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Taurine attenuates amyloid β 1–42-induced mitochondrial dysfunction by activating of SIRT1 in SK-N-SH cells

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ABSTRACT

Amyloid β (Aβ) plays a critical role in the pathogenesis of Alzheimer disease (AD). Studies indicate that Aβ causes reactive oxygen species (ROS) generation, mitochondrial dysfunction and neurons loss *in vivo* and *in vitro*. Taurine, a naturally occurring β-amino acid in the brain, has been demonstrated to have neuroprotective properties. In the present study, the effects of taurine on cell viability and mitochondrial function in Aβ1–42-treated SK-N-SH cells were investigated. Pretreatment of taurine significantly attenuated Aβ1–42-induced neuronal death. Similarly, taurine suppressed the mPTP opening and reversed mitochondrial function in the presence of Aβ1–42. Additionally, taurine attenuated the intracellular Ca^{2+} and ROS generation induced by Aβ1–42. Moreover, the expression of Sirtuin 1 (SIRT1) was obviously recovered by taurine in Aβ1–42-treated SK-N-SH cells. Our results suggest that taurine prevents Aβ1–42-induced mitochondrial dysfunction by activation of SIRT1. This study implies that taurine is a prospective additive for AD patients.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in elderly people with deterioration of cognition and memory [1]. Amyloid β (Aβ) plays a central role in the occurrence and progression of AD. Aβ1–42, cleaved from amyloid beta precursor protein (APP) through β-site APP-cleaving enzyme-1 (BACE1) and γ-secretase, is the most component in senile plaques [2]. Studies have shown that Aβ1–42 increases ROS generation and intracellular calcium ($[Ca^{2+}]i$) level which causes the mitochondrial permeability transition pore (mPTP) opening, mitochondrial membrane potential collapse, decline of ATP generation and rupture of mitochondria and neuronal death [3,4].

Silent information regulator 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase, attenuates oxidative stress and improves mitochondrial biogenesis in cultured neurons and animal models [5,6]. Several studies suggest that activation of SIRT1 may inhibit ROS generation, rescue mitochondrial function and block apoptosis in AD [7,8]. Recently, evidences indicate that taurine (2-aminoethanesulfur acid), a β-amino acid found in many tissues particularly in brain, inhibits oxidative stress by restoring the expression of SIRT1 in cultured SH-SY5Y cells and liver cells from zebrafish [9,10]. In particular, taurine has also been shown to protect mitochondria against oxidative stress by regulating mitochondrial protein synthesis and enhancing electron transport chain activity [11,12]. It has been also suggested that taurine attenuates Aβ1–42-induced neurons impairment *in vitro* as well as cognitive deficits in the transgenic mice model of AD via its antioxidant and neuroprotective properties [13–15]. However, the potential protective effects of taurine against Aβ1–42-induced mitochondrial dysfunctions and neuronal death still need to be well clarified.

In the present study, we investigated neuroprotective effects of taurine against Aβ1–42-induced mitochondrial dysfunction and neuronal death in SK-N-SH cells. Furthermore, we explored the underlying mechanisms of taurine on mitochondrial function and neuronal loss.

2. Materials and methods

2.1. Cell lines, culture conditions, and treatment with reagents

Human SK-N-SH neuroblastoma cells (ATCC) were cultured in DMEM supplemented with 10% (v/v) heat-inactivated fetal calf

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β; $\Delta\Psi m$, mitochondrial membrane potential; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species.

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serum (Invitrogen) and 100 U/mL penicillin/streptomycin (Invitrogen). Cells were maintained at 37 °C in humidified 5% CO_2 and 95% air and the culture medium was replaced every 2 days. Cells were permitted to attach for 24 h and grown to 70% confluence. Taurine (Sigma, purity >99%) was dissolved in ddH_2O freshly. Oligomer Aβ1–42 (Sigma) was prepared as describe [16]. The final concentration of DMSO did not exceed 0.1%. All treated SK-N-SH cells were divided into 3 groups as follows: Control group (non-treated cells), Aβ1–42 group (cells treated with 5 μM Aβ1–42 for 24 h) and taurine pretreated group (cells pretreated with taurine 2 h prior to 5 μM Aβ1–42). All experiments were carried out after incubation for 24 h.

