Ginsenoside Rg1 ameliorates hippocampal long-term potentiation and memory in an Alzheimer's disease model

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Abstract. The complex etiopathogenesis of Alzheimer's disease (AD) has limited progression in the identification of effective therapeutic agents. Amyloid precursor protein (APP) and presenilin-1 (PS1) are always overexpressed in AD, and are considered to be the initiators of the formation of β-amyloid plaques and the symptoms of AD. In the present study, a transgenic AD model, constructed via the overexpression of APP and PS1, was used to verify the protective effects of ginsenoside Rg1 on memory performance and synaptic plasticity. AD mice (6-month-old) were treated via intraperitoneal injection of 0.1-10 mg/kg ginsenoside Rg1. Long-term memory, synaptic plasticity, and the levels of AD-associated and synaptic plasticity-associated proteins were measured following treatment. Memory was measured using a fear conditioning task and protein expression levels were investigated using western blotting. All the data was analyzed by one-way analysis of variance or t-test. Following 30 days of consecutive treatment, memory in the AD mouse model was ameliorated in the 10 mg/kg ginsenoside Rg1 treatment group. As demonstrated by biochemical experiments, ginsenoside Rg1 treatment reduced the accumulations of β-amyloid 1-42 and phosphorylated (p)-Tau in the AD model. Additionally, brain-derived neurotrophic factor (BDNF) and p-TrkB synaptic plasticity-associated proteins were upregulated following ginsenoside Rg1 application. Correspondingly, long-term potentiation (LTP) was restored following ginsenoside Rg1 application in the AD mice model. Taken together, ginsenoside Rg1 repaired hippocampal LTP and memory, likely through facilitating the clearance of AD-associated proteins and through activation of the BDNF-TrkB pathway. Therefore, ginsenoside Rg1 may be a candidate drug for the treatment of AD.

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Introduction

Alzheimer's disease (AD) remains the most severe form of neurodegenerative disease, and is characterized by a decline in memory performance and other cognitive abilities. It is estimated that ~25,000,000 individuals are affected worldwide, particularly in the elderly population (1). At present, there is no cure for AD, however, certain symptomatic therapeutics are available (2-4). Although the etiology of AD remains to be fully elucidated, there is a general consensus in favor of the plaque hypothesis. The hallmark appearance of amyloid plaques and intracellular neurofibrillary tangles of Tau are reported to contribute to neuron loss in AD (5,6). The formation of β-amyloid plaques in AD patients affects neuronal synaptic plasticity in the early phase, and progressively leads to cell death in the later phase (7-9). Therefore, plaque formation and synaptic plasticity, particularly in the hippocampus, which is a region responsible for memory formation, are critical indices in evaluating anti-AD efficacy.

The use of Chinese medicines has a long-term history in clinical practice, and has been suggested to offer potential in improving memory (10,11). Among the effective herbs, ginseng is considered to promote the health of middle-aged and elderly populations (12). Ginseng has been used as an adaptogenic herb in traditional Chinese medicine for >2,000 years, and the long-term application of ginseng improves the ability to combat stress, trauma, anxiety and fatigue (13). Additional pharmacological activities, including in the prevention of cancer and neurodegenerative diseases, have also been reported (14,15). Ginsenosides, the active compounds of the *Panax* species, have been widely investigated in basic and clinical settings. A substantial number of ginsenosides have been found to improve the decline in memory induced by lipopolysaccharide or okadaic acid (16-19). However, the effects of ginsenosides on memory decline induced by genetic interruption have not been reported, particularly its mechanisms. A previous study suggested that ginsenoside Rg1 is able to pass through blood-brain barrier to distribute in the cortex and hippocampus (20,21). In the present study,

an AD transgenic mouse model (APPswe/PSEN1dE9) was used to investigate the effects of ginsenoside Rg1 on memory, and to examine its underlying mechanisms. In combination with other evidence (22,23), the present study hypothesized that ginsenoside Rg1 is a candidate memory enhancer, not only in age-related and drug-induced memory decline, but also in the genetic AD model. The present study may provide novel evidence to suggest a therapeutic effect of ginsenoside Rg1 on AD.

