Trichostatin A increases the levels of plasma gelsolin and amyloid beta-protein in a transgenic mouse model of Alzheimer's disease

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Aims: Gelsolin (GSN), a multifunctional protein, binds to amyloid beta-protein (Aβ), inhibits its fibrillization, solubilizes preformed Aβ fibrils, and helps in its clearance from the brain. Trichostatin A (TSA), a histone deacetylase (HDAC) inhibitor, induces the protein expression of gelsolin. In the present study, we investigated how TSA-treatment of APPswe/PS1ΔE9 transgenic (Tg) mice of Alzheimer's disease (AD) will affect the plasma levels of gelsolin and Aβ.

Main methods: TSA (5 mg/kg body weight on alternate days for two months) was intraperitoneally injected to AD Tg mice. Gelsolin was measured by Western blotting and Aβ1–42 was measured by enzyme-linked immunosorbent assay.

Key findings: TSA-treatment significantly increased the levels of plasma gelsolin by 1.79-fold as compared with vehicle-treated control mice (p < 0.01). The levels of Aβ1–40 and Aβ1–42 in the plasma were also higher in TSA-treated mice in comparison with vehicle-treated mice. The treatment of transgenic AD mice with TSA did not affect the body weight in both male and female groups as compared to vehicle-treated animals. A positive correlation was observed between the plasma levels of gelsolin and Aβ1–40 (r = 0.594, p = 0.042) or Aβ1–42 (r = 0.616, p = 0.033) in AD Tg mice.

Significance: These results suggest that TSA increases the levels of plasma gelsolin and Aβ in AD Tg mice, which may have implications in gelsolin-mediated clearance of Aβ.

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Introduction

Gelsolin (GSN), a multifunctional 90 kDa protein, is a major actin-binding protein. It plays important roles in various diseases such as cancer, Alzheimer's disease (AD), pulmonary disease, cardiac injury, infections, and as well as in apoptosis (Li et al., 2012). It is present intracellularly as a cytoplasmic protein, and in the biological fluids, i.e., plasma/cerebrospinal fluid (CSF) as a secreted protein (Kwiatkowski et al., 1988). Both forms of gelsolin are products of alternative splicing of a single 70 kbp-long gene. However, they differ in the length and the presence of disulfide groups. Plasma gelsolin has a 25 amino acid signal peptide at its amino-terminus (Yin et al., 1984). There are five cysteine (Cys) residues in gelsolin. All five Cys residues in cytoplasmic gelsolin are free thiols; whereas in plasma gelsolin, three Cys residues are free thiols and the other two are disulfide-linked (Wen et al., 1996).

Extracellular deposition of fibrillar amyloid beta-protein (Aβ) as amyloid plaque, and intracellular formation of neurofibrillary tangles due to hyperphosphorylation of tau are two hallmarks of AD (Glenner, 1983; Huang and Jiang, 2009). Aβ is formed by proteolytic cleavage of amyloid precursor protein (APP) (Pluta et al., 2013). Aβ is normally present as a soluble protein. However, in pathological conditions such as AD, it gets fibrillized and deposited as amyloid plaque in the brain. Fibrillar Aβ1–40 and Aβ1–42 are two major constituents of amyloid plaques in AD. Various attempts have been made to prevent the fibrillization of Aβ1 in both human and transgenic (Tg) animal model of AD (Antequera et al., 2009; Lahiri et al., 2005; Matsuoka et al., 2003). Since our initial reports on binding of gelsolin to Aβ (Chauhan et al., 1999; Ji et al., 2008, 2010) and inhibition of Aβ fibrillization as well as solubilization of Aβ fibrils by gelsolin (Ray et al., 2000), several studies have confirmed anti-amyloidogenic role of gelsolin in transgenic animal models of AD where it could reduce amyloid load (Antequera et al., 2009; Hirko et al., 2007; Lahiri et al., 2005; Matsuoka et al., 2003). Matsuoka et al. (2003) reported that peripheral administration of plasma gelsolin could reduce the amyloid load in mutant APP-Tg mice. Similarly, Hirko et al. (2007) showed that peripheral administration of plasma gelsolin could reduce amyloid load in double-transgenic APP/PS1 mice. In a recent study, peripheral administration of gelsolin reduced the cerebral amyloid angiopathy (accumulation of Aβ in the walls of leptomeningeal and cortical blood vessels of brains) in Tg2576 mice model of AD (Gregory et al., 2012).