2.2. Cell viability assay

A quantitative colorimetric assay with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was employed to measure cell viability. Briefly, SK-N-SH cells were cultured on 96-well plates and permitted grown to 70% confluence. Cells pretreated with or without 100 μM taurine were exposed to 5 μM Aβ1–42 for 24 h. A final concentration of 0.5 mg/mL of the MTT solution was added to each well (20 μL/well) and incubated for 4 h at 37 °C. The MTT solution was removed gently and 150 μL of DMSO was added to each well for 15 min. The absorbance of the final compound was measured at 490 nm by using a microplate reader (Bio-Rad).

2.3. Determination of intracellular Ca^{2+} ($[Ca^{2+}]i$)

The level of $[Ca^{2+}]i$ in SK-N-SH cells was measured by using fura-2 AM, a fluorescence Ca^{2+} indicator. Briefly, SK-N-SH cells were seeded in 24-well plates and permitted grown to 70% confluence. Cells pretreated with and without 100 μM taurine for 2 h were exposed to 5 μM Aβ1–42 for 24 h. Fura-2 AM (5 μg/mL) was then added to the cells. After 30 min, cells were rinsed twice with 2% Hank's buffer and incubated for 10 min at 37 °C. The fluorescence intensity at 340 nm or 380 nm was detected simultaneously by a fluorescence microplate reader (Bio-rad).

2.4. Mitochondrial permeability transition pore (mPTP) assay

According to the manufacturer's instructions, the mPTP opening was detected by using the mPTP Assay Kit (Genmed Scientifics). Briefly, SK-N-SH cells were plated on a 24-well plate and permitted grown to 70% confluence. Cells pretreated with or without 100 μM taurine for 2 h were exposed to 5 μM Aβ1–42 for 24 h. Cells were washed by Reagent A, and then incubated with the mixture of Reagent B and Reagent C (1:50) at 37 °C for 20 min. After washed twice with Reagent A, the fluorescence intensity was measured by using a fluorescence microplate reader (Bio-rad). The protein concentration was measured by using the Bradford assay kit (Invitrogen). The mPTP inhibitor cyclosporin A (CsA) (1 μM) (LC labtories) was used as a positive control.

2.5. ATP level measurement

According to the manufactory instruction, the cellular ATP level was determined by the ATP Determination Kit (Roche). Briefly, SK-N-SH cells were plated on a 6-well plate and permitted grown to 70% confluence. Cells pretreated with or without 100 μM taurine for 2 h were exposed to 5 μM Aβ1–42 for 24 h. SK-N-SH cells were homogenized by using cell lysis buffer, incubated on ice for 15 min, and centrifuged at 14,000×*g* for 15 min at 4 °C. The supernatants were collected and measured by employing a Beckman Coulter DTX880 (Beckman) with an integration time of 10 s.

2.6. Mitochondrial membrane potential ($\Delta\Psi m$) measurement

Rhodamine 123 was employed to detect $\Delta\Psi m$ according to the manufacturer's instructions. SK-N-SH cells cultured on a 96-well plate were treated with Aβ1–42 (5 μM) 2 h in advance with or without taurine (100 μM) for 24 h. After treatments, SK-N-SH cells were stained by Rhodamine 123 (2 nM, Invitrogen) for 20 min at 37 °C and then washed with culture medium twice. The fluorescence intensity was measured using a fluorescence microplate reader (Bio-rad) and the data were showed as a percentage of the fluorescence intensity normalized with that in the control cells.

