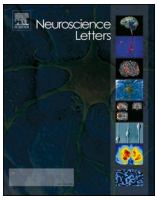
Neuroscience Letters 791 (2022) 136887

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Sodium propionate improves cognitive and memory function in mouse models of Alzheimer's disease

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ARTICLE INFO

Keywords:
Sodium propionate
Short-chain fatty acids
Alzheimer's disease
Synaptic plasticity
Cognitive behavior

ABSTRACT

This study was designed to explore whether sodium propionate (SP) alleviates cognitive damage in a mouse model of Alzheimer's disease (AD). We evaluated behavioral and biochemical aspects in an animal model of AD made by intracerebroventricular injection of $A\beta_{1\text{-}42}$ peptide. Two-month-old ICR mice were treated with SP or normal saline for 21 days (control group, $A\beta_{1\text{-}42}$ group, $A\beta_{1\text{-}42}$ + SP50 mg/kg group, $A\beta_{1\text{-}42}$ + SP100 mg/kg group, and $A\beta_{1\text{-}42}$ + SP200 mg/kg group). Behavioral tests showed that SP alleviated cognitive and memory impairments in AD mice. Moreover, SP treatment significantly suppressed the level of inducible nitric oxide synthase (iNOS) in the hippocampus. Concomitantly, the overexpression of interleukin-1α (IL-1α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) in the hippocampus induced by $A\beta_{1\text{-}42}$ was significantly reduced following treatment with SP. In addition, SP was able to increase the levels of synaptophysin (SYN) and postsynaptic dense protein 95 (PSD95). Our study shows that SP could significantly improve $A\beta_{1\text{-}42}$-induced spatial learning and memory impairment by reducing neuroinflammation via inhibition of proinflammatory cytokines and iNOS activation and restoring synapse plasticity by increasing synaptically associated protein levels, suggesting that SP has a positive effect and potential for AD therapies.

1. Introduction

Alzheimer's disease (AD) is a neural degenerative disorder that often manifests as memory impairment, and its pathological features are the accumulation of neurofibrillary tangles and amyloid β (Aβ) plaques [1]. AD patients suffer from neuroinflammation, characterized by activation of microglia and astrocytes, with synaptic and neuronal loss resulting in cognitive decline [2]. One of the cytotoxic mechanisms in neuroinflammation is the activation of iNOS, which mediates the synthesis of high levels of nitric oxide, known to be toxic to cells [3]. iNOS expression is significantly increased in AD patients and is accompanied by major neuronal damage [4]. With the development of the inflammatory response, proinflammatory microglial activities are believed to exacerbate the brain environment and contribute to neurodegeneration [5]. Moreover, PSD95, an important scaffolding protein that regulates synaptic distribution and activity, is functionally disrupted by Aβ. PSD95 dysregulation is likely an important intermediate step in the pathological cascade of events caused by Aβ [6]. Therefore, antioxidants and improved synaptic functions may have therapeutic potential for reducing Aβ-induced synaptic injury and cognitive impairment in AD.

Sodium propionate is one of the main short-chain fatty acids (SCFAs) that can be produced naturally through host metabolic pathways [7]. Some studies have shown the beneficial effects of SCFAs [8], in which the effect of SP on inflammation may be due to its ability to suppress histone deacetylase. It has also been reported that SP has protective effects against neurotoxicity and spinal cord injury caused by $A\beta_{1\text{-}42}$ [7]. Furthermore, it was reported that SP decreased the expression of cicloxigenase-2 and iNOS in a concentration-dependent manner following LPS stimulation [9]. Recent studies have reported that the beneficial impact of SP in people living with HIV reflects its potential in improving metabolic parameters and modulating proinflammatory immune responses [10].

In this study, an AD mouse model was used to investigate the effect of SP on cognitive impairment. Inflammatory marker proteins, proinflammatory cytokines and synapse-associated proteins involved in the prevention of learning and spatial memory deficits were also studied.

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https://doi.org/10.1016/j.neulet.2022.136887
Received 19 March 2022; Received in revised form 1 September 2022; Accepted 22 September 2022
Available online 26 September 2022

This work provides new ideas and strategies for the treatment of AD.

