Ginseng improves cognitive deficit via the RAGE/NF-κB pathway in advanced glycation end product-induced rats

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A B S T R A C T

Background: Ginseng, the root of Panax ginseng (PG), is used widely as a herbal medicine to prevent and treat various diseases. Panax ginseng has pharmacological effects on neurodegenerative diseases such as Alzheimer’s disease (AD). The present study evaluated the neuroprotective effects of PG and its possible neuroprotective mechanisms in advanced glycation end product (AGE)-induced AD in a rat model.

Methods: Advanced glycation end products were injected bilaterally into the CA3 region of the rats’ brains. The Morris water maze test and step-down type passive avoidance test were performed to evaluate their memory and cognitive abilities. The oxidation indexes in the hippocampus were detected.

Results: Behavioral results showed that PG (1 g/kg, 0.5 g/kg, and 0.25 g/kg) significantly increased the number of crossing times, significantly shortened the escape latency, remarkably increased the number of crossing times, significantly decreased the escape latency, remarkably decreased the number of crossing times, markedly increased the number of crossing times, significantly decreased the number of crossing times, and prolonged the latency in rats with AGE-induced AD. Panax ginseng also significantly reduced the malondialdehyde level, increased the glutathione content, and increased superoxide dismutase activity in the hippocampus. Panax ginseng significantly decreased the expression of RAGE and NF-κB. The blockade of anti-RAGE antibody could significantly reduce AGE-induced impairments and attenuate the pathological changes of AD.

Conclusion: Our results demonstrated that PG significantly inhibits AGE-induced memory impairment and attenuates Alzheimer-like pathophysiological changes. These neuroprotective effects of PG may be associated with the RAGE/NF-κB pathway. Our results provided the experimental basis for applying PG in preventing and treating AD.

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1. Introduction

Alzheimer’s disease (AD) is a severe neurodegenerative disorder of the central nervous system characterized by senile plaque deposition, neurofibrillary tangle formation, memory loss, and cognitive impairment. The pathogenesis of AD is not fully understood, although multiple lines of evidence suggest the importance of amyloid-β (Aβ) in the progression of the disease [1]. Recent research indicates that advanced glycation end products (AGEs) derived from the Maillard reaction of glucose and proteins and lipids can activate receptors for AGEs (RAGE) and lead to the pathological changes of AD [2]. Advanced glycation end products
are colocalized in amyloid plaques in the brains of AD patients [3–5]. Many experimental studies indicate that the interaction between AGEs and RAGE elicits intracellular oxidative stress, proinflammatory apoptosis, and oxidative stress responses, which lead to nerve cell damage [6,7]. These signal transduction pathways may be associated with RAGE/nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) pathway [8]. These studies suggest that the AGE/RAGE/NF-κB signaling pathway has important roles in the lesions or progression of AD [9].

Ginseng, the root of Panax ginseng (PG), has been traditionally used as a herbal medicine in Asia for at least 2000 years—particularly in China, Korea, and Japan. Many studies show that PG has a beneficial effect on the cognitive performance of AD patients [10–14]. The compounds of PG can prevent Aβ formation and thereby improve spatial memory impairment in rats [15]. Panax ginseng also attenuates AGE-induced nerve cell damage through reducing AGEs formation [16]. However, the underlying mechanism of PG extract on the beneficial effects of AD remains largely unknown.

The goals of the present study are: (1) to fully assess the effects of PG on learning/memory capacity in AGE-induced AD in rats and (2) to elucidate the underlying mechanism of the neuroprotective effect of PG on AGE-induced nerve damage. Our findings in this study may provide a new insight for understanding the therapeutic effect of PG on the development of AD.