Materials and methods

Animals. APP/PS1 mice (n=80; B6C3-Tg) were obtained from the Jackson Laboratory (Farmington, CT, USA) and were bred amongst the colony. The offspring were genotyped using primers for APP and PS1 (Sangon Biotech Co., Ltd., Shanghai, China), which were as follows: Sense, 5'-GACTGACCACTC GACCAGGTTCTG-3' and antisense, 5'-CTTGTAAGTTGG ATTCTCATATCCG-3' for APP; sense, 5'-AATAGAGAA CGGCAGGAGCA-3' and antisense, 5'-GCCATGAGGGCA CTAATCAT-3' for PS1 reference; and sense, 5'-CCTCTT TGTGACTATGTGGACTGATGTCGG-3' and antisense, 5'-GTGGATAACCCCTCCCCCAGCCTAGACC-3' also for PS1, which distinguishes AD. C57 BL/6J mice (n=30) were purchased from the Animal Center of the Chinese Academy of Sciences (Shanghai, China). The mice (male; age, 6 months; weight, 30 g) used in the experiments were housed together in a 12 h light/dark cycle at 22±3˚C, with food and water *ad libitum*. All experimental procedures were approved by the ethics committee of Weifang Medical University (Weifang, China).

Ginsenoside Rg1 treatment. APP/PS1 mice were chronically administered with Rg1 (Sigma-Aldrich, St. Louis, MO, USA) by intraperitoneal injection, at concentrations of 0.1, 1 or 10 mg/kg once each day for 30 days consecutively. This concentration range was selected based on previous publications (22,24). The control mice received the same volume of saline. During the drug administration, diet, water intake and body weights were monitored. At 30 days post-administration, behavioral, electrophysiological and biochemical experiments were performed.

Electrophysiological experiments. After 30 days, at least 4 mice from each group were sacrificed by decapitation. From each group, 4-8 slices were prepared. Acute hippocampal slices (300 μm) were prepared following decapitation in cutting solution (Beyotime Institute of Biotechnology, Haimen, China). The components of the cutting solution were as follows: 124 mM NaCl, 26 mM $NaHCO_3$, 10 mM D-glucose, 3 mM KCl, 1.25 mM KH_2PO_4, 5 mM $MgSO_4$ and 3.4 mM $CaCl_2$. The slices were then transferred to an interface recording chamber (BSC-ZT; Warner Instruments LLC, Hamden, CT, USA) and exposed to a warm, humidified atmosphere of 95% O_2/5% CO_2 and continuously perfused (for ~4 h) with oxygenated and preheated (32±0.5˚C) artificial cerebrospinal fluid (aCSF; Beyotime Institute of Biotechnology, Inc.) comprising 110 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$, 1.5 mM $MgSO_4$, 1.24 mM KH_2PO_4, 10 mM D-glucose and 27.4 mM $NaHCO_3$. The aCSF flow speed was adjusted to 1.4 ml/min. Following a 2 h recovery period, the field-excitatory postsynaptic potential (fEPSP), elicited by stimulation of the Schaffer collateral pathway with twisted nichrome wires (Warner Instruments LLC), was recorded. The input-output and paired-pulse facilitation at 30, 50 and 100 msec intervals were assessed. Long-term potentiation was induced using a θ-burst stimulation (TBS) protocol. Long-term depression (LTD) was induced by low-frequency stimulation (LFS).

ELISA. To quantify levels the of β-amyloid 1-42, the hippocampus from four sacrificed mice from each of the groups were homogenized in homogenization buffer (5 M guanidine HCl/50 mM Tris-HCl; Beyotime Institute of Biotechnology) and centrifuged at 10,000 x g for 10 min at 4˚C. The protein concentrations of the supernatants were determined using a Bicinchoninic Acid (BCA) Assay kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The supernatant fractions were analyzed using a β-amyloid 1-42 ELISA kit (cat no. KHB3441; Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's protocol. The absorbance was determined for each well at 450 nm using a microplate reader (Fluoroskan Ascent™; Thermo Fisher Scientific, Inc.).

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis. Total RNA was extracted from the hippocampus using TRIzol reagent (Invitrogen; Thermo Fisher Scientific, Inc.). Reverse transcription was performed using Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI, USA). RNA purity was defined by optical density $(OD)_{260}/OD_{280}$ on a Fluoroskan Ascent™ microplate reader. qPCR was performed to quantify the expression of APP in the hippocampus, using a quantitative thermal cycler (Mastercyclerep realplex; Eppendorf, Hamburg, Germany). The system included 2 μl cDNA, 2 μl dNTPs, 2 μl $MgCl_2$ and ddH_2O to 25 μl. The thermocycling conditions were as follows: Initial denaturation, 5 min at 95˚C; and 30 cycles of denaturation at 30 sec at 95˚C, annealing at 58˚C for 30 sec and extension at 72˚C for 30 sec. The relative expression values were calculated as a ratio of target cDNA to β-actin and the expression of target genes was calculated by $2^{-\Delta\Delta Cq}$ (25). The primers used in qPCR were obtained from Sangon Biotech Co., Ltd. as follows: APP, sense 5'-TGCTGG CAGAACCCCAGATCG-3' and antisense 5'-TTCTGGATG GTCACTGGCTGG-3'; β-actin sense 5-ATGAGGTAGTCT GTCAGGT-3 and antisense 5-ATGGATGACGATATCGCT-3.