Since our reports, peripheral administration of plasma gelsolin reduced the cerebral amyloid angiopathy (accumulation of Aβ in the walls of leptomeningeal and cortical blood vessels of brains) in Tg2576 mice model of AD (Gregory et al., 2012).
The levels of gelsolin can be increased epigenetically by inhibition of histone deacetylase. Histone deacetylase inhibitors such as sodium butyrate (Kamitani et al., 2002) and trichostatin A (TSA) (Hoshikawa et al., 1994; Kamitani et al., 2002; Yildirim et al., 2008) have been reported to increase the expression of gelsolin in cell cultures and brain. However, a relationship between TSA-induced gelsolin and Aβ in transgenic AD mice has not been studied. Therefore, we studied whether TSA can be used as a potential therapeutic agent in AD for clearance of Aβ by increasing the levels of plasma gelsolin in APPswe/PS1Δ9 γ transgenic mice. We report here that TSA increases the levels of gelsolin, Aβ1-40 and Aβ1-42 in the plasma. The levels of plasma gelsolin correlated with the levels of plasma Aβ1-40 and Aβ1-42, suggesting that plasma gelsolin probably acts as a "peripheral sink protein" to bind Aβ peptides, and may help in Aβ clearance from the brain or other tissues.

Materials and methods

Animal treatment

Twenty six APPswe/PS1Δ9 γ transgenic mice (13 males and 13 females) at the age of 4 months were purchased from Jackson Laboratory (Bar Harbor, ME) and kept in the animal colony with the food and water ad libitum. All instructions were followed according to the National Institutes of Health Guidelines for the Humane Treatment of Animals, and the protocol was approved by the Animal Welfare Committee of NYS Institute for Basic Research in Developmental Disabilities.

The mice were divided randomly into two treatment groups: TSA (7 females, 7 males) and vehicle control (6 females, 6 males). The intra-peritoneal injections of TSA or vehicle to the mice were started at the age of 9 months, and continued for 60 days.

Five milligrams of TSA (Selleck Chemicals, Houston, TX) was dissolved in 0.1 ml of dimethyl sulfoxide (DMSO), and then diluted with 9.9 ml of phosphate buffered saline (PBS). The mice were intraperitoneally injected with TSA at a dose of 0.1 ml/10 g (i.e., 5 mg/kg body weight) every alternate day for a total of 30 treatments. The injection spot was alternated between the left and right sides to avoid peritonitis. The control mice were injected with the same dose of vehicle (no TSA, i.e., DMSO diluted in PBS). The body weights of mice were monitored every week, and the dose of TSA was calculated on the basis of weekly body weight.

After 30 treatments, the mice were anesthetized with ether and sacrificed. The blood samples were withdrawn and transferred into tubes containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant. After centrifugation at 1000 g for 10 min at 4 °C, the plasma samples were collected and stored at −80 °C for further use.

Western blotting for gelsolin

The protein concentrations of plasma samples were measured with the BCA (bicinchoninic acid) Protein Assay Kit (Thermo Scientific, Rockford, IL). The plasma samples were diluted ten-fold with PBS. The samples were mixed with loading buffer, and boiled for 5 min. The denatured plasma proteins were separated on a 10% SDS-PAGE gel, and then transferred to a nitrocellulose membrane (0.45 μm; Bio-Rad Laboratories, Hercules, CA). After blocking with 5% non-fat milk for 1 h at room temperature (RT), the membrane was incubated overnight at 4 °C with 5% non-fat milk containing rabbit monoclonal anti-gelsolin antibody (1:25,000; Abcam, Cambridge, MA). After 3 washes with Tris-buffered saline-0.05% Tween-20 (TBST), the membrane was further incubated with the horseradish peroxidase-conjugated secondary antibody (1:5000; Thermo Scientific, Rockford, IL) for 1 h at RT. The membrane was again washed 3 times, and the immunoreactive proteins were visualized using the ECL substrate (Thermo Scientific, Rockford, IL). The densities of the gelsolin bands were measured using ImageJ software (NIH, Bethesda, MD). The data was normalized with total protein content of the samples.