2. Materials and methods

2.1. Reagents

Bovine serum albumin (BSA), d-glucose and donepezil were obtained from Sigma-Aldrich (St. Louis, MO, USA). Superoxide dismutase (SOD), malondialdehyde (MDA), and glutathione (GSH) kits were ordered from Nanjing Jiancheng Bio Co., Ltd. (Nanjing, China). Rat NF-κB p65 IgG, anti-RAGE antibody (anti-RAGE) and RAGE antibody were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA, USA). The AGEs enzyme-linked immunosorbent assay (ELISA) kit was obtained from Shanghai Kaibo Biochemical Reagents Ltd. (Shanghai, China). The other reagents were of analytically pure grade.

2.2. Preparation of PG extract

The roots of Panax ginseng were purchased from Jiangsu Medicine Company (Nanjing, China) and authenticated by Professor Min-Jian Qin (Department of Medicinal Plants of the China Pharmaceutical University, Nanjing, China). The voucher specimens were deposited in the Key Laboratory of Delivery Systems of Chinese Materia Medica at the Jiangsu Provincial Academy of Chinese Medicine (Jiangsu, China). The dried medicinal materials of 1000 g were cut into slices and extracted by reflux extraction in 20 L distilled water twice (2 h each time). After filtration and concentration with a rotary evaporator, the PG extract was obtained (the yield of PG was 10.4%).

2.3. High-performance liquid chromatography analysis of PG compounds

The Agilent 1260 high-performance liquid chromatography (HPLC) system (Agilent Technologies, Palo Alto, MA, USA) was used for the analysis of compounds of the PG extract. It was equipped with a quaternary pump, online vacuum degassing pump, autosampler, column oven, diode array detector, and Agilent chemstation software. The separation column was the Prevail C18 column (i.d., 5 μm; 4.6 mm × 250 mm) (RYSS, Shanghai, China). The mobile phase consisted of water (solvent A) and acetonitrile (solvent B) with a linear gradient elution program: 0–25 min, 2–23% B; 25–35 min, 23–29% B; 35–55 min, 29–40% B; 55–65 min, 40–40% B. The column temperature was 30°C and the injection volume was 10 μL. The flow rate was maintained at 0.8 mL/min.

2.4. Animals

Adult male Sprague-Dawley rats (280–300 g) were obtained from the Experimental Animal Center in Jiangsu Province (Nanjing, China) and housed for 7 d to adapt them to the environment; they were maintained in a temperature-controlled room (25°C ± 2°C) and maintained on a 12-h/12-h light/dark cycle with food and water available ad libitum. All experiments and animal care were performed strictly in accordance with the Provision and General Recommendation of Chinese Experimental Animals Administration Legislation and were approved by the Science and Technology Department of Jiangsu Province.

2.5. Preparation of AGEs

The preparation of AGE proteins (i.e., AGEs-BSA) was performed as described previously [7]. Bovine serum albumin (5 g) was incubated with and without d-glucose (9 g) in 0.2M phosphate buffer saline (PBS; pH, 7.2). After being filtrated through a 0.22-μm microporous film, the mixture was maintained at 37°C for 3 months under sterile conditions. Unincorporated glucose was then removed by dialysis through a semipermeable membrane against PBS for 48 h. The prepared AGEs were sterilized by filtration and maintained at 20°C. Advanced glycation end product-specific fluorescence was measured at excitation/emission of 370 nm/440 nm using a fluorescence spectrophotometer (PerkinElmer, Waltham, MA, USA) and the content was detected by an AGEs ELISA kit (final concentration, 862 μg/mL).

