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Investigating the effects of taurine on Aβ-degradation proteins and neurogenesis-related genes in an LPS-induced neuroinflammatory SH-SY5Y cell model

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ABSTRACT

Objective(s): Taurine, a brain-abundant sulfonic acid, shows potential neuroprotective effects and may counter neurodegenerative processes. This study investigated the effects of taurine on neuroinflammation, focusing on Aβ-degrading proteins and gene expression related to neurogenesis in an LPS-stimulated SH-SY5Y cell model.

Materials and Methods: The effects of taurine (0.5 and 1 mg/ml) and LPS (0.5 and 10 µg/ml) on SH-SY5Y cell viability were assessed using the MTT assay. IL-1β and IL-6 expression was measured by real-time PCR, while matrix metalloproteinases (MMPs) and angiotensin-converting enzyme (ACE) levels were quantified via ELISA. Neurogenesis-related gene expression was evaluated using the Neurogenesis Plus RT² Profiler PCR array.

Results: The MTT assay results demonstrated that taurine treatment at concentrations of 0.5 and 1 mg/ml significantly attenuated the cytotoxicity induced by LPS stimulation in SH-SY5Y cells. Also, treatment with taurine significantly reduced the expression levels of the inflammatory genes IL-1β and IL-6 in LPS-stimulated SH-SY5Y cells ($P<0.05$). ELISA results further revealed that taurine treatment significantly increased the secretion levels of ACE and MMP-9 enzymes in LPS-stimulated SH-SY5Y cells ($P<0.05$). LPS exposure in SH-SY5Y cells significantly up-regulated genes related to apoptosis, cell migration, and synaptic function ($P<0.005$). Conversely, taurine treatment significantly increased the expression of genes involved in cell adhesion, synaptic function, growth factors, cytokines, differentiation, cell cycle, signaling, transcription, and cofactor activity ($P<0.005$).

Conclusion: These results suggest that taurine may act as a potential neuroprotective agent by increasing the secretion of MMP-9 and ACE, regulating neurogenesis-related genes, and reducing LPS-induced neuroinflammation.

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Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, the prevalence of which is increasing dramatically in the elderly population. A set of pathological changes in the brain, including chronic neuroinflammation and progressive neuronal destruction, characterizes it. The consequence of these processes is the impairment of cognitive functions, especially memory and learning (1). Despite extensive efforts, a definitive cure for AD has not yet been introduced, and current therapeutic approaches mainly focus on reducing symptoms and improving the quality of life of patients (2). A defining pathological characteristic of AD is the buildup of amyloid-beta (Aβ) plaques in the brain, which impair neuronal communication and lead to neuronal death (3). Beyond the production of amyloid precursor protein (APP) in the amyloidogenic pathway, the extent of Aβ accumulation also hinges on its degradation (4). The formation and removal of these plaques are carefully controlled by various enzymes, such as matrix metalloproteinases (MMPs) and angiotensin-converting enzyme (ACE), both of which are crucial in the degradation of Aβ (5, 6). The ACE enzyme, a metalloprotease with two homologous regions called the N and C domains, exhibits proteolytic activity in both. It is primarily expressed by endothelial, epithelial, and neuronal cells, and is well-established in its role of regulating blood pressure by converting angiotensin-1 to angiotensin-2 and inactivating bradykinin (7). Research shows that ACE can break down amyloid beta peptide and prevent its accumulation and deposition in laboratory settings (8, 9). MMP-9 is another enzyme that depends on calcium and zinc and belongs to the gelatinase subfamily. These enzymes are activated extracellularly and participate in a range of physiological processes, such as extracellular matrix regeneration and nerve growth. Activated outside the cell, it is involved in various physiological processes, including

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extracellular matrix regeneration and nerve growth. MMP-9 is also implicated in pathological conditions such as neuroinflammation and tumor invasion. Animal studies have shown that MMP-9 is expressed in astrocytes surrounding amyloid plaques and plays a role in the degradation of amyloid proteins (10, 11). Understanding the regulation of these enzymes is vital for developing strategies to mitigate Aβ accumulation and slow the progression of AD.