Measurement of plasma Aβ1-40 and Aβ1-42 levels by sandwich enzyme-linked immunosorbent assay [ELISA]

The levels of Aβ1-40 and Aβ1-42 in the plasma samples of TSA- and vehicle-treated AD Tg mice were measured by ELISA as described previously but with minor modifications (Mehta et al., 2000). Briefly, 100 μl of monoclonal Aβ1 antibody 6E10 (2.5 μg/ml) diluted in carbonate-bicarbonate buffer (pH 9.6) was coated in the wells of microtiter plate, and allowed to incubate overnight at 4 °C. After washing the plates with PBS containing 0.05% Tween 20 (PBST), the wells were blocked for 1 h with 200 μl of 10% normal sheep serum in PBS to avoid non-specific binding. The plates were again washed, and 100 μl of standards (Aβ1-40 and Aβ1-42; Bachem, Torrance, CA) diluted in PBST with 0.5% bovine serum albumin (BSA) or plasma samples (diluted 1:2) were added and incubated for 2 h at RT, followed by overnight incubation at 4 °C. After washing, the plates were incubated with rabbit monoclonal antibody (clone 5-139) specific to a peptide corresponding to Aβ1-40 or rabbit monoclonal antibody (clone 11-4) specific to a peptide corresponding to Aβ1-42 diluted in PBST with 0.5% BSA at RT for 2 h. After washing, goat anti-rabbit IgG peroxidase (Invitrogen, Grand Island, NY) diluted in PBST was added to the wells, and the plates were incubated for 2 h at RT. The plates were again washed, and QuantaBlu fluorogenic peroxidase substrate (Thermoscientific, Rockland, IL) was added. The reaction was stopped after 30 min by adding QuantaBlu stop solution. The relative fluorescence units (RFU) for each well were measured according to the kit instructions. The relationship between RFU and the Aβ1-40 or Aβ1-42 peptide concentrations was determined using a 4-parameter logistic logarithm function.

Statistical analysis

Data is presented as Mean ± SEM. The unpaired Student’s t-test was used to compare the data between the TSA-treated group and vehicle-treated control group by using GraphPad prism 5.0 (GraphPad Software, Inc., La Jolla, CA). Linear regression analysis was done to study the correlation between the levels of plasma gelsolin and Aβ1-40/Aβ1-42, and the Pearson correlation coefficient (r) and p values were obtained. In addition, 95% confidence interval (CI) of vehicle-treated control group was used as the normal range to evaluate whether the data of the TSA-treated group were out of the normal range. The p values less than 0.05 were considered as the significant difference.

Results

Effect of TSA-treatment on the body weight of mice

The body weights of TSA-treated and vehicle-treated control AD Tg mice were measured every week. Percent increases in body weight of TSA-treated or vehicle-treated control mice (males or females) are shown in Fig. 1. There was no effect of TSA-treatment for two months (9th to 11th months of age) on the body weight of either female (Fig. 1A) or male Tg mice (Fig. 1B) as compared to vehicle-treated control Tg mice.

TSA-treatment increases levels of gelsolin in the plasma of AD Tg mice

Fig. 2A shows the Western blot of plasma gelsolin of TSA-treated and vehicle-treated AD Tg mice. The density of the gelsolin bands was normalized by the total protein content of the samples. TSA-treatment increased the plasma concentration of gelsolin by 82% in female (39.98 ± 8.41 μg protein, n = 7) (Fig. 2B) and by 76% in male mice (45.68 ± 5.98 μg protein, n = 7) (Fig. 2C) as compared to vehicle-treated control mice (female group, 21.91 ± 4.24 μg protein, n = 6, and male group, 26.01 ± 3.72 μg protein, n = 6). A significant difference
in the concentration of plasma gelsolin was observed in male mice ($p < 0.05$) as compared to control mice (Fig. 2C). When both male and female samples were combined (Fig. 2D), gelsolin contents in the TSA-treated mice were also found to be significantly increased as compared to the vehicle-treated mice ($p < 0.01$). If a 95% CI of the vehicle-treated group (17.88–30.03, $n = 12$) was taken as a reference range, 10 of 14 (71.4%) TSA-treated mice had higher plasma levels of gelsolin than the upper limit of 95% CI of the vehicle-treated control group.