Western blot analysis. The whole hippocampus homogenates were obtained and lysed, and the protein concentrations were measured using a BCA protein assay kit (Thermo Fisher Scientific, Inc.), as described above. Equivalent quantities of proteins (20 μg) were processed for 12% SDS-PAGE (Beyotime Institute of Biotechnology) and western blot analysis. The proteins were transferred to nitrocellulose membranes (Bio-Rad Laboratories, Inc., Hercules, CA, USA) using a wet transfer and the membranes were blocked in 5% nonfat milk for 2 h and washed three times in phosphate-buffered saline with Tween 20 (PBST). The membrane was incubated with primary antibodies overnight at 4˚C, as follows: Rabbit polyclonal BDNF (1:1,000; EMD Millipore, Billerica, MA, USA; cat. no. AB1534SP), rabbit actin (1:10,000; EMD Millipore;

cat. no. MAB1501), rabbit monoclonal phosphorylated (p)-TrkB (1:3,000; Cell Signaling Technology, Inc., Danvers, MA, USA; cat. no. 4619), rabbit monoclonal Trk B (1:3,000; Cell Signaling Technology, Inc.; cat. no. 4607), rabbit polyclonal p-Tau (1:3,000; Cell Signaling Technology, Inc.; cat. no. 11834), rabbit monoclonal Tau (1:3,000; Cell Signaling Technology, Inc.; cat. no. 4019), C-terminal fragments (CTFs; 1:1,000; EMD Millipore; cat. no. AB5352), rabbit polyclonal postsynaptic density protein 95 (PSD-95; 1:3,000; Cell Signaling Technology, Inc.; cat. no. 2507) and rabbit polyclonal synaptophysin (1:3,000; Cell Signaling Technology, Inc.; cat. no. 4329). Following incubation with primary antibodies, the membranes were washed with PBST 3 times for 10 min and then incubated with the mouse anti-rabbit monoclonal secondary antibody (1:10,000; Cell Signaling Technology, Inc.; cat. no. 5127) for 2 h at room temperature. Protein levels were quantified by densitometry analysis using Quantity One software (version 4.5.2; Bio-Rad Laboratories, Inc.).

Fear conditioning. The fear conditioning experiment was performed, as previously described (26). The mice were handled daily for 5 days consecutively prior to training. On the training day, the mice were placed in the fear-conditioning chamber and allowed 5 min for exploration. Subsequently, three tone-footshock pairings, separated by 1 min intervals were delivered to the animals. The footshocks were 0.70 mA for 2 sec and a tone of 85 dB 2 kHz for 30 sec. The mice were retained in the training chamber for another 30 sec, following which they were transferred to their home cages. A context assessment (5 min) was performed 24 h post-training. On day 3, the animals were subjected to a tone test in the same conditioning chamber, which was modified by a change in the color of the walls. The freezing level (5 min) in this altered context was measured (moving frequency, <25 msec), and a tone (85 dB; 2 kHz) was delivered for 1 min to measure freezing to tone. The frequency of freezing was recorded using FreezeFrame software (version 3; Coulbourn Instruments, Holliston, MA, USA) and analyzed using FreezeView software (version 3; Coulbourn Instruments). In each group, there were five animals. The percentage of time in which the animal froze was calculated.

Statistical analysis. Data are presented as the mean ± standard error of the mean. All statistical analyses were performed using one-way analysis of variance with GraphPad Prism 6.0 software (GraphPad Software, Inc., La Jolla, CA, USA). Bonferroni's correction with a post-hoc *t*-test was performed to compare the differences between groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Chronic treatment with ginsenoside Rg1 ameliorates long-term memory in AD model mice. In the present study, long-term memory was measured using a fear conditioning experiment. Ginsenoside Rg1 was administered to the mice at a range of doses (10, 1 and 0.1 mg/kg) for 30 days. The dietary intake, drinking and body weights of the animals were unaffected during the drug treatment. As shown in Fig. 1A, context memory was markedly improved following treatment with