2.7. Protein extraction and Western blot analysis

SK-N-SH cells cultured on a 6-well plate were treated with Aβ1–42 (5 μM) 2 h in advance with or without taurine (100 μM) for 24 h. After treatments, SK-N-SH cells were washed twice by using ice-cold PBS, and then cells were homogenized at 1:5 (wt/vol) in an ice-cold lysis buffer. Samples were subjected to SDS–PAGE and transferred to Hybond-ECL nitrocellulose membranes (Bio-rad). The blots were probed with the following primary antibodies: polyclonal mouse anti β-actin (Sigma), monoclonal mouse anti-COX IV (Cell Signaling) and monoclonal mouse anti-SIRT1 (Cell Signaling) followed by incubation with species-matched horseradish peroxidase-conjugated secondary antibodies. The blots were developed with a chemiluminescence substrate solution (Pierce) and exposed to X-ray film. The optical density of immunoreactive bands was quantified by using Image J (NIH).

2.8. Statistical analysis

All values in experiments were expressed as mean ± standard error (SE). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by the Tukey–Kramer test for multiple comparisons when appropriate using SPSS software (version 16.0, SPSS). A value of $P < 0.05$ was considered to be statistically significant. All experiments were repeated more than three times.

3. Results

3.1. Taurine reduced Aβ1–42-induced neuronal death in SK-N-SH cells

As shown in Fig. 1A, compared with control cells, cells with 1 or 2.5 μM scarcely showed any decline of viability while 10 μM Aβ1–42 severely impaired the cells. Cells treated with 5 μM Aβ1–42 showed a nearly 50% reduction of viability, so 5 μM Aβ1–42 was selected to be used in the subsequent experiments ($P < 0.01$). In addition, there were no significant differences in cell viability between SK-N-SH cells treated with and without taurine (Fig. 1B). To explore the protective effects of taurine on SK-N-SH cells exposed to Aβ1–42, different concentrations of taurine (1, 10, 50, 100, 500 μM) were subjected to cells 2 h prior to addition of Aβ1–42 at 5 μM for next 24 h. Cells pretreated with 50, 100 and 500 μM of taurine displayed significant difference compared with Aβ1–42 treated cells, and 100 μM taurine treatment nearly completely recovered cell viability ($P < 0.01$) and 100 μM taurine was used in the subsequent experiments. But 1 and 10 μM taurine administration did not show significant improvement (Fig 1C).

3.2. Taurine inhibited Aβ1–42-induced mPTP opening and mitochondrial dysfunction

Calcein-AM/cobalt method was employed to determine the mPTP opening. A remarkably decrease in the fluorescence intensity

