays**

The hippocampus and cortex tissues were homogenized with cold saline. The homogenate was centrifuged at 12,000×g for 15 min at 4 °C. Supernatant was collected to detect the levels of ROS, which was measured by DCFH-DA as a redox sensitive fluorescent dye. DCFH was oxidized to strong green, fluorescent substance DCF in the presence of ROS, which has a maximum peak at excitation wavelength of 502 nm and emission wavelength of 530 nm and intensity is proportional to intracellular reactive oxygen species. Supernatant was collected to be added with the reagents according to the instructions of the MDA kit. The mixture was incubated at 95 °C for 40 min, then centrifuged at 3500 r/min for 10 min, the absorbance was measured at 532 nm. The SOD detection buffer, the NBT/enzyme working solution and the reaction starting working solution were sequentially added into supernatant. Then the samples were incubated at 37 °C for 30 min and measured the absorbance at 560 nm.
Isolation of brain microvascular endothelial cells (BMECs)

The BMECs were isolated from brain and identified as described before (Navone et al. 2013). Transfer the brain into a sterile glass dish with D-PBS with 0.1% (vol/vol) penicillin–streptomycin. By using sterile scissors and a scalpel, fragment the tissue sample into pieces. Centrifuge at 276 × g for 10 min. Aspirate the supernatant and resuspend the homogenate pellet with Liberase Blendzyme 2 at a concentration of 0.625 mg/ml. Incubate the suspension at 37 °C on a rotator for 1-h. Resuspend the homogenate with D-PBS. Centrifuge the suspension at 276 × g for 10 min. Aspirate the supernatant. Coat a 25 cm² flask with collagen type I and incubate it for 20 min at 37 °C. Aspirate the collagen solution from the flask, then wash with D-PBS. Resuspend the pellet in culture medium and transfer the suspension to the flask. Maintain the cellular suspension at 37 °C in an atmosphere of 5% CO₂. The BMECs isolated from mouse could be identified by cytoplasmic staining for CD31 or flow cytometry of CD31, CD34, CD146 and Tie-2. The BMECs were collected were rapidly stored at -20 °C.

Western blot analysis

The BMECs, hippocampus and cortex tissues were homogenized and lysed by ice-cold RIPA buffer (containing 1:100 inhibitor proteases and phosphatases cocktail) for 30 min. The lysate was centrifuged at 12,000 × g for 10 min at 4 °C, the supernatant was collected to determine the total protein concentration by using a bicinchoninic acid (BCA) and then denatured by boiling at 100 °C with 1:4 loading buffer. The protein was fractionated and subsequently transferred onto PVDF membranes. The membranes were blocked in 5% skim milk for 1-h at room temperature. The membranes containing the protein were incubated with anti-SYP, anti-PSD93, anti-PSD95, anti-BDNF, anti-NGF, anti-GLUT1, anti-LRP1, anti-RAGE, anti-Ab, anti-CD31 and mouse anti-β-actin overnight at 4 °C. Then the membrane was incubated with horseradish peroxidase conjugated anti-rabbit or anti-mouse for 1-h at room temperature. Routinely, protein load was monitored by using a super enhanced chemiluminescence reagent (Applygen Technologies Inc., Beijing, China). Blots digital images were visualized with an Image Lab 3.0 (Bio-Rad).

Statistical analysis

Experimental values were given as means ± S.E.M. SPSS 19.0 statistical software (IBM, Endicott, NY) was evaluated to perform all statistical analysis. One-way ANOVA and student t-test were used for the analysis between two groups, followed by Dunnett’s significant post hoc test for pairwise multiple comparisons. Data processing was performed using GraphPad Prism 8 software (GraphPad, Inc.). Differences were considered as statistically significant at p < 0.05.

Results

STS Improves Cognitive Impairment in APP/PS1 Mice

The design of the present study is shown in Fig. 2A. In the Morris water maze test, the time for APP/PS1 group to find central platform was significantly longer than WT group. Compared with the APP/PS1 group, the STS-H group was with shorter escape latency (Fig. 2B). As was shown in Fig. 2C, crossing times of the platform in APP/PS1 group were greatly less than WT group. Both STS-L and STS-H group were with more crossing times than APP/PS1 group. In addition, the APP/PS1 group took less time to stay in the target quadrant than the WT group, while the STS-H group spent more time than APP/PS1 group (Fig. 2D).

Additionally, Y-maze spontaneous alternation test was performed to assess the memory and learning ability of APP/PS1 mice. In contrast to WT group, a prominent decrease of spontaneous alternation index was observed in the APP/PS1 group while (Fig. 2E). However, the spontaneous alternation index was improved after STS treatment. As shown in Fig. 2F, the APP/PS1 group entered the novel arm less frequently than the WT group. STS treatment remarkably increased the frequency.