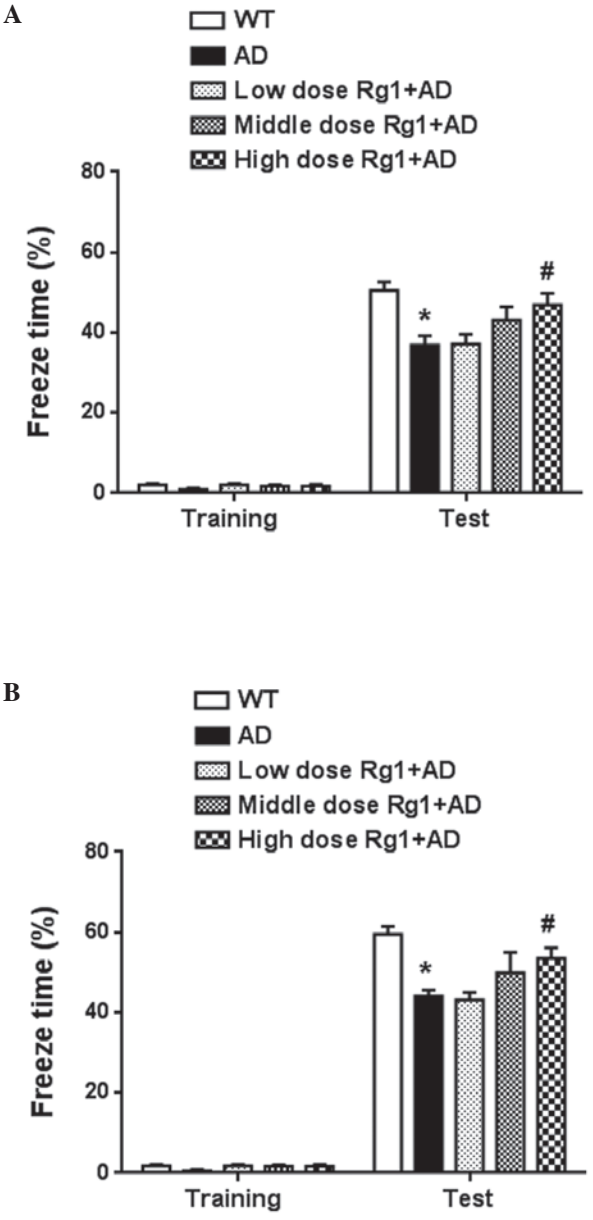

Figure 1. Chronic treatment with ginsenoside Rg1 improves memory in transgenic AD mice. (A) Context. (B) Tone. Each group comprised five animals. High (10 mg/kg), middle (1 mg/kg) and low (0.1 mg/kg) doses of ginsenoside Rg1 were administered to the mice for a consecutive 30 day period, respectively. Data are presented at the mean ± standard error of the mean. *P<0.05, compared with WT; #P<0.05, compared with AD. AD, Alzheimer's disease; WT, wild-type.

10 mg/kg ginsenoside Rg1 (P<0.05). The intermediate dose showed improved memory, but without statistical significance (P>0.05). No significant effect was observed following treatment with the low dose of ginsenoside Rg1. Tone memory was also measured. As shown in Fig. 1B, treatment with ginsenoside Rg1 at the dose of 10 mg/kg improved tone memory (P<0.05). The intermediate dose of ginsenoside Rg1 also had an ameliorating effect. These results confirmed that ginsenoside Rg1 improved long-term memory in the transgenic AD model.

Chronic treatment with ginsenoside Rg1 reverses LTP deficit in the AD model. To confirm the effect of ginsenoside Rg1 on hippocampal synaptic transmission and plasticity, the