**TSA-treatment increases Aβ1–40 levels in the plasma of AD Tg mice**

Plasma Aβ1–40 levels of TSA-treated AD Tg mice and vehicle-treated AD Tg mice are shown in Fig. 3A. The concentration of plasma Aβ1–40 was 153.81 ± 64.66 pg/ml in TSA-treated female AD Tg mice, 69.60 ± 23.81 pg/ml in vehicle-treated female AD Tg mice, and 302.11 ± 79.1 pg/ml in TSA-treated male AD Tg mice, 189.57 ± 73.06 pg/ml in vehicle-treated male AD Tg mice. TSA-treatment increased the concentration of Aβ1–40 by 2.21-fold (153.81 vs 69.60) in female mice and by 1.59-fold (302.11 vs 189.57) in male mice as compared to vehicle-treated control mice. A significant difference was observed ($p < 0.05$) when data was plotted with both female and male groups together and one outlier of the vehicle-treated mouse was excluded because of unusually high value of Aβ1 (Fig. 3A). When 95% CI of the vehicle-treated group (48.55–137.50, $n = 11$) was taken as the reference range, eight of 14 (57.1%) TSA-treated Tg mice had a higher concentration of Aβ1–40 than the upper limit of 95% CI of the vehicle-treated control group.

![Body weight change of transgenic mice treated with TSA or vehicle. AD Tg mice were injected intraperitoneally with TSA or vehicle from 9 to 11 months of age. Female and male groups are represented in A and B respectively.](image1)

![Levels of plasma gelsolin in TSA- and vehicle-treated female and male AD Tg mice. AD Tg mice were intraperitoneally injected with TSA (5 mg/kg body weight) or vehicle every alternate day for 2 months. Western blot analysis (A) and densitometric quantification of gelsolin by ImageJ software (NIH, Bethesda, MD, USA) in females (B), males (C) and combined female and male group (D) show elevated levels of gelsolin [GSN] in the plasma from the TSA-treated AD Tg mice compared to the vehicle group. Values are presented as Mean ± SEM and density of gelsolin was normalized with the total protein in the loading sample. *p < 0.05, **p < 0.01 compared to the vehicle group, unpaired Student’s t-test.](image2)
TSA-treatment increases $\beta$-1–42 levels in the plasma of AD Tg mice

Plasma $\beta$-1–42 levels of TSA-treated AD Tg mice and vehicle-treated AD Tg mice are shown in Fig. 3B. The concentration of $\beta$-1–42 was $47.51 \pm 15.49$ pg/ml in TSA-treated female AD Tg mice, $33.50 \pm 7.61$ pg/ml in vehicle-treated female AD Tg mice, and $66.14 \pm 21.84$ pg/ml in TSA-treated AD Tg mice, $62.15 \pm 14.81$ pg/ml in vehicle-treated male AD Tg mice. Due to a large variation in the levels of $\beta$-1–42 in the samples, no significant difference was observed between the TSA- and vehicle-treated groups. However, when 95% CI (27.93–67.72, $n = 12$) of the vehicle-treated group was taken as the reference range, five of 14 (35.7%) TSA-treated Tg mice had higher concentration of $\beta$-1–42 than the upper limit of 95% CI of the vehicle-treated group. We also observed that levels of $\beta$-1–42 were 36.9% lower than $\beta$-1–40 levels in the vehicle-treated AD Tg mice.

Correlation between plasma gelsolin and $\beta$-1–40 or $\beta$-1–42 in TSA-treated AD Tg mice

Linear regression analysis between gelsolin and $\beta$-1–40/$\beta$-1–42 levels in the plasma showed a significant positive relationship between the levels of gelsolin and $\beta$-1–40 ($r = 0.594, p = 0.042$) (Fig. 4A) or $\beta$-1–42 ($r = 0.616, p = 0.033$) (Fig. 4B) in the TSA-treated Tg mice. When performing correlation analysis, two outliers were excluded because one mouse had very high plasma gelsolin and the other mouse had unusually high $\beta$-1 levels.

Discussion

Fibrillization of $\beta$ in the brain is a major event in the pathology of AD. $\beta$-1–42 is more amyloidogenic than $\beta$-1–40. However, the levels of $\beta$-1–42 are 1/3 to 1/4 lower than $\beta$-1–40 in the plasma of patients with AD (Mehta et al., 2000). In our studies, we also observed 36.9% lower levels of $\beta$-1–42 than $\beta$-1–40 in vehicle-treated AD Tg mice. We also observed that levels of $\beta$-1–42 were 36.9% lower than $\beta$-1–40 levels in the vehicle-treated AD Tg mice.