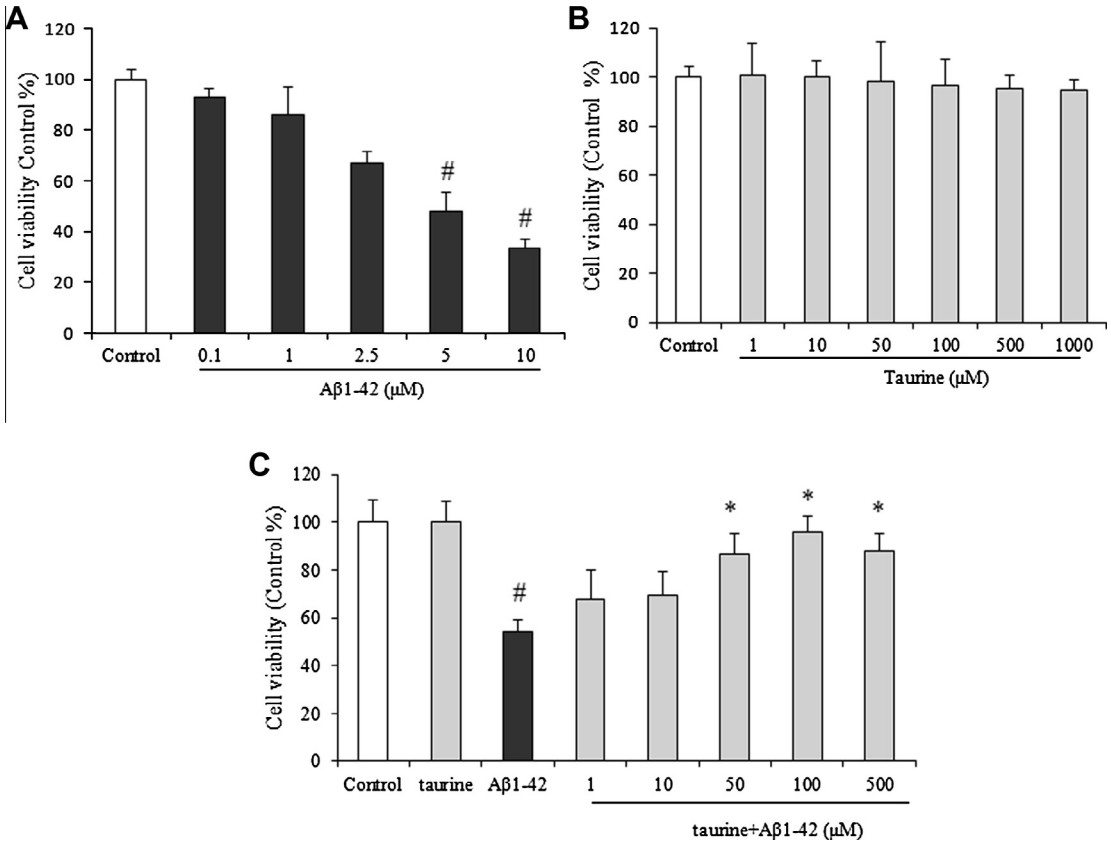

Fig. 1. Taurine pretreatment attenuated Aβ1–42-induced SK-N-SH cell death. Viability of cells was identified by MTT assay. Percentage of cell viability was relative to the control non-treated cells. (A) SK-N-SH cells were treated with different concentrations (0–10 μM) of Aβ1–42 for 24 h. (B) SK-N-SH cells were treated with different concentrations (0–1000 μM) of taurine for 24 h. (C) SK-N-SH cells were pretreated with different concentrations of taurine (1, 10, 50, 100, 500 μM) for 2 h and then incubated with Aβ1–42 (5 μM) for 24 h. $^{\#}P < 0.05$ *vs* Control; $^{*}P < 0.05$ *vs* Aβ1–42 ($n = 3$).

of Aβ1–42 treated SK-N-SH cells was observed compared with that in the control non-treated cells ($P < 0.01$). However, pretreatment of 100 μM taurine significantly increased the fluorescence intensity of compared with that in Aβ1–42 treated cells ($P < 0.01$). Notably, there was no significant difference between the taurine pretreated group and the control group. CsA, the mPTP inhibitor, was used as positive control to confirm the effect of the mPTP opening (Fig. 2A).

To further investigate the mitochondrial function, mitochondrial membrane potential ($\Delta\Psi$m) and cellular ATP level were determined. $\Delta\Psi$m was determined by using Rhodamine 123 and the data were expressed as the fluorescence intensity. As shown in Fig. 2B, Aβ1–42 treated SK-N-SH cells showed significantly lower fluorescence intensity than that in the control cells ($P < 0.01$), which was markedly recovered by pretreatment of 100 μM taurine ($P < 0.01$, Fig. 2B). ATP level in the Aβ1–42 group was remarkably reduced compared with that in the control group ($P < 0.01$, Fig. 2B). Cells with pretreatment of 100 μM taurine showed significantly increased ATP level compared with cells in the Aβ1–42 group ($P < 0.01$).

3.3. Taurine decreased intracellular ROS generation in SK-N-SH cells in Aβ1–42 rich environment

The level of intracellular ROS was examined by using the fluorescent probe DCFH–DA and was expressed as the fluorescence intensity. The fluorescence intensity of 5 μM Aβ1–42 treated cells was significantly stronger than that in cells in the control non-treated cells ($P < 0.01$). However, pretreatment with 100 μM taurine markedly decreased the fluorescence intensity of SK-N-SH cells in the presence of Aβ1–42 (Fig 3A, $P < 0.01$).