2. Materials and methods

2.1. Animals

Two-month-old male Institute of Cancer Research (ICR) mice that weighed 30 ± 5 g were purchased from Shenyang Changsheng Biological Company. (Shenyang, PRC). The mice were kept under an environment (22 °C ± 2 °C with 50–60 % humidity, on a normal 12-h light/dark period) and with free access to food and water. Every assay was completed strictly as per the PRC guidelines on the usage and welfare of lab animals. The behavioral assay was initiated on the 13th day of sodium propionate exposure before the schedule displayed in Fig. 1.

2.2. Surgical operation and grouping

Mice were fed for one week and anesthetized with isoflurane. The mice were fixed on the brain stereo locator, the microinjector was vertically inserted into the lateral ventricle, 3 μL (410 pmol) $A\beta_{1\text{-}42}$ (Abcam, Cambridge, UK, ab120959) was injected slowly for 5 min, and the needle was left for 3 min [11,12]. The control group was only subjected to the surgical procedure and received saline as a vehicle. The incisions were sutured and disinfected, and the mice were raised in cages.

Animals were stochastically separated into five groups: control, $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}42}$ + SP50 mg/kg, $A\beta_{1\text{-}42}$ + SP100 mg/kg, and $A\beta_{1\text{-}42}$ + SP200 mg/kg, with 12 mice in each group. In the four $A\beta_{1\text{-}42}$-treated groups, $A\beta_{1\text{-}42}$ was stereotactically injected into the lateral ventricle (AP: −1.1 mm, ML: −0.5 mm, DV: −3.0 mm relative to the bregma). The mice in the control group were injected with the same volume of normal saline. After surgery, the mice in the SP groups were injected intraperitoneally with SP at different doses every day. The control group and $A\beta_{1\text{-}42}$ group were given normal saline. The behavioral assay was initiated on the 13th day of SP (Sigma–Aldrich, USA) exposure.

2.3. Novel object recognition assay (NOR)

A plastic open-air field (50 cm × 50 cm × 40 cm, self-restraint) was installed. The first day involved adaptation for 5 min. The next day constituted the familiarization and test phases. During the familiarization phase, two identical objects were placed in the plastic box, and each mouse was placed in the box in turn to explore freely for 5 min. The overall detection duration for these two objects was documented. The recognitional index was computed as the exploration duration of one object/the overall exploration duration of two objects × 100 %. Then, for the testing phase, one of the objects was changed to a new object of the same material with different colors and shapes. The animals were put in the same position and could explore freely for 5 min. The discrimination index (DI) was computed via DI = [(TN-Ti)/(Tn + Ti)] × 100 %, where Tn denotes the duration of exploring novel objects, and Ti denotes the exploration duration of familiar objects.

2.4. Morris water maze (MWM) assay

The test comprised a white round pool (120 cm diameter × 45 cm height) (Shanghai Jiliang Co., ltd), a movable black platform, and the water was kept at 25 °C ± 1 °C. The animals were trained once in the morning and afternoon for 5 running days. The mice swam and discovered the platform and then stayed on it for 10 s. If the animal could not discover it in 1 min, it was instructed to stay on it for 10 s. The duration every animal landed on it was documented as the escape latency. On Day 6, the mice were tested for memory ability; the hidden platform was removed, and the mice were placed in the pool. Swimming velocity, number of platform crossings, and swimming duration in the targeted quadrant within 1 min were documented.

2.5. Tissue preparation and immunofluorescent assay

Brain tissues were fixed in 4 % PFA at 4 °C for 24 h before embedding in wax blocks. Briefly, dewaxing and hydration: Antigen repair: Tissular sections were put in a repair box with ethylenediamine tetraacetic acid antigen repair buffer solution (pH 6.0) for antigenic repair in a microwave device. After cooling naturally, the slices were placed in PBS (pH 7.4) and shaken on a deodorizing shaking device three times for 5 min each. After 30 min, iNOS (1:300, Abcam, Cambridge, UK, ab178945), SYN (1:100, CST, USA, 36406 T) and PSD95 (1:100, CST, USA, 3450 T) were added, and the slides were incubated at 4 °C overnight and then with secondary antibody at 37 °C for 60 min, followed by immunofluorescent staining. The nuclei were dyed with 4′6-diamidino-2-phenylindol (DAPI). The images were obtained by a fluorescence microscope. We used CaseViewer software to view the immunofluorescence images. The fluorescence intensity was measured by ImageJ (version 1.4.3.67).