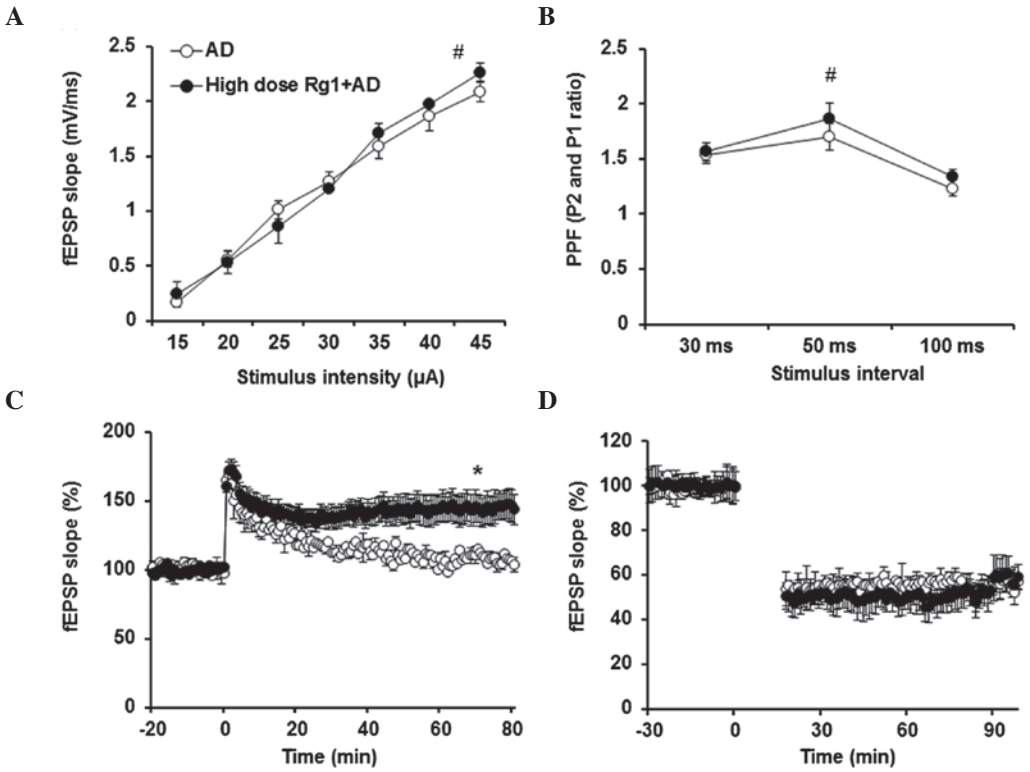

Figure 2. Chronic treatment with ginsenoside Rg1 increases LTP. (A) Input-output was not affected by ginsenoside Rg1 treatment. (B) PPF was not affected by ginsenoside Rg1 treatment. (C) TBS-induced LTP was improved by ginsenoside Rg1 treatment. (D) LFS-induced LTD was not affected by ginsenoside Rg1 treatment. Data are presented at the mean + standard error of the mean. In each group, 5-10 slices from five animals were included. *P<0.05, $^{\#}$P>0.05 vs. the AD group. AD, Alzheimer's disease; TBS, θ-burst stimulation; LTP, long-term potentiation; LFS, low-frequency stimulation; LTD, long-term depression; fEPSP. field-excitatory postsynaptic potential; PPF, paired-pulse facilitation.