Correlation between the plasma levels of $\beta$-1–40 and $\beta$-1–42 in TSA-treated AD Tg mice

Although the levels of plasma $\beta$-1–40 (Mean ± SEM: 228.0 ± 53.21, $n = 14$) were higher than $\beta$-1–42 (Mean ± SEM: 56.83 ± 13.12, $n = 14$) in the TSA-treated AD Tg mice, it was not clear whether the increase in both $\beta$-1 peptides was similar or different. Linear regression analysis between the levels of $\beta$-1–40 and $\beta$-1–42 (Fig. 5) showed a positive and highly significant relationship between the levels of $\beta$-1–40 and $\beta$-1–42 in the TSA-treated AD Tg mice ($r = 0.92; p < 0.0001$).

Fig. 3. Levels of plasma $\beta$-1–40 and $\beta$-1–42 in TSA- and vehicle-treated female and male AD Tg mice. AD Tg mice were intraperitoneally injected with TSA (5 mg/kg body weight) or vehicle every alternate day for 2 months. The levels of $\beta$-1–40 (A) and $\beta$-1–42 (B) in the plasma were assayed by ELISA. *$p < 0.05$ compared to the vehicle group, unpaired Student’s t-test. 

Fig. 4. Correlation between plasma gelsolin (GSN) and levels of plasma $\beta$-1–40 (A) and $\beta$-1–42 (B). Linear regression analysis was done to calculate pearson correlation coefficient ($r$) between the levels of GSN and $\beta$-1–40 or $\beta$-1–42. A positive correlation between the levels of GSN and $\beta$-1–40 ($r = 0.594, p = 0.042$) or $\beta$-1–42 ($r = 0.616, p = 0.033$) was observed.

Fig. 5. Correlation between plasma $\beta$-1–40 and $\beta$-1–42. The plasma $\beta$-1–40 and $\beta$-1–42 levels were determined by ELISA. A highly positive correlation between the levels of plasma $\beta$-1–40 and $\beta$-1–42 (Pearson coefficient $r = 0.92, p < 0.0001$) was observed.
modulate the transfer of Aββ between the brain and plasma (DeMattos et al., 2001, 2002a,b). Therefore, compounds that can bind to Aββ in the periphery without penetrating blood brain barrier may be ideal candidates as effective therapeutic agents for AD. One such candidate is gelsolin of 90 kDa protein, which is present as circulating and also intracellular protein.

We have previously reported that gelsolin is an anti-amyloidogenic protein (Chauhan et al., 2008; Ji et al., 2009), which binds to Aββ (Chauhan et al., 1999; Ji et al., 2008, 2010), inhibits Aββ fibrillation and also promotes its de fibrillation (Ray et al., 2000). Interestingly, Guntert et al. (2010) analyzed the plasma protein levels of gelsolin in slow cognitive declining AD patients, rapid cognitive declining AD patients and non-demented controls using isobaric mass tagging approach. These authors reported that AD patients had significantly lower plasma gelsolin levels compared to non-demented controls, and gelsolin levels correlated with disease progression rate estimated by Mini-Mental Status Examination decline per year. Apart from binding of gelsolin to Aββ and inhibition of its fibrillation, gelsolin protects cells against apoptosis by blocking cytochrome C release (Koya et al., 2000; Qiao et al., 2005). It also modulates mitochondrial function by increasing mitochondrial complex IV activity (Antequera et al., 2009), which is decreased in AD patients and animal models of AD (Morais and De Strooper, 2010; Moran et al., 2012). Antequera et al. (2009) reported that inhibition of gelsolin gene expression in APP/PS1 transgenic mouse model of AD resulted in increased amyloid burden and apoptotic response.

Many studies have focused on reducing the amyloid load by gelsolin. Anti-amyloidogenic role of gelsolin has been reviewed by us (Chauhan et al., 2008; Ji et al., 2009). Other groups have also confirmed anti-amyloidogenic role of gelsolin (Antequera et al., 2009; Hirko et al., 2007; Matsuoka et al., 2003). Hirko et al. (2007) reported that peripheral transgene expression of plasma gelsolin reduces amyloid load in transgenic mouse model of AD. In mutant APP-transgenic mouse model of AD, intraperitoneal injection of gelsolin resulted in reduced amyloid load in the brain and increased levels of gelsolin in the plasma (Matsuoka et al., 2003). Lemere et al. (2003) also reported increased serum Aββ levels upon Aββ immunization of transgenic PS1/APP mice. The efflux/clearance of Aββ from brain to plasma is reported by DeMattos et al. (2001, 2002a,b). When cytoplasmic gelsolin was increased by viral-directed overexpression of gelsolin in APP/PS1 transgenic mice, a decrease in the brain Aββ burden was observed (Antequera et al., 2009). From these studies, it can be concluded that increased levels of plasma gelsolin reflect reduced amyloid load in the brain. Although our data of increased plasma gelsolin in TSA-treated mice indirectly suggest increased clearance of Aββ from the brain, it cannot be ruled out that TSA may also be affecting the processing of APP which may lead to reduced amyloid load in the brain independent of gelsolin levels. In both scenarios, TSA may have beneficial effect in reducing the amyloid load in the brain.