2.6. Measurement of proinflammatory cytokines

The levels of IL-1α, IL-1β and IL-6 in hippocampal tissue were measured by ELISA kits (Shanghai Jingkang Biological Engineering Co., ltd., China, JLC3559, JLC3580, JLC3601) according to the manufacturer's instructions.

2.7. Western blot

The mouse hippocampi were weighed and prepared with lysis buffer. After homogenization, the protein content of the supernatant was measured after centrifugation. The supernatant containing quantitative protein from each sample was heated and denatured, and then the protein was separated by vertical electrophoresis with sodium dodecyl sulfate polyacrylamide gel electrophoresis (10 % separated gel + 5 % concentrated gel). After treatment, the isolated target protein was transferred to a polyvinylidene fluoride film. The film was sealed in 5 % skim milk powder and incubated overnight with iNOS (1:1000 Abcam),

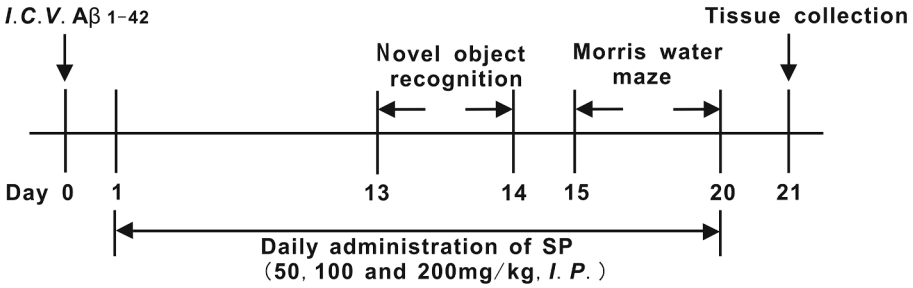

Fig. 1. The schedule of the experiments performed. The NOR assay was executed from the 13th to the 14th day. The MWM assay was implemented from the 15th to the 20th day. Tissue was collected on the 21st day.

PSD95 (1:1000 CST), and SYN (1:1000 CST) antibodies at 4 °C. The next day, the PVDF film was cleaned thrice with TBST for 10 min each. The second antisubstance (goat antirabbit IgG, 1:3000) was supplemented and cultivated under ambient temperature for 90 min. The films were then cleaned in tris-buffered saline containing TBST thrice for chemiluminescence. The protein signal intensity analysis was performed with ImageJ, and the intensity of β-actin was taken as the standard.

2.8. Statistics

SPSS 22.0 software was used for statistical analysis, and the results are expressed as the mean ± SEM. Data normality and homogeneity of variance were tested by the Shapiro–Wilk test and Levene test, respectively. If the data were consistent with a normal distribution and homogeneity of variance, one-way ANOVA was used, and LSD (least significance method) was used for pairwise comparisons among groups. The Kruskal–WallisWallis H (K) test was used if it did not conform to a normal distribution or variance. Test level $\alpha = 0.05$, bilateral test, $P < 0.05$ is statistically significant.

3. Results

3.1. Effect of sodium propionate on the novel object recognition assay

As shown in Fig. 2A, B, C, the overall exploration duration, recognition index in the acquisition stage and overall exploration duration in the test stage of animals in every group were similar ($P > 0.05$). A significant reduction in DI in the test stage was found in the $A\beta_{1\text{-}42}$ group, while this reduction was reversed by treatment with SP (100 mg/kg and 200 mg/kg) but not 50 mg/kg. 2D.

3.2. Effect of sodium propionate on $A\beta_{1\text{-}42}$-induced memory impairment

As shown in Fig. 3B, a significant increase in escape latency was found in the $A\beta_{1\text{-}42}$ group, while this increase was reversed by treatment with SP (100 mg/kg and 200 mg/kg) but not 50 mg/kg. The swimming velocity of the animals in every group was similar ($P > 0.05$) (Fig. 3C). A significant reduction in the quantity of platform crossings and target quadrant swimming duration was found in the $A\beta_{1\text{-}42}$ group, while this reduction was reversed by treatment with SP (100 mg/kg and 200 mg/kg) but not 50 mg/kg. 3D, E). SP decreased spatial learning and memory impairment in $A\beta_{1\text{-}42}$-treated mice, and the swimming trace is shown in Fig. 3A.