Neuroinflammation, involving microglia and astrocyte activation, critically influences neurogenesis regulation and disruption in the adult brain. Elevated inflammatory cytokines like IL-1β, IL-6, and TNF-α—common in neurodegenerative diseases—can hinder neural progenitor cell survival, proliferation, and differentiation, thereby decreasing new neuron formation (12). Key genes also govern neurogenesis; for instance, NOTCH1, part of the Notch pathway, is essential for maintaining neural progenitor cells and controlling their division in adult neurogenesis, with pathway disruption shifting the balance between proliferation and differentiation (13). Similarly, NEUROD1, a bHLH transcription factor, is involved in neuronal differentiation, and lower activity levels correlate with impaired neuronal development (14). BDNF, a neurotrophic factor, supports survival, plasticity, and growth of neurons; its reduction during neuroinflammation can impair neurogenesis and synaptic connectivity (15). Additionally, molecules like DCX, a marker of young neurons, and CXCL1, a chemokine, are involved in migration, survival, and maturation processes, with their expression balance affected by inflammation (12). Therefore, investigating how the expression of these genes changes in neuroinflammation models can contribute to a better understanding of the molecular mechanisms of neurogenesis impairment in neurodegenerative diseases and provide a suitable basis for evaluating the effects of therapeutic agents such as taurine.

Taurine, a sulfur-containing β-amino acid, plays a vital role in the central nervous system by regulating osmosis, serving as an antioxidant, modulating neural activity, and managing intracellular calcium levels. During spinal cord injuries, taurine levels rise, potentially aiding in tissue protection and regeneration (16). Recent research has highlighted taurine's potential neuroprotective effects, suggesting it may influence processes involved in neurodegeneration, such as inflammation, and apoptosis (17, 18). Given its abundance in the central nervous system, taurine is thought to play a role in maintaining neuronal health, possibly through the modulation of enzymes involved in Aβ degradation (19). In addition to its effects on Aβ-related enzymes, taurine has been implicated in the regulation of neurogenesis—the process by which new neurons are formed in the brain (20). Neurogenesis is crucial for maintaining cognitive function, particularly in the hippocampus, a region severely affected in AD. Genes involved in neurogenesis are essential for neuronal differentiation, survival, and synaptic plasticity (21). Therefore, understanding how taurine affects the expression of these genes could provide valuable insights into its potential as a therapeutic agent for neurodegenerative diseases.

The SH-SY5Y cell line, derived from human neuroblastoma, is used as a common laboratory model to investigate neuronal function and mechanisms involved in neurological diseases. It is particularly useful for investigating the molecular and cellular responses to various treatments, including those targeting neuroprotection and neurogenesis (18). In this study, SH-SY5Y cells were exposed to LPS to induce inflammation, and the effects of taurine on Aβ-degrading enzymes, specifically MMP-9 and ACE, as well as on the expression of genes involved in neurogenesis, were investigated. This study aimed to clarify the role of taurine in modulating key Aβ-degrading proteins, regulating gene pathways related to neurogenesis, and reducing LPS-induced neuroinflammation.

Materials and Methods

Culture conditions

The SH-SY5Y cells used in this research were sourced from the Pasteur Institute, Iran, and cultured according to standard protocols to ensure optimal growth conditions. SH-SY5Y cells were cultured in DMEM/HG (Biological Industries) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine (Biological Industries), and 1% penicillin-streptomycin (Biological Industries). Cells were incubated for 24 hr under standard conditions of 37 °C, 95% relative humidity, and 5% CO2 to achieve optimal conditions for cell growth and stability. To evaluate the dose-dependent effects of taurine on LPS-induced neuroinflammation, SH-SY5Y cells were randomly assigned to seven experimental groups. The groups included: control (untreated cells), LPS (0.5 µg/ml), LPS (10 µg/ml), LPS (0.5 µg/ml) + taurine (0.5 mg/ml), LPS (0.5 µg/ml) + taurine (1 mg/ml), LPS (10 µg/ml) + taurine (0.5 mg/ml), and LPS (10 µg/ml) + taurine (1 mg/ml). LPS was used to establish the inflammatory cellular model, and taurine treatments were applied to investigate its potential dose-dependent neuroprotective effects.