3.4. Taurine blocked the overload of intracellular calcium ([Ca^{2+}]i) in the presence of Aβ1–42

The Fura-2/AM fluorescence probe was used to determine the intracellular Ca^{2+} ([Ca^{2+}]i) level in SK-N-SH cells. As shown in Fig. 3B, the fluorescence intensity of the Aβ1–42 treated cells was significantly stronger than that in the control non-treated cells ($P < 0.01$). In contrast, taurine pretreated cells did not show so strong fluorescence intensity ($P < 0.01$), and there was no significant difference in the fluorescence intensity between the taurine pretreated cells and the control non-treated cells ($P > 0.05$) (Fig. 3B).

3.5. Taurine recovered the expression of SIRT1 Aβ1–42 in rich environment which blocked by application of SIRT1 siRNA

We examined the expression of SIRT1 by Western blot. Compared with the control group, SK-N-SH cells treated with Aβ1–42 showed significantly lower expression of SIRT1 ($P < 0.01$). As expected, 100 μM taurine significantly increased the expression of SIRT1 in the SK-N-SH cells in Aβ1–42 rich environment ($P < 0.01$). To confirm the effect, SIRT1 siRNA was transfected to SK-N-SH cells before pretreatment of taurine and Aβ1–42. The protection of taurine was inhibited by SIRT1 siRNA ($P < 0.01$, Fig. 4A and B).

4. Discussion

Aβ plays a central role in the pathogenesis of AD. Aβ1–42 induces neurodegeneration in cortical and hippocampus through disturbing calcium homeostasis oxidative stress, ROS accumulation, and mitochondrial dysfunction. Taurine was reported to display potential

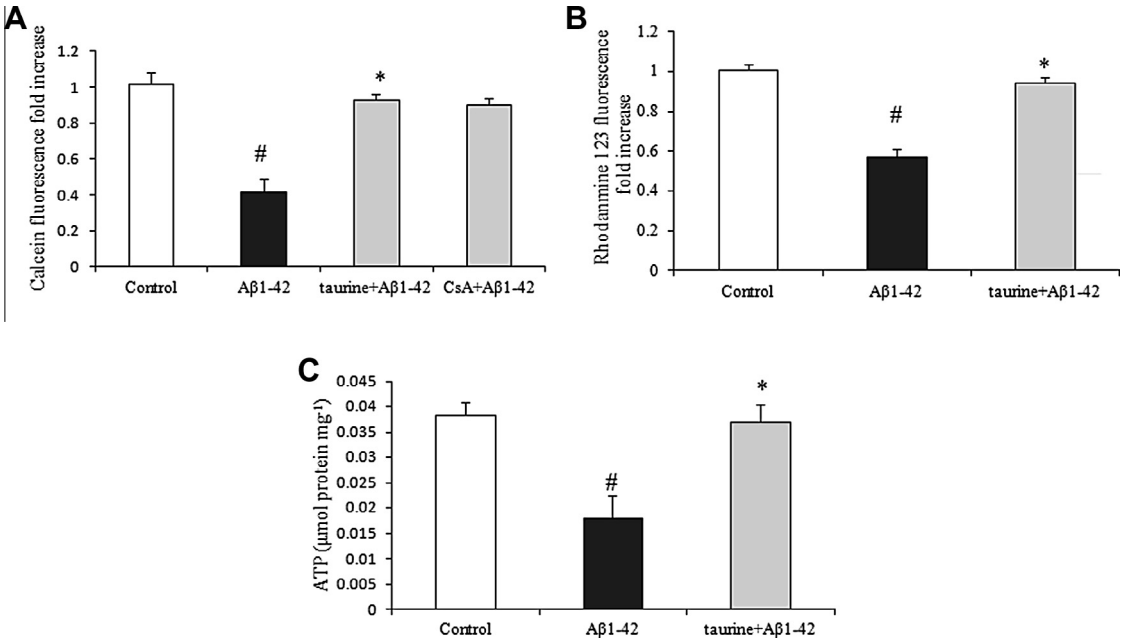

Fig. 2. Taurine inhibited Aβ1–42-induced mPTP opening and mitochondrial dysfunction. (A) The mPTP opening was detected by Calcein-AM method. 1 μM CsA was applied as positive control. (B) Mitochondrial membrane potential ($\Delta\Psi$m) was measured by Rhodamine 123. (C) ATP level was detected by the ATP Determination Kit. $^{\#}P < 0.05$ *vs* Control; $^{*}P < 0.05$ *vs* Aβ1–42 ($n = 6$).