3.3. Effect of sodium propionate on proinflammatory cytokines

We detected the levels of proinflammatory mediators (IL-1α, IL-1β, IL-6) in the hippocampus. As shown in Fig. 4A, B, C, a significant increase in the expression of IL-1α, IL-1β and IL-6 protein was observed in the $A\beta_{1\text{-}42}$ group compared with the control group ($P < 0.001$). Compared with the $A\beta_{1\text{-}42}$ group, the 100 mg/kg SP treatment group had inhibitory effects on IL-1β and IL-6 ($P < 0.05$), and the 200 mg/kg SP treatment group had inhibitory effects on IL-1α, IL-1β and IL-6 ($P < 0.01$). No significant effect was found in 50 mg/kg SP treatment on proinflammatory cytokines.

3.4. Effect of sodium propionate on iNOS, SYN and PSD95 protein expression

As shown in Fig. 5B, the iNOS fluorescence-positive substance was stronger in the $A\beta_{1\text{-}42}$ group than in the control group ($P < 0.01$). In contrast to the $A\beta_{1\text{-}42}$ group, the 200 mg/kg SP exposure group was weaker ($P < 0.01$). A significant reduction in SYN and PSD95 fluorescence-positive substances was found in the $A\beta_{1\text{-}42}$ group, while this reduction was reversed by treatment with SP (200 mg/kg) but not 50 mg/kg or 100 mg/kg. (Fig. 5C, D).

As shown in Fig. 6A, a significant increase in the expression of iNOS protein was observed in the $A\beta_{1\text{-}42}$ group compared with the control group ($P < 0.05$). The increase in iNOS protein levels in the $A\beta_{1\text{-}42}$-treated mice was significantly reduced after treatment with SP in the

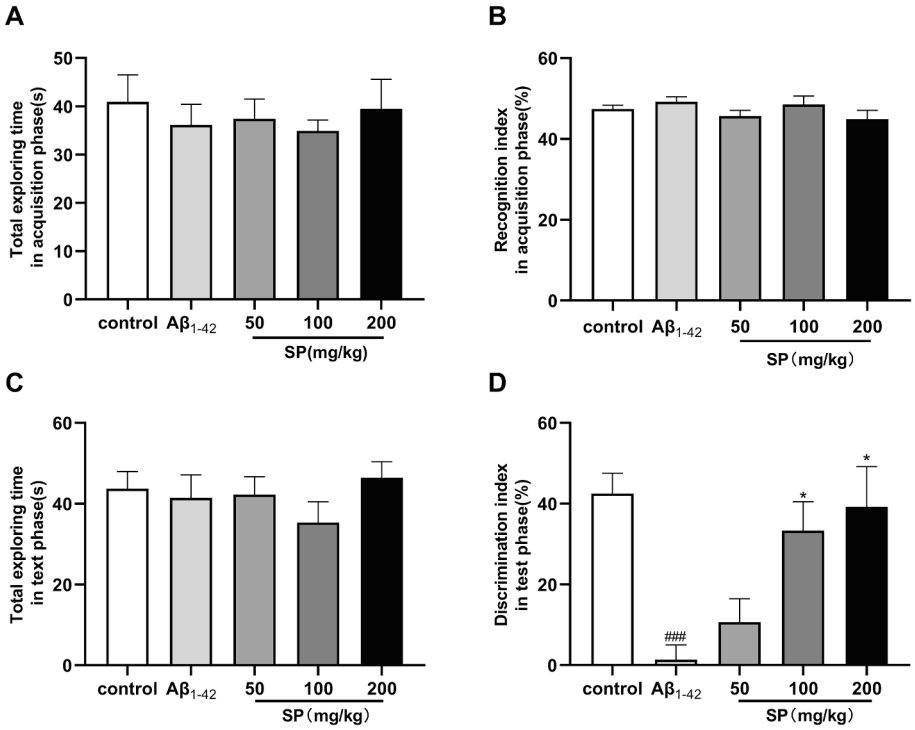

Fig. 2. Effect of SP on the novel object recognition task in mice intracerebroventricularly injected with $A\beta_{1\text{–}42}$. Overall exploration duration in the acquisition stage (A), recognition index in the acquisition stage (B), overall exploration duration in the test stage (C), and DI in the test stage (D) computed in the NOR assay. Data are represented as the mean ± SEM (n = 12), $^{\#\#\#}P < 0.001$ vs controls, $^{*}P < 0.05$ vs the $A\beta_{1\text{–}42}$ group.