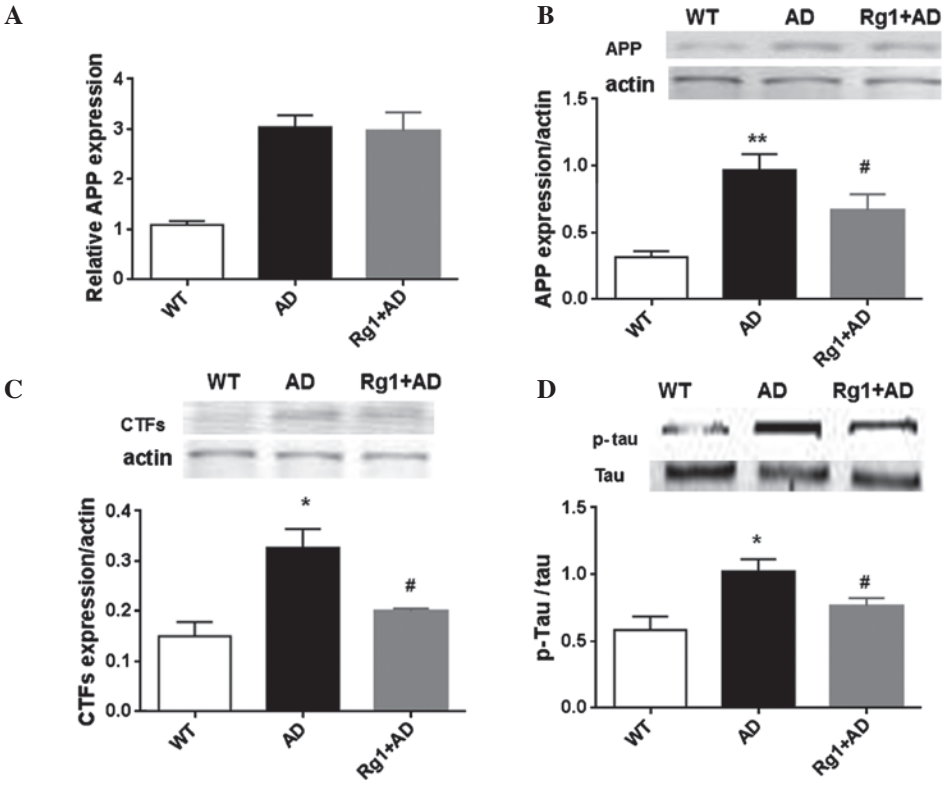

Figure 3. Chronic treatment with ginsenoside Rg1 downregulates the expression levels of APP, CTFs and p-Tau. (A) mRNA expression of APP; (B) protein expression of APP. Representative blots of APP and Actin are shown above. (C) Expression of CTFs. Representative blots of CTFs and Actin are shown above. (D) Expression of p-Tau. Representative blots of p-Tau and total Tau are shown above. Data are presented as the mean ± standard error of the mean. Data were obtained from five animals in each group. *P<0.05 and **P<0.01, compared with WT; $^{\#}$P<0.05, compared with AD. APP, amyloid precursor protein; CTFs, C-terminal fragments; p-Tau, phosphorylated Tau; AD, Alzheimer's disease; WT, wild-type.

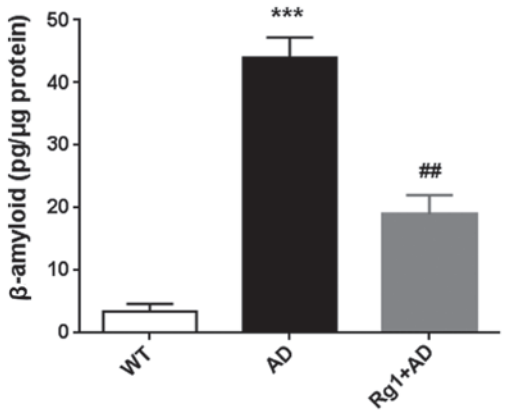

Figure 4. Chronic treatment with ginsenoside Rg1 downregulates levels of β-amyloid 1-42 in the AD model. Data are presented at the mean ± standard error of the mean from five animals in each group. ***P<0.001, compared with WT; ##P<0.01, compared with AD. AD, Alzheimer's disease; WT, wild-type.

fEPSPs at Schaffer collateral-CA1 synapses were measured. As shown in Fig. 2A and B, ginsenoside Rg1 had no effect on the input-output. Paired-pulse facilitation was also unaffected by ginsenoside Rg1 treatment (P>0.05). The induction of LTP by TBS was impaired in the slices obtained from the AD mice (Fig. 2C). However, following ginsenoside Rg1 treatment, TBS-LTP was ameliorated (P<0.05), compared with in the AD model. LFS-LTD was not affected by ginsenoside Rg1 treatment (Fig. 2D).

Chronic treatment with ginsenoside Rg1 attenuates the expression of AD-associated proteins. The expression levels of APP and PS1 in the hippocampus were measured using RT-qPCR and Western blot analyses. Compared with the wild-type mice, the mRNA expression of APP increased ~3-fold in the AD model mice (Fig. 3A; P<0.05). Ginsenoside Rg1 did not alter the mRNA expression levels of APP. The protein levels were also determined. As shown in Fig. 3B, the protein level of APP also appeared to be enhanced in the AD model mice, compared with the wild-type mice. Of note, ginsenoside Rg1 decreased the protein levels following 1 month of treatment (P<0.05). In addition, the present study detected the expression of CTFs. In the model mice, the expression of CTFs was significantly increased (P<0.05), however, the expression was reduced by ginsenoside Rg1 treatment (P<0.05; Fig. 3C). The expression of p-Tau was also measured. Compared with the wild-type mice, the expression of p-Tau was increased in the model mice (P<0.05). Following treatment with ginsenoside Rg1, the protein level was also attenuated (P<0.05; Fig. 3D). The level of β-amyloid 1-42 was reduced following treatment with ginsenoside Rg1 (Fig. 4). These results suggested that ginsenoside Rg1 treatment ameliorated the accumulation of AD-associated proteins in the AD model mice.