In a recent study, Gregory et al. (2012) reported that reducing available soluble Aββ prevents progression of cerebral amyloid angiopathy in Tg 2576 model of AD mice. However, the present study is the first report by which we have chemically increased the levels of plasma gelsolin in AD Tg mice, i.e., by using TSA, a class I and II inhibitor of HDACs and studied its effect on the levels of Aββ. TSA has pleiotropic effects as it promotes expression of several genes by inhibition of histone acetylation. One of the genes induced by TSA is gelsolin. Our results indicate that TSA increases the levels of plasma gelsolin and Aββ 1–40/Aββ 1–42, and there is a significant positive correlation between the levels of gelsolin and Aββ 1–40/Aββ 1–42 in these mice. A positive correlation between the levels of Aββ 1–40 and Aββ 1–42 suggests that gelsolin sequesters Aββ 1–40 and Aββ 1–42 with similar affinity for these peptides. Because TSA-treatment of mice for two months did not affect the body weight, TSA-treatment may not have any deleterious effects on health.

Other HDAC inhibitors have also been shown to have beneficial effects in animal models of AD. Valproic acid (VPA) has been shown to down regulate APP in cancer cells (Venkataramani et al., 2010). VPA inhibits the production of Aββ peptide in HEK293 cells transfected with Swedish APP751 (Su et al., 2004). VPA is also found to reduce Aββ production (Qing et al., 2008). Francis et al. (2009) reported that histone acetylation plays an important role in hippocampal long-term potentiation and memory. They observed that levels of hippocampal acetylated histone 4 (H4) in APP/PS1 mice were decreased by 50% as compared to wild type mice after fear conditioning training. An acute treatment with TSA prior to training rescued both acetylated H4 levels and contextual freezing performance close to wild type animals.

However, there are some differences in the alterations of plasma Aββ levels in various studies, where peripheral Aββ sequestration approaches were used. We observed increased levels of both Aββ 1–40 and Aββ 1–42 in the plasma of mice treated with TSA. On the other hand, Matsuoka et al. reported that plasma levels of Aββ 1–40 and Aββ 1–42 were not affected in vehicle-treated mice and mice with peripherally administrated gelsolin (Matsuoka et al., 2003). In another study, Hirko et al. observed that levels of plasma Aββ 1–42 were increased but the levels of Aββ 1–40 were decreased after transgene overexpression of plasma gelsolin (Hirko et al., 2007). At present, it is not clear why different methods of gelsolin administration affect Aββ levels in different manner. In our studies, a positive correlation was also observed between plasma gelsolin and Aββ 1–40/Aββ 1–42 levels, suggesting that increased plasma gelsolin may be acting as a peripheral sink to reduce brain Aββ. This study further suggests that gelsolin may be acting by binding to Aββ 1–40 and Aββ 1–42. It is also supported by our previous in vitro study where we reported that plasma gelsolin and cytoplasmic gelsolin bind to Aββ 1–40 and Aββ 1–42 (Ji et al., 2008), and inhibit its fibrillation (Ray et al., 2000). While our studies suggest that TSA-induced increased levels of Aββ peptides in the plasma of AD Tg mice come from sequestration of brain Aββ peptides by gelsolin, it is also possible that these peptides may also arise from increased APP processing in peripheral tissues.

In summary, our results indicate that plasma levels of gelsolin and Aββ 1–40 and Aββ 1–42 can be increased by TSA. A correlation between the levels of plasma gelsolin and plasma Aββ 1–40 or Aββ 1–42 suggests that TSA may help in the clearance of Aββ from the brain or other tissues, and may act as a potential therapeutic agent in AD.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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