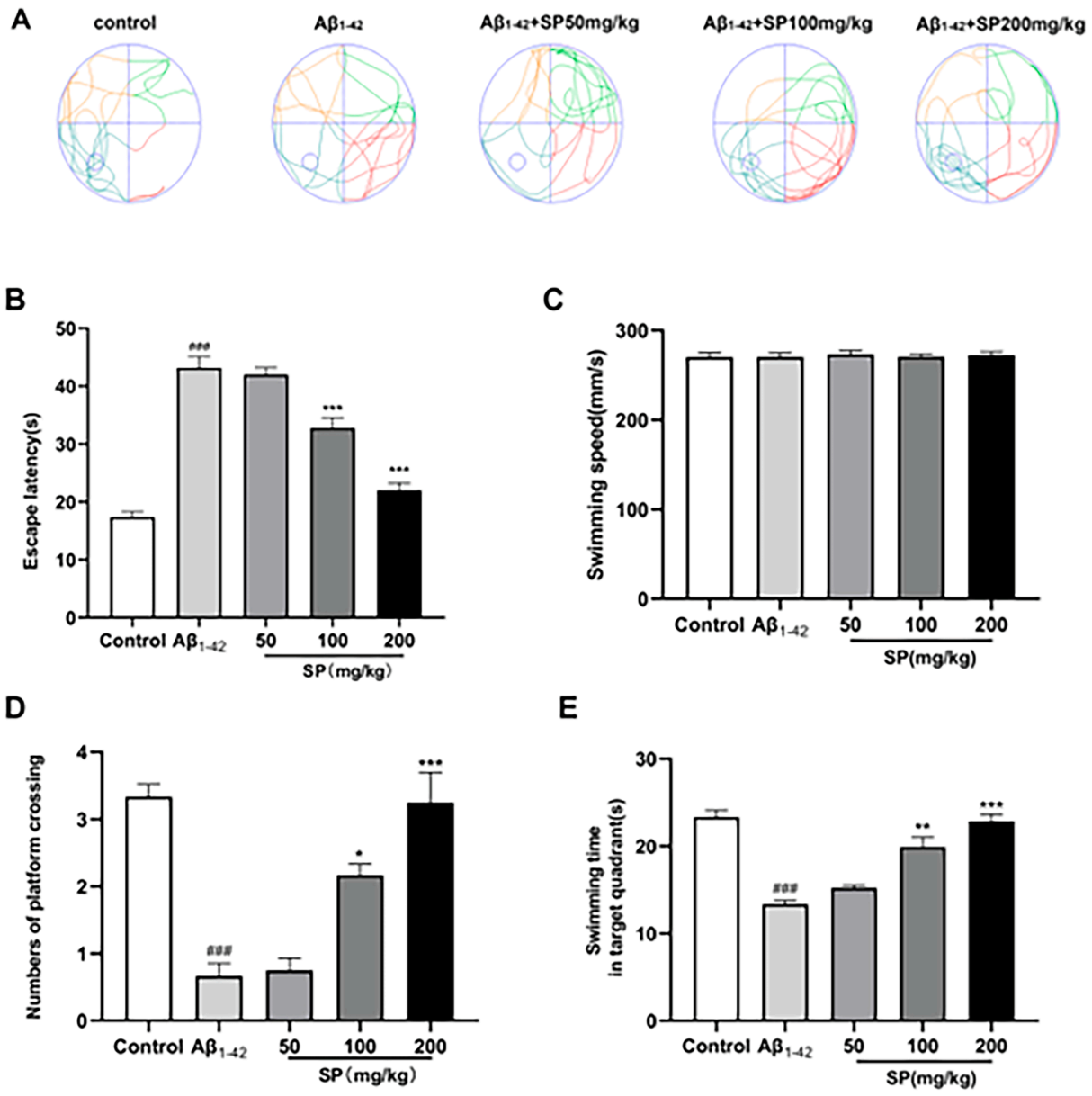

Fig. 3. Spatial memory was studied by the MWM experiment. The incubation period of escape in mice on Day 5 of the positioning cruise was recorded (B). During space exploration, swimming speed (C), platform crossing times (D) and swimming time in the target quadrant (E) were recorded. Typical traces (A) for every group are displayed. Data are described as the mean ± SEM (n = 12), $^{###}P < 0.001$ vs controls, $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs $A\beta_{1-42}$ group.