Chronic treatment with ginsenoside Rg1 improves activation of the BDNF-TrkB pathway in AD model mice. Synaptic-associated proteins in the hippocampus were also measured in the present study, including BDNF, p-TrkB, synaptophysin and PSD-95. As shown in Fig. 5A and B, the expression of BDNF increased following treatment with ginsenoside Rg1 (P<0.05). Correspondingly, the level of

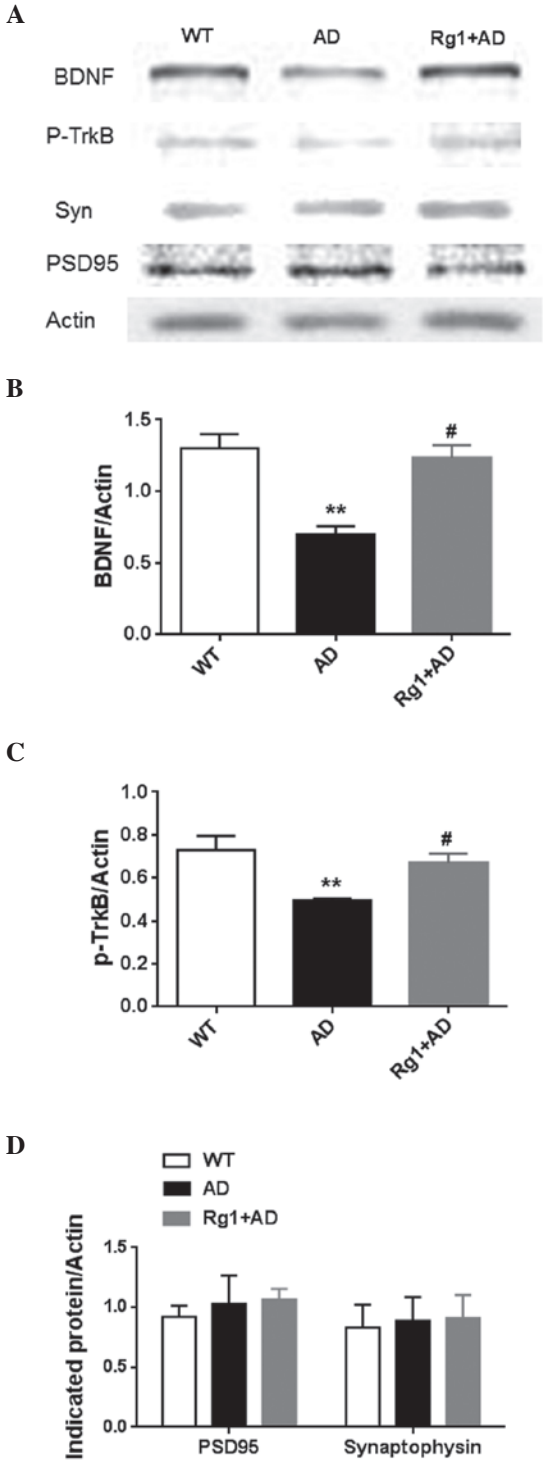

Figure 5. Chronic treatment with ginsenoside Rg1 activates the expression of BDNF and p-TrkB. (A) Representative blots of BDNF, p-TrkB, synaptophysin and PSD95. (B) Quantification of data of the expression of BDNF. (C) Quantification of data of the expression of p-TrkB. (D) Quantification data of the expres asion levels of synaptophysin and PSD95. Data are presented as the mean ± standard error of the mean from five animals in each group. **P<0.01, compared with WT; #P<0.05, compared with AD. BDNF, brain-derived neurotrophic factor; p-TrkB. phosphorylated tropomyosin receptor kinase B; Syn, synaptophysin; PSD95, postsynaptic density protein 95; AD, Alzheimer's disease; WT, wild-type.

p-TrkB was also upregulated following treatment with ginsenoside Rg1 (P<0.05; Fig. 5C). By contrast, no effects were observed on the presynaptic marker, synaptophsin or post-

synaptic marker, PSD-95 (Fig. 5D) following treatment with ginsenoside Rg1. These results indicated that ginsenoside Rg1 may have improved plasticity, but did not alter basal synapses in the AD model.

Discussion

In the present study, it was demonstrated that ginsenoside Rg1 treatment improved memory and hippocampal LTP in the AD model. The expression levels of AD-associated proteins were attenuated, and the BDNF-TrkB pathway was improved following ginsenoside Rg1 treatment.