STS ameliorates the oxidative stress in APP/PS1 mice

We also detected the oxidative stress state in APP/PS1 mice brain. As shown in Fig. 3, the levels of MDA and ROS in the hippocampus and cortex of the APP/PS1 group were significantly higher, while the SOD activity was significantly lower than WT group. After STS administration, the levels of MDA and ROS showed a remarkable decrease, and the activity of SOD increased significantly.

STS prevents the dysfunction of cholinergic system in APP/PS1 mice

Cholinergic system plays a vital role in determining the function of cortex and hippocampus (Faiq et al. 2019). In Fig. 4A and C, the AChE activity of hippocampus and cortex in APP/PS1 group was significantly higher than that in WT group. The activity was significantly reduced after STS treatment. Nevertheless, the ChAT activity of hippocampus and cortex was decreased in APP/PS1 group. STS treatment increased the ChAT activity (Fig. 4B and D).
STS enhances the synaptic plasticity of APP/PS1 mice

Neurotrophic factors (BDNF and NGF) are propitious to prevent neurodegeneration, further alleviating the learning and memory impairment of APP/PS1 mice (Allen et al. 2013). As shown in Fig. 5 and 6, compared with the WT group, the expressions of BDNF and NGF in APP/PS1 group decreased significantly. STS treatment increased the expressions of synaptic proteins. Therefore, this treatment may improve learning and memory of APP/PS1 mice through increasing the synaptic plasticity.

STS reduces the expression of Aβ and mediates the Aβ transportation of BMECs in APP/PS1 mice

AD brain endothelium expresses low levels of GLUT1, which leads to diminished glucose transport, and thus the damage to the function of BBB (Winkler et al. 2015). LRP1 is a major Aβ clearance receptor at the BBB,
Fig. 3 STS alleviates the oxidative stress in APP/PS1 mice. The levels of MDA (A), ROS (B) and the activity of SOD (C) in hippocampus. The levels of MDA (D), ROS (E) and the activity of SOD (F) in cortex. Data are represented as mean ± S.E.M. n = 6 per group. **P < 0.01 vs. wild-type (WT) mice group; *P < 0.05, ##P < 0.01 vs. APP/PS1 mice group.
while RAGE transports Aβ in the opposite direction to LRP1, mediating the reentry of Aβ into the brain. Here, we isolated the BMECs from brain as described before (Navone et al. 2013), which was identified by expression of CD31 (Supplementary Fig. 1). As shown in Fig. 7, STS could significantly reduce the expression of Aβ in the brain of APP/PS1 mice. Compared with the WT group, the expressions of GLUT1 and LRP1 in the BMECs of APP/PS1 group decreased significantly, while increased after STS treatment. The level of RAGE was barely affected in any group. Abovementioned results revealed that STS could reduce the expression of Aβ and mediate the Aβ transportation of APP/PS1 mice through increasing the expressions of GLUT1 and LRP1 of the BMECs.

**Discussion**

Here, APP/PS1 mouse model was used to explore the potential mechanism of STS against AD. Our innovation lies in the discovery of the GLUT1/LRP1 pathway involved in STS protecting against AD. Our experiments had shown that STS could improve learning and memory abilities in APP/PS1 mice. The neuroprotective effects of STS on APP/PS1 mice were closely related to the mechanism of improving Aβ transportation, meanwhile, ameliorating oxidative stress, protecting cholinergic system and synaptic plasticity.

Aβ plaques play an important role in AD, acting as a pathological trigger for a cascade, such as oxidative stress, cholinergic system damage, synaptic dysfunction, and even neuronal damage loss (Barage and Sonawane 2015) STS
is formed by introducing sodium sulfonate groups into the chemical structure of Tanshinone IIA, resulting in higher water solubility and efficiency (Zhou et al. 2019). According to our previous in vivo study, we found that STS could improve scopolamine-induced cognitive impairment and the damage of cholinergic system in mice (Xu et al. 2016), then in vitro study, we found that STS could protect against Aβ-induced damage by modulating Aβ degradation and generation in SH-SY5Y cell (Zhang et al. 2020) and protect Aβ-induced injury by anti-apoptosis, anti-oxidative stress, relieving ER stress, and increasing the expression levels of IDE and NEP to clear Aβ in HT22 cell (Liu et al. 2020). Here our experiments further confirmed that STS effectively improve the learning and memory ability in APP/PS1 mice (Fig. 2B-F).

Oxidative stress, which is defined as the imbalance between pro-oxidants such as MDA and antioxidants such as SOD (Jones 2006), has been recognized as a contributing factor in AD. It has been reported that mitochondrial damage caused by oxidative stress could contribute to the accumulation of Aβ (Uttara et al. 2009), leading to the early stages of AD prior to the onset of clinical symptoms. Previous investigations have shown that STS can alleviate oxidative stress in Aβ1-42-induced HT22 cell, and chronic obstructive pulmonary disease or intermittent hypoxia mice (Ji et al. 2017; Liu et al. 2020; Xu et al. 2021). In the present study, the levels of MDA and ROS were significantly reduced, and the activity of SOD was increased significantly after STS treatment (Fig. 3), which further indicated that STS could inhibit the formation of reactive oxygen radicals and lipid-free radicals in APP/PS1 mice.