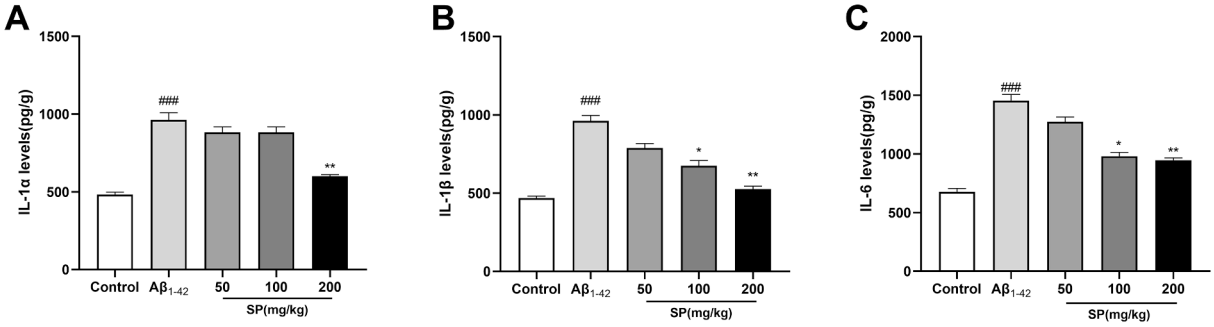

Fig. 4. Effects of SP on proinflammatory cytokines in the hippocampus of $A\beta_{1-42}$-treated mice. Levels of IL-1α (A), IL-1β (B), and IL-6 (C) detected via ELISA in the hippocampus. Data are described as the mean ± SEM (n = 5). $^{###}P < 0.001$ vs controls, $^{*}P < 0.05$ and $^{**}P < 0.01$ vs $A\beta_{1-42}$ group.