Ginsenoside Rg1 ameliorates long-term memory in pathological disease models. A series of studies have reported that ginsenosides improve memory in exogenous toxin-induced memory deficits (16-19,27,28). In addition, ginsenosides also improve memory in aging or aged animals (23,29,30). These data indicate that ginsenosides are effective in improving memory. In the present study, ginsenoside Rg1 was selected as the target therapeutic drug, and a transgenic AD model was used to screen the effective doses. The results of the present and previous studies demonstrated that the APP/PS1 transgenic mice exhibited a decline in memory performance at 6 months of age (25). In the present study, intraperitoneal injection of Rg1 at concentrations between 1 and 10 mg/kg was selected, based on previous publications (22,24). As shown by Zhang *et a*l (22), this dose range is normal in mice and rats, following conversion from humans. Chronic treatment for 1 month with 10 mg/kg ginsenoside Rg1 significantly ameliorated long-term memory. Although the low dose of ginsenoside Rg1 (0.1 mg/kg) did not cause amelioration in the AD model, the middle dose (1 mg/kg) demonstrated a protective effect. These results showed a dose-dependent effect of ginsenoside Rg1 on memory. Due to the chemical structure of ginsenoside Rg1, effective technology to improve its capacity to pass through the blood brain barrier is urgently required. Although β-amyloid peptide 1-42-induced functional loss is ameliorated by ginsenoside Rg1 application (24,31), the present study demonstrated a similar effect of ginsenoside Rg1 using a transgenic AD model and fear conditioning experiment. The present study also aimed to clarify the potential mechanisms underlying the memory improvement observed following ginsenoside Rg1 treatment. As no commercial ginsenoside Rg1 injection is available, an effective dose range for oral application requires screening for clinical practice.

Ginsenoside Rg1 facilitates the clearance of AD-associated proteins. Amyloid plaques are considered to be a detrimental toxin, contributing to the impairment of hippocampal synaptic plasticity and to hippocampal cell death (7-9). In the APP/PS1 transgenic mice, APP was overexpressed, and led to an increase in the accumulation of amyloid 1-42 in the hippocampus. In addition, the AD protein, p-Tau, was enhanced at 6 months of age. These abnormalities caused by the overexpression of APP and PS1 may be responsible for the subsequent memory decline. In ginsenoside Rg1-treated mice, the expression levels of APP and PS1 were unaffected. However, the accumulation of p-Tau and amyloid 1-42 in the hippocampus were significantly reduced. The decreases in p-Tau and amyloid 1-42 may be caused by two factors. Protein synthesis may have been inhibited by ginsenoside Rg1 treatment. This possibility is supported by a previous study, which showed that ginsenoside Rg1 inhibits amyloid generation through regulation of the transcription or translation of BACE1 (32), or via inhibition of γ-secretase activity (33). The activity of the protein degradation system was enhanced following treatment with ginsenoside Rg1, leading to the degradation of β-amyloid, however, further clarification of this is required.

The majority of previous studies have focused on the amelioration of ginsenoside Rg1 in the later stage of AD. Ginsenoside Rg1 may prevent against β-amyloid plague accumulation to inhibit apoptosis (34-36).

Ginsenoside Rg1 ameliorates synaptic plasticity in the AD mice model. In addition to the clearance of AD-associated proteins, ginsenoside Rg1 also facilitated the recovery of long-term potentiation. Initially, ginsenoside Rg1 treatment did not affect basal synaptic transmission, in terms of input-output and paired-pulse facilitation. These results suggested that ginsenoside Rg1 did not affect basal synaptic transmission, either presynaptically or postsynaptically. These physiological data were consistent with the unaltered expression levels of PSD-95 and synaptophysin. By contrast, plasticity was enhanced following ginsenoside Rg1 treatment in the AD model. The effects on LTP may be due to the clearance of AD-associated proteins. The present study found that the expression of BDNF was upregulated by ginsenoside Rg1 treatment and, correspondingly, p-TrkB was activated following ginsenoside Rg1 treatment. Therefore, activation of the BDNF-TrkB pathway may contribute to the recovery of LTP in the transgenic AD model. In a senescence-accelerated mouse prone 8 model, the levels of BDNF are also improved following treatment with ginsenoside Rg1 (37). These findings indicate the general pharmacological activity of ginsenoside Rg1 in the AD model. In addition, other synaptic plasticity-associated proteins, including NR1 and NR2B, are reported to be upregulated in the AD model to increase memory (38). How ginsenoside Rg1 functions in the hippocampus remains to be fully elucidated and, although the present study did not distinguish the potential target, estrogen receptors have been implicated (39).

In the present study, data indicating memory amelioration following ginsenoside Rg1 treatment were obtained in a transgenic AD model. Clearance of AD-associated proteins and activation of the BDNF-TrkB pathway may contribute to the effect of ginsenoside Rg1 on hippocampal LTP. These results suggested that ginsenoside Rg1 may be a potential memory enhancer in the transgenic AD model.

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