2.6. Drugs and treatment

Rats were anesthetized by an intraperitoneal injection of chloral hydrate (320 mg/kg) and placed into a stereotaxic device. Two holes were created for injection at the following coordinates: −3.4 mm posterior to the bregma, ±2.5 mm lateral to midline, and −3.0 mm dorsal to the ventral dura [17]. Rats were randomly divided into eight groups (with 10 rats per group), as follows: (1) normal; (2) BSA; (3) AGEs; (4) AGEs+anti-RAGE; (5) AGEs+donepezil; (6) AGEs+PG (1.0); (7) AGEs+PG (0.5); and (8) AGEs+PG (0.25 g/kg). Bovine serum albumin (500 μg) or AGEs (500 μg) or AGEs (500 μg)+anti-RAGE antibody (50 μg) was injected bilaterally into the CA3 region of the brains [18]. The rats were then maintained in a temperature-controlled chamber until they recovered from anesthesia. Penicillin-G 200,000 IU/mL was intramuscularly administered for 3 d to prevent infection [19]. One day after the operation, the rats in the normal group, BSA group, and AGEs group received saline water. Donepezil hydrochloride (2 mg/kg) by oral administration was used for the positive control [19]. The rats in the AGEs+PG groups received PG dissolved in saline water at dose of 1 g/kg, 0.5 g/kg, or 0.25 g/kg. All drugs were administered orally for 30 consecutive d.

2.7. Morris water maze test

After drug administration for 25 d, the spatial memory ability of rats was determined by the Morris water maze test [18]. The test was performed in a black circular pool (180 cm in diameter and 60 cm in height) with a featureless inner surface. A round platform was placed 1 cm below the water surface in the center of the target
quadrant. Rats were administered two trials each day for 4 d consecutively with an intertrial interval of 5 h. Their escape latencies were recorded. Once the rat located the platform, it was allowed to remain on it for 10 s. If the rat did not locate the platform within 120 s, it was placed on the platform for 15 s and the escape latency was recorded as 120 s. After the 5-d training, the platform was removed for the probe test and each rat was allowed to swim freely for 120 s. The number of times of crossing the platform was measured and the swimming trajectory was recorded.

2.8. Step-down type passive avoidance test

The step-down type passive avoidance test was performed in accordance with a previously described method of the Morris water maze test [20]. Rats were placed in the box to adapt for 3 min. When electric currents (0.5 mA for 2 s) were delivered, the rats would jump onto the platform to avoid the electric shock. Once the rats stepped down from the platform, they would be subjected to an electric shock again, and the electric currents were maintained for 3 min. After a 24-h interval, the rats were placed on the platform again, and the latency to step down on the grid with two paws for the first time was recorded. The number of errors that were subjected to shock within 3 min was measured as learning performance.

2.9. Assays for SOD activity and the content of MDA and GSH

Six rats in each group were sacrificed after the behavioral tests. Their brains were removed and the hippocampi were immediately dissected on a cold plate, weighed and quickly homogenized with 0.9% ice-cold saline water. The homogenate was centrifuged at 1000 × g for 10 min at 4 °C and the supernatants were collected for the measurement of SOD activity and levels of MDA and GSH in accordance with the manufacturer’s instruction.

2.10. Immunohistochemistry for RAGE and NF-κB expressions

The remaining rats from each group were anesthetized with chloral hydrate (320 mg/kg, i.p.) and sacrificed by a transcardial perfusion of 0.1M PBS (pH, 7.4), followed by 4% paraformaldehyde. After fixation for 24 h, the brains were dehydrated by serial gradient concentrations of alcohol, and then embedded in paraffin blocks. Immunohistochemistry was performed on the paraffin-embedded tissue sections (4 μm each piece), as previously described [21]. After quenching endogenous peroxidase and blocking with normal goat serum, the sections were incubated overnight at 4 °C with rabbit anti-rat antibodies specific against RAGE and NF-κB p65, respectively. After washing with PBS, the sections were incubated at 37 °C for 2 h with the secondary antibodies, and then stained by 3,3’-diaminobenzidine in chromogen solution. The staining of RAGE and NF-κB was measured by Image Pro Plus software (IPP 6.0, Media Cybernetics, Rockville, MD, USA). Brown staining on the cell membrane or in the cytoplasm represented positive staining, and the staining density indicated the expression levels of RAGE and NF-κB.