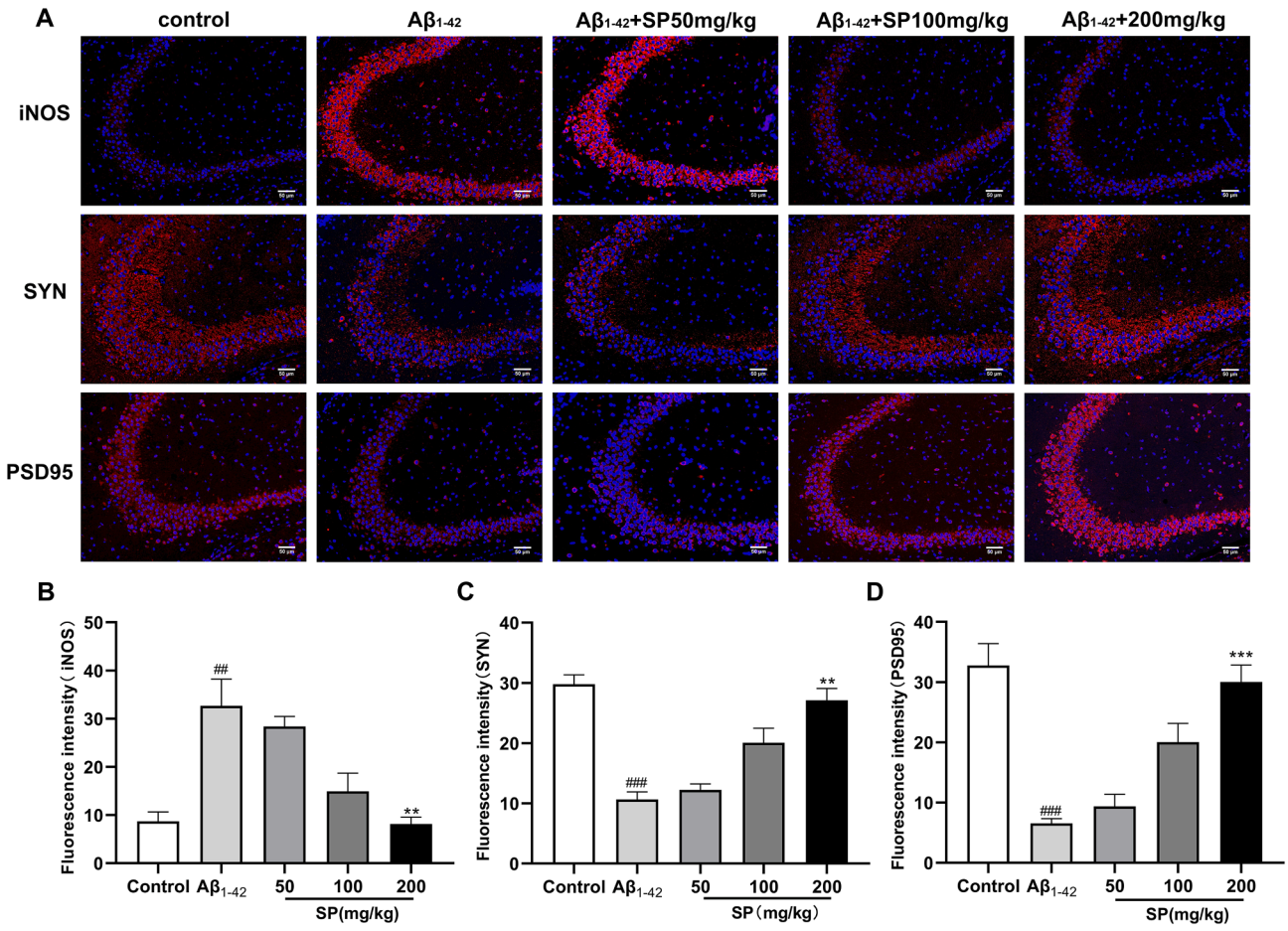

Fig. 5. Role of SP in the expression of iNOS, SYN, and PSD95 in $A\beta_{1\text{-}42}$-treated mice. iNOS, SYN, and PSD95 are displayed via special antibody (red) immune fluorescence. Nuclei are displayed via DAPI (blue). (A) Representative images of iNOS, SYN, and PSD95 expression in the hippocampal brain regions are shown. Scale bars represent 50 μm; the amplification is 200 ×. (B, C, D) Average fluorescence intensity analysis of iNOS, SYN and PSD95. Data are expressed as the mean ± SEM (n = 3), $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ vs controls, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs the $A\beta_{1\text{–}42}$ group.

200 mg/kg groups ($P < 0.05$) but not the 50 mg/kg and 100 mg/kg groups. A significant reduction in the protein expression of SYN and PSD95 was observed in the $A\beta_{1\text{-}42}$ group, while this reduction was reversed by treatment with SP (200 mg/kg, $P < 0.05$) but not 50 mg/kg or 100 mg/kg. (Fig. 6B, C).

4. Discussion

In the past few decades, AD has been a hotspot for research on neurodegenerative diseases, and its pathogenesis remains unclear. Several effective drugs have been approved to treat AD; those treatments control symptoms rather than change the progression of AD [13]. In this study, the novel object recognition and Morris water maze tests demonstrated that mice exposed to $A\beta_{1\text{-}42}$ presented a significant impairment in learning and memory. We demonstrated that SP at doses of 100 mg/kg and 200 mg/kg, but not 50 mg/kg, improved the learning and memory deficits induced by $A\beta_{1\text{-}42}$. Moreover, our results revealed that SP at a dose of 200 mg/kg, but not 50 mg/kg, significantly

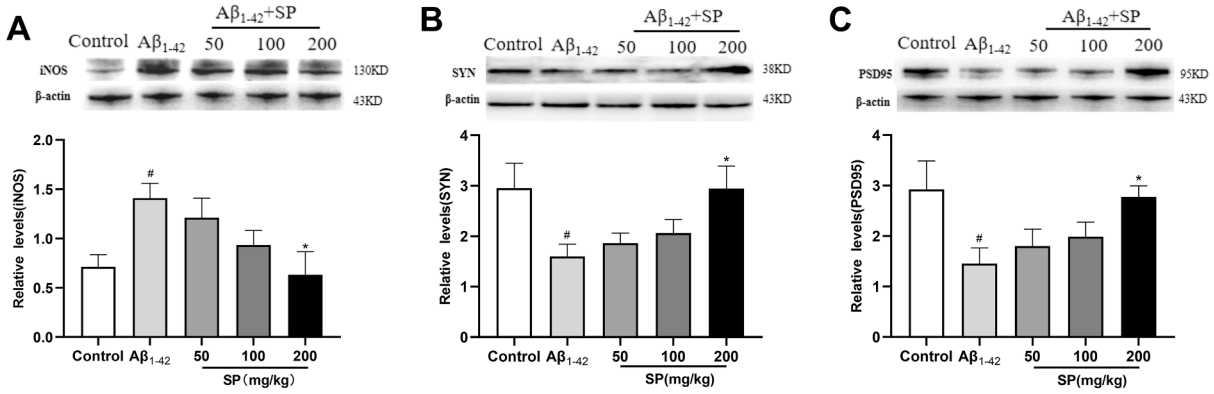

Fig. 6. Role of SP on iNOS, SYN, and PSD95 protein expression in $A\beta_{1\text{-}42}$-treated mice. Quantitation assay of iNOS (A), SYN (B), and PSD95 (C) in the hippocampal brain regions. Data are expressed as the mean ± SEM (n = 5–6), $^{\#}P < 0.05$ vs controls, $^{*}P < 0.05$ vs the $A\beta_{1\text{–}42}$ group.