The impairment of the cholinergic system often manifests in patients with dementia, including AD (Davies and Maloney 1976; Whitehouse et al. 1982). It has been reported that Aβ reduced acetylcholine (Ach) production and discharge, which is synthesized by ChAT and played a vital role in the peripheral and central nervous systems (Ferreira-Vieira et al. 2016), and AChE, involved in
hydrolytic cleavage of Ach, could induce Aβ aggregation via forming binding sites with it (Carvajal and Inestrosa 2011; Gauthier 2002). Our previous research had already showed that STS could improve cholinergic system to attenuate scopolamine-induced cognitive dysfunctions for the first time (Xu et al. 2016). In the present study, we showed that compared with the APP/PS1 group the activity of ChAT was increased, while the activity of AChE was decreased in the STS groups (Fig. 4). These results indicated that STS may improve cognitive dysfunctions through cholinergic neuron system in APP/PS1 mice.

The downstream cascade of Aβ also includes synapses dysfunction. Aβ could impair synaptic plasticity and even induce synaptic dysfunction by affecting the activity of N-methyl-D-aspartate (NMDA) receptors or combining with α-amino-3-hydroxy-5-methyl-4-isoxa-zolepropionic acid (AMPA) receptors (Hsia et al. 1999; Hsieh et al. 2006; Newcomer et al. 2000). Reduced expression of synaptic markers such as PSD95, PSD93 and SYP has been reported in the brains of transgenic APP/PS1 mutant mice (Hsia et al. 1999; Mucke et al. 2000). NGF metabolic pathway has also been demonstrated to be impaired in AD (Allen et al. 2013), and there have been a lot of preclinical studies suggesting that replacement of BDNF may ameliorate both age-related and AD-associated problems (Arancibia et al. 2008; Mamounas et al. 1995). In the present study, STS treatment improved the expressions of PSD93, PSD95, and SYP in both hippocampus and cortex of APP/PS1 mice. Significant reductions of NGF and BDNF were found in APP/PS1 mice. After STS treatment, the NGF and BDNF were reinstated (Fig. 5 and 6). Our results demonstrated that STS improve learning and memory of APP/PS1 mice might through increasing the synaptic plasticity.

Our previous studies have showed that STS could increase Aβ degradation by improving the expressions of Aβ-degrading enzymes and inhibit Aβ generation by

![Fig. 6](image-url)
decreasing β-secretase activity in vitro model (Liu et al. 2020; Zhang et al. 2020). Whether STS could affect Aβ transport was still unclear. Low Aβ levels in healthy brain are maintained mainly through transport across the BBB (Tarasoff-Conway et al. 2015). RAGE takes up Aβ from the blood to brain, whereas LRP1 transports Aβ from
brain to the blood (Osgood et al. 2017). GLUT1 provides energy for BBB by transporting glucose, whose reduction may result in BBB breakdown. It has been reported that GLUT1 deficiency in mice might lead to early cerebral microvascular degeneration and BBB breakdown, further cause the decrease of LRPI and then the reduction of Aβ clearance (Winkler et al. 2015). STS has been mainly used for treatments of cardiovascular and cerebrovascular diseases. It has been reported that STS could ameliorate BBB damage in acute ischemic stroke patients (Ji et al. 2017) and in a rat model induced by middle cerebral artery occlusion and 3 days of reperfusion (Xu et al. 2021). According to the effect of BBB damage on Aβ transportation, we speculated that STS might improve cognitive impairment of APP/PS1 mice by regulating Aβ transportation. Here, we found that STS can significantly reduce the Aβ expression level in the brain of APP/PS1 mice, which might be one kind of the Aβ oligomers. Then, we isolated the BMECs from brain, which is the main component of BBB, and found that STS could significantly improve the expression of GLUT1 and LRPI of BMECs, while has no effect on the level of RAGE (Fig. 7). Our results firstly demonstrated that STS might improve GLUT1 level to improve BBB integrity, and increase the expression of LRPI to promote the Aβ transportation in APP/PS1 mice.

In conclusion, we demonstrated that STS could effectively improve the learning and memory in APP/PS1 double transgenic mice. Then, we showed that STS could ameliorate oxidative stress, protect cholinergic system and synaptic plasticity, and the possible mechanism might be associated with improving Aβ transportation. This study enriched a scientific basis for prevention and treatment of STS in AD. Further mechanisms and clinical trials of STS on AD treatment are needed.

Acknowledgements Further mechanisms and clinical trials of STS on AD treat-
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