2.11. Statistical analysis

All values were expressed as the means ± the standard deviation and analyzed by one-way analysis of variance (ANOVA), followed by Duncan’s multiple range test using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered significant and p < 0.01 was considered statistically very significant.

3. Results

3.1. The major compounds of PG extract

A HPLC system was used to determine the major compounds of PG extract. As Fig. 1A, B show, the PG extract contains primarily ginsenosides Rg1, Rb1, Rh1, Rb2, and Rc, after being compared with mixed standard substances. The retention times of the five ginsenosides were 35.74 min (Rg1), 49.61 min (Rb1), 51.38 min (Rh1), 52.47 min (Rb2), and 53.12 min (Rc). The contents of Rg1, Rb1, Rh1, Rb2, and Rc were 1.24%, 1.18%, 0.41%, 0.37%, and 0.11%, respectively. This analysis could provide detailed information on ingredients in PG samples.

3.2. PG increases the learning and memory ability of AD rats undergoing the Morris water maze test

The Morris water maze test was used to assess the spatial learning and memory ability of the rats. As Fig. 2A shows, the mean latency to find the platform declined progressively during the 4 d of training. There was no significant statistical difference between the normal and BSA groups. The rats treated with 500 μg AGEs spent remarkably more time on finding the platform, compared to the control rats (Days 1–4, p < 0.01). These results revealed that AGEs-treated rats had obvious cognitive impairment. What is more important is that the increase in the escape latency was shortened by treatment with PG (1 g/kg, 0.5 g/kg, and 0.25 g/kg) from the 2nd d to the 4th d (p < 0.01 and p < 0.05, vs. the model). The positive control—the cholinesterase inhibitor donepezil (2 mg/kg)—improved cognitive performance from the 3rd d to the 4th d (p < 0.01, vs. the model). The anti-RAGE (50 μg) antibody significantly shortened the escape latency from the 2nd d to the 4th d (p < 0.01 and p < 0.05, vs. the model). Fig. 2B illustrates the swim paths of rats in the second trial on the 2nd d and the 4th d. Rats tended to explore all four quadrants of the pool on the 4th d. On the 4th d, the control rats swam in the direction of the platform, whereas the AGEs-treated rats took longer swimming paths. In the probe test, as shown in Fig. 2B, the control rats had more crossing times (Normal group 6.1 ± 2.0 and BSA group 5.3 ± 1.6, respectively), compared to the AGEs-treated rats (1.3 ± 1.0, p < 0.01). In addition, the rats treated with PG (1 g/kg, 0.5 g/kg, and 0.25 g/kg) and anti-RAGE antibody had more crossing times (p < 0.05 and p < 0.01, vs. the model group).

We also measured the time spent in the target quadrant. However, no significant improvement was observed (data not shown). These results suggested that PG could improve the learning and memory ability in AGE-induced AD in the rat models.

3.3. Step-down type passive avoidance test

The step-down type passive avoidance test was used to evaluate the effect of PG on memory ability. Compared to the normal and BSA rats, AGEs-treated rats exhibited poor performances: the number of errors significantly increased while latency was shortened (p < 0.01; Fig. 3A, B). At the doses of 1 g/kg and 0.5 g/kg, PG treatment significantly decreased the number of errors (p < 0.01 or p < 0.05) and prolonged the latency (p < 0.05 or p < 0.01, vs. the model group). Treatment with donepezil and the blockade of anti-RAGE displayed a similar effect (p < 0.05 and p < 0.01, vs. the AGEs-treated rats). These results suggested that PG could improve the cognitive function of AGE-induced AD in the rat models in a dose-dependent manner. Furthermore, this activity may be associated with the blockade of RAGE.
1. Rg1 (C42H72O14, MW=801.01)
2. Rb1 (C54H92O23, MW=1109.26)
3. Rh1 (C36H62O9, MW=638.87)
4. Rb2 (C53H90O22, MW=1079.27)
5. Rc (C53H90O22, MW=1079.27)