attenuated proinflammatory cytokine and iNOS activation in the hippocampus and increased synaptically associated protein levels. In addition, 100 mg/kg SP administration attenuated the proinflammatory cytokines IL-1β and IL-6. These results indicate that SP could ameliorate neuronal injury and cognitive decline in mice exposed to $A\beta_{1\text{-}42}$.

Aβ leads to degeneration and neuronal loss in a variety of ways, ultimately leading to cognitive function disorder. Oxidation stress is one such event [14]. In addition, proinflammatory microglial activities are believed to exacerbate the brain environment and contribute to neurodegeneration [5]. One of the causal links of cytotoxicity caused by proinflammatory cell factors in neural inflammation is the stimulation of iNOS, which is responsible for the mediation of the production of substantial NO and has cytotoxicity [3]. Nathan et al. [15] showed that mice with inactive expression of iNOS had reduced plaque formation, reduced brain Aβ levels, and reduced phosphorylated Tau protein. In this study, we found that SP was able to significantly decrease the expression of proinflammatory cytokines such as IL-1α, IL-1β and IL-6. Moreover, SP attenuated the expression of iNOS protein in the hippocampus. Taken together, our results suggest that SP could attenuate $A\beta_{1\text{-}42}$-mediated inflammation via inhibition of proinflammatory cytokine activation and iNOS activation, thus protecting the nervous system against oxidative damage.

Soluble Aβ oligomers induce synaptic loss in AD [6]. Synaptic loss has been observed in AD mice, leading to learning and memory disorders [16]. SYN is a postsynaptic biomarker of presynapse plasticity and is pivotal for the release of neurotransmitters, and PSD95 is a postsynaptic marker [17]. PSD95 dysfunction may be a vital intermediate step in Aβ-induced pathology cascades [6]. In our experimental model, $A\beta_{1\text{-}42}$ caused a significant decrease in hippocampal levels of SYN and PSD95. Interestingly, the expression of SYN and PSD95 was significantly elevated after treatment with SP, suggesting that the protective effect of SP on intact synapses in the hippocampus may be a neurobiological basis for improving cognitive function.

In our study, we showed the effect of SP on improving cognitive and memory function in mouse models of Alzheimer's disease. In contradiction to our results, Colombo et al. reported that microbiota-derived SCFAs are critical mediators along the gut-brain axis that promote Aβ deposition likely via modulation of the microglial phenotype [18]. This discrepancy may be due to the model and the route of compound administration. Other studies support the hypothesis that intestinal microbiota may help protect against AD, in part, by supporting the generation of select SCFAs, which interfere with the formation of toxic soluble Aβ aggregates [19]. Therefore, more studies are required to clarify the direct effect of SCFAs on AD progression.

5. Conclusion

Taken together, our team offers experimental evidence for the treatment potential of SP in an $A\beta_{1\text{-}42}$-induced AD mouse model. SP decreased iNOS and proinflammatory cytokine activation, increased the expression of the synapse-related proteins SYN and PSD95, and effectively improved cognition and memory in AD mice. Our outcomes reveal a vital efficacy of SP in AD and offer a novel approach for its therapy.

CRediT authorship contribution statement

Wenxuan Lang: Writing – original draft, Data curation. **Xiaochen Li:** Software. **Yiying Wang:** Formal analysis. **Yuntao Duan:** Formal analysis. **Yu Wang:** Investigation, Validation. **Pengsheng Wei:** Investigation, Validation. **Xue Li:** Investigation, Validation. **Qiwen Zhu:** Project administration. **Yue Cui:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

This study was supported by grants from the Liaoning Education Department Project (SYYX202009) and Liaoning Province "Liaoning Talents Project" Project High-level Innovation and Entrepreneurship Team: XLYC1808012.

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