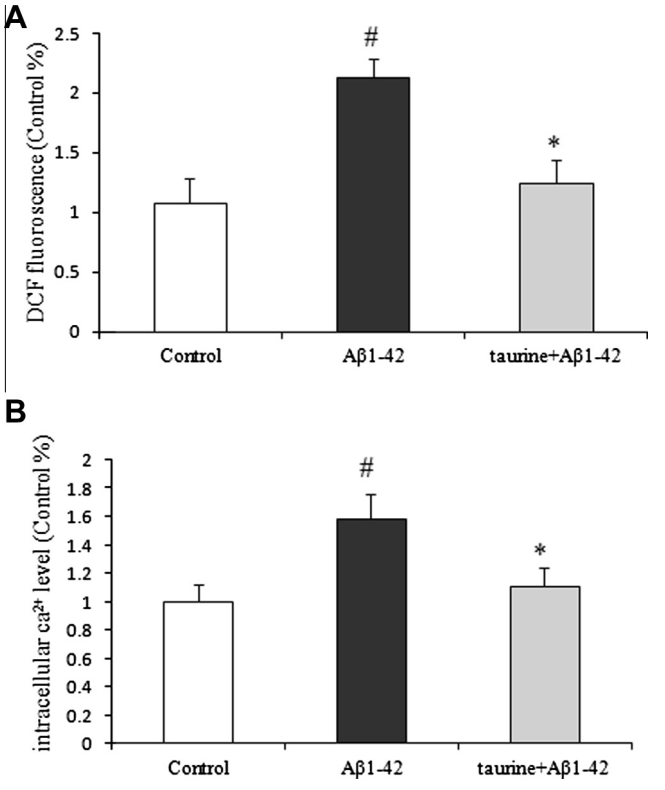

Fig. 3. Effect of taurine on ROS accumulation and elevated $[Ca^{2+}]i$ induced by Aβ1–42. (A) The ROS generation was detected by using the fluorescent probe DCFH–DA. (B) The level of $[Ca^{2+}]i$ was determined by using fura-2 AM. Values shown are the mean %Control. $^{\#}P < 0.05$ *vs* Control; $^{*}P < 0.05$ *vs* Aβ1–42, $n = 4$.

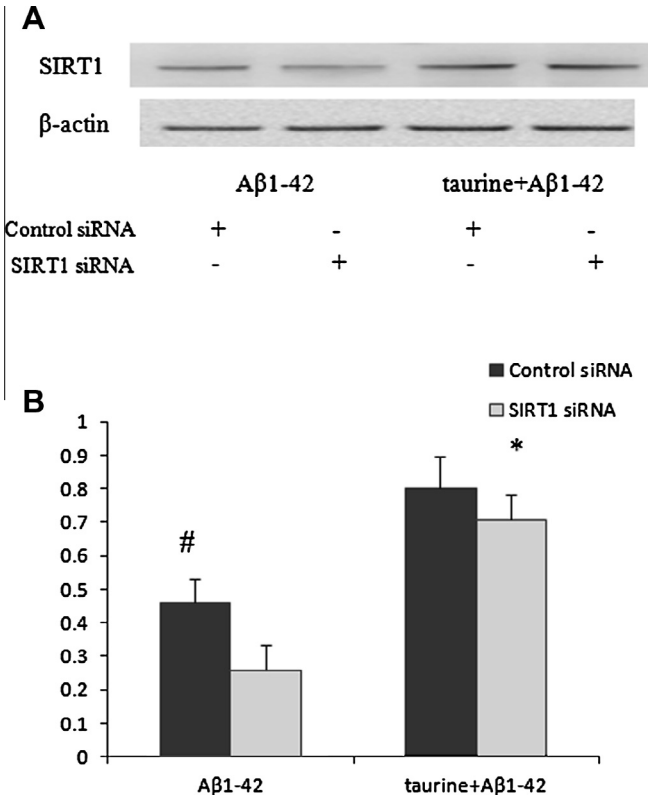

Fig. 4. Taurine recovered the expression of SIRT1 in SK-N-SH cells with Aβ1–42, and this effect was blocked by SIRT1 siRNA. (A) The expression of SIRT1 was examined by Western blot in different groups. Protein expression levels were normalized to β-actin. (B) Quantitative analysis of SIRT1 expression. $^{\#}P < 0.01$ *vs* Control, $^{*}P < 0.01$ *vs* Aβ1–42, $n = 3$.