Fig. 1. (A) The HPLC analysis for the following compounds in the PG sample and in the mixed standards: Rg1 (1), Rb1 (2), Rh1 (3), Rb2 (4), and Rc (5). (B) The chemical structures of the ginsenosides. HPLC, high-performance liquid chromatography; PG, Panax ginseng.
3.4. Effects of PG on SOD activity and levels of MDA and GSH in the hippocampus

Superoxide dismutase activity, MDA level, and GSH content were measured to evaluate the attenuation effect of PG on AGE-induced oxidative damage (Table 1). According to the free radical theory of aging, the accumulation of reactive oxygen species that are generated from biological oxidations of normal metabolism causes oxidative damage and leads to cellular dysfunction [22]. Superoxide dismutase is regarded as the first line in the antioxidant defense system. In the present study, SOD activity was remarkably inhibited by intracerebral injection of AGEs (p < 0.01). The oral administration of PG showed a significant increase in SOD activity (p < 0.01 and p < 0.05, vs. the model group), and the positive drug donepezil and anti-RAGE antibody had a similar protective effect (p < 0.01 and p < 0.05).

Malondialdehyde is a product of lipid peroxidation from oxidative damage. Therefore, an elevated level of MDA is associated with the degree of neuronal degeneration. In this study, the MDA content in AGEs group was significantly increased, compared to the control groups (p < 0.01). However, this increase was significantly reversed by PG (1 g/kg, 0.5 g/kg, and 0.25 g/kg), anti-RAGE antibody, and donepezil.

Glutathione, an endogenous antioxidant against free radicals, was decreased significantly in the hippocampus of AGEs-treated mice (p < 0.01, vs. the controls). This decrease was interestingly reversed by PG treatment (p < 0.01 and p < 0.05, vs. the model). This phenomenon also occurred in the anti-RAGE antibody and
donepezil treatment groups. Based on all aforementioned results, we believed that the reduction of AGE-induced oxidative damage by PG contributed to its beneficial effect. This function may be associated with the blockade of the RAGE target.

3.5. The effect of PG on the expressions of RAGE and NF-κB in the cortex and hippocampus

Studies have shown that RAGE is markedly expressed in neurons, microglia, and astrocytes in AD brains. The expression of RAGE is positively correlated with the severity of AD pathology [23]. The protein complex NF-κB is activated and involved in regulating many aspects of cellular activity and stress under physiological and pathological conditions [24]. In our present experiment, the expressions of RAGE and NF-κB in the cortex and hippocampus of the rats were analyzed by immunohistochemistry. In the cortex and hippocampus of rats with AGE-induced AD, the mean densities of brown staining of RAGE and NF-κB were significantly increased (Figs. 4C, 5C, respectively). However, PG and anti-RAGE antibody significantly downregulated the mean densities of RAGE and NF-κB in a dose-dependent manner (p < 0.01 and p < 0.05, vs. the AD model group). These data indicated that PG may attenuate AGE-induced cognitive impairment via modulating the RAGE/NF-κB pathway.

4. Discussion

In this study, the Morris water maze test and step-down type passive avoidance test were conducted to explore the learning performances and spatial memory ability of the experimental animals. Immunohistochemistry was used to measure the RAGE and NF-κB expressions in the cortex and hippocampus of the brains, whereas SOD activity and levels of MDA and GSH in the hippocampus were measured to evaluate the attenuation of PG on AGE-induced oxidative damage in vivo. Our work showed that PG attenuated AGE-induced Alzheimer-like behaviors in the rats. The mechanism of this result may be that PG can inhibit RAGE and NF-κB expressions and reduce the antioxidation effect in hippocampus.

Advanced glycation end products, which are the nonenzymatic glycation products from reducing the sugar and amino groups of proteins, lipids, and other molecules, have been implicated as important contributors in the pathogenesis of AD. The roles of AGEs and its receptor (i.e., RAGE) in AD have resulted in increased scientific focus [2]. The accumulation of AGEs in intracellular deposits in normal brains and AD brains is age-dependent and stage-dependent [25,26]. The binding of AGEs to RAGE activates oxidative stress and other cascades of signaling events, and finally activates redox-sensitive transcription factors such as NF-κB [27]. In our study, the injection of AGEs in the CA3 area of the rat brain impaired the performance of the rats in the Morris water maze test and in the step-down passive avoidance test; these findings were in accordance with previous findings [20]. The better cognitive functions of PG indicate that PG has potential benefit for ameliorating cognitive deficits induced by AGEs.

The RAGE is an immunoglobulin superfamily cell surface molecule that was originally discovered as an AGEs-binding receptor. Increasing evidence shows that interaction between AGEs and their receptors could activate the NF-κB pathway and result in neurodegeneration [28]. To further confirm the role of RAGE in AGE-induced nerve damage, a RAGE blocker (i.e., anti-RAGE antibody) was used to block AGE-induced pathological damage. The blockade of anti-RAGE antibody or PG nearly abolished Alzheimer-like pathophysiological changes induced by AGEs.

Previous reports have demonstrated that PG can improve cognitive performance of AD patients [10,11]. The consistency of our findings with previous research results supports the fact that PG could attenuate AGE-induced nerve cell damage through regulating RAGE activation [16]. The attenuation of PG on AGE-induced Alzheimer-like pathophysiological changes may be associated with its blockade on the interaction between AGEs and RAGE or on the RAGE-mediated signaling pathway.
Oxidative stress is implicated in the pathogenesis of AD. Under the conditions of high concentrations of AGEs, the endogenous mechanisms for the maintenance of redox homeostasis are overwhelmed [29]. Recent evidence indicates that oxidative stress participates in the induction of Aβ levels and has a central role in the cellular mechanisms of stress tolerance [30]. Accumulating evidence sheds insight that RAGE-mediated oxidative damage is an important contributor to neurodegeneration in AD [31]. Ginsenosides may be primarily responsible for the effect of PG on oxidative stress by reducing hydroxyl radicals and hypochlorous acid [32]. Our results demonstrated that PG could attenuate AGE-induced oxidative damage through reducing the levels of MDA (malondialdehyde, MDA) and by increasing the activity of SOD and the content of GSH. The improvement of PG on AGE-induced oxidative damage was similar with anti-RAGE antibody. The attenuation of PG on oxidative damage may be a RAGE-mediated oxidative stress response in AGE-induced Alzheimer-like pathophysiological changes.

The molecule NF-κB, which is in the transcription factor protein family, serves as an important regulator for downstream signaling pathways that contribute to the Alzheimer-like pathophysiological changes. Oxidative stress could activate the NF-κB signaling...
The beneficial effect of PG on AGE-induced oxidative damage suggested that PG could inhibit AGE-induced brain damage through downregulating RAGE and thus inhibiting the activation of NF-κB in the cortex and hippocampus. This reduction indicated that the beneficial effect of PG on AGE-induced cognitive deficits may be associated with its regulation of NF-κB activation and oxidative stress through downregulating RAGE. However, the downstream signaling pathways need to be further investigated to reveal this mechanism.

In conclusion, our results provide insights into the improvement of PG on AGE-induced AD-like pathophysiological changes. Panax ginseng could enhance significantly the learning and memory ability of AD rats and attenuate oxidative stress damage. A possible mechanism may be associated with its blockade of RAGE/NF-κB activation. Further studies are required to elucidate the signaling events of PG that contribute to its protection mechanisms on AGE-induced AD. Furthermore, more studies need to explore the primary effective components in PG. Our results provide the
experimental basis for the application of PG in preventive or therapeuti
c strategies in AD.

Conflicts of interest

The authors have no conflicts of interest to declare.

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