antioxidant and neuroprotective properties. It is reported that taurine significantly attenuated neuronal death in ischemia-injured brain [17]. Our results showed that taurine could exert a protective effect against the neuronal loss induced by Aβ1–42.

A growing number of studies show that intracellular ROS accumulation and elevation of $[Ca^{2+}]i$ in neurons of cerebral cortex and hippocampus in AD [18,19]. Here, the results showed that Aβ1–42

significantly increased intracellular ROS generation as well as the level of $[Ca^{2+}]i$ in SK-N-SH cells which were reversed by administration of taurine in the presence of Aβ1–42. It has been reported that taurine plays a role in modulating $[Ca^{2+}]i$ in neurons and cardiomyocytes [20,21]. Other studies support that taurine exerts an anti-oxidative effect. Therefore, we may have a conclusion that taurine protects neuronal cells against Aβ through inhibiting ROS generation and buffering $[Ca^{2+}]i$ as well.

Studies show that excessive amounts of $[Ca^{2+}]i$, as well as elevated intracellular ROS, are main factors to trigger the opening of the mPTP [22]. Therefore, we hypothesized that the neuroprotection of taurine is related to the regulation of the mPTP. As expected, we observed that taurine blocked mPTP opening in SK-N-SH cells in Aβ1–42 rich environment. The result is similar with the experimental results from hopaxia model reported by Chen et al. [23].

The mPTP consists of the voltage-dependent anion channel (VDAC), adenine nucleotide translocator (ANT) and cyclophilin D (CypD). The opening of the mPTP allows molecules <1.5 kDa across the mitochondrial membrane which causes uncoupling of the electron respiratory chain, mitochondrial depolarization and rupture of mitochondrial outer membrane, which finally leads to cell death [24]. In our experiments, taurine recovered mitochondrial membrane potential and ATP level in SK-N-SH cells in the presence of Aβ1–42, which strengthens the notion that the neuroprotection of taurine is due to its prevention in the mPTP opening. These results are consistent with the reports that taurine protects cerebellar granual cells from glutamate toxicity by enhancing the mitochondrial activity [25,26]. Overall, these data indicate that taurine inhibit the mPTP opening by modulating $[Ca^{2+}]i$ and ROS generation.

Over recent years, evidences have demonstrated that the expression of SIRT1 is significantly decreased in cerebral cortex of AD patients and AD transgenic mice [27,28]. To further explore the underlying mechanisms of taurine's protection against Aβ1–42 neurotoxicity, we examined the expression of SIRT1. Taurine recovered the expression of SIRT1 in Aβ1–42 treated SK-N-SH cells, and this effect was blocked by SIRT1 siRNA. These results indicate that taurine rescues mitochondrial function through activating SIRT1.

Taken together, in this study, we found taurine significantly promoted cell viability by reducing ROS generation and intracellular Ca^{2+} level in SK-N-SH cells in Aβ1–42 rich environment. Taurine inhibited the mPTP opening and maintained mitochondrial membrane potential and ATP level in SK-N-SH cells treated with Aβ1–42. Moreover, taurine recovered the expression of SIRT1, which was interrupted by SIRT1 siRNA.

In conclusion, our results provide evidences that taurine can rescue mitochondrial dysfunction and protect neuronal cells by activating SIRT1. This study implies that taurine is a prospective additive for AD patients. In further *in vivo* studies are needed to confirm the therapeutic effects of taurine by using younger transgenic mice.

Conflict of interest statement

All authors have no conflict of interest to disclose.

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