Cell viability assay

Initially, SH-SY5Y cells were seeded at a density of 1×10^5 cells per well in 96-well plates. Then, the groups were determined, and except for the control group, the remaining groups were exposed to LPS (0.5 and 10 µg/ml) (22, 23) for 24 hr. Then, taurine (Cat. No: 107-35-7; Sigma-Aldrich, St. Louis, MO, USA) concentrations (0.5 and 1 mg/ml) (24, 25) were added, and the cells were exposed to taurine for another 24 hr. The effect of taurine, LPS, and LPS+Tau on the toxicity of SH-SY5Y cells was evaluated using the MTT assay (Gibco, USA). Following 24 hr of treatment, 20 µl of MTT solution (5 mg/ml in PBS) was added to each well and incubated at 37 °C for 4 hr to facilitate formazan crystal formation. Subsequently, 50 µl of DMSO was introduced to each well, and the reaction was halted by incubating for an additional 30 min. The resulting formazan dye, reflecting cell viability, was quantitatively measured using a Microplate reader (Multiskan FC; Thermo Fisher Scientific) at 450 nm absorbance with a 620 nm reference wavelength.

Alzheimer's cell model

In this study, SH-SY5Y cells, which are known as a suitable model for studying neuronal phenotype degradation, especially in AD, due to their expression of proteins such as Aβ, tau, inflammatory factors, and other neuronal-specific proteins, were used (18). These cells were cultured in a 6-well plate at a density of 5×10^4 cells per well and incubated for 24 hr under standard conditions (37 °C, 5% CO_2, and 95% humidity) to achieve proper cell adhesion and stability of the growth medium. After the initial incubation period, the culture medium was replaced with fresh medium containing LPS. In order to simulate inflammatory conditions similar to AD, the cells were treated with two different concentrations of LPS (0.5 and

Table 1. Primer sequences used for gene expression analysis

Gene name	Forward primer (5′→3′)	Universal reverse primer (5′→3′)
IL-1β	CCTTGTCGAGAATGGGCAGT	TTCTGTCGACAATGCTGCCT
IL-6	AGAGACTTCCAGCCAGTTGC	AGTCTCCTCTCCGGACTTGT
β-actin	AGAGCTACGAGCTGCCTGAC	AGCACTGTGTTGGCGTACAG

10 µg/ml). LPS treatment was continued for 12 and 24 hr, a period sufficient to induce molecular changes associated with neuroinflammation, including increased levels of inflammatory cytokines such as IL-6, and IL-1β. At the end of treatment, cells were used for further experiments.

Evaluation of IL-1β and IL-6 in the SH–SY5Y cells

Following the previous treatment, SH-SY5Y cells were further incubated with taurine at concentrations of 0.5 and 1 mg/ml for additional periods of 12 and 24 hr. Following this treatment, total RNA was isolated using the RNeasy Kit (Cat. No: FABRK001, Favorgen, Taiwan). RNA integrity and concentration were evaluated through 1% agarose gel electrophoresis and quantified using a NanoDrop spectrophotometer (Thermo Scientific, USA). Complementary DNA (cDNA) synthesis was subsequently conducted utilizing the RT2 First Strand Kit (YTA, Cat. No: YT4500, Austria).

Quantitative PCR (qPCR) was carried out with the Chromo4 Real-Time PCR Detection System (Bio-Rad, USA), employing the SYBR® Premix Ex Taq™ II reagent (Takara, Japan). Each 10 µl PCR reaction mixture contained 5 µl of SYBR pre-mix, 1 µl of synthesized cDNA, and 0.5 µl of both forward and reverse primers (5 µM). The PCR amplification program included an initial denaturation step at 94 °C for 60 sec, followed by 40 cycles of denaturation at 94 °C for 15 sec, annealing for 25 sec, and extension at 72 °C for 15 sec. The specific primer sequences for IL-1β and IL-6 are listed in Table 1.

Measurement of MMP-9 and ACE levels

To measure MMP-9 and ACE levels, we used the Human MMP9 ELISA Kit (Cat. No: ARG80129: Arigo, Taiwan) and the Human ACE/Cd143 PicoKine™ ELISA Kit (Cat. No: EK0557: Boster Biological Technology, Pleasanton CA, USA). SH-SY5Y cells were seeded at 1×10^5 cells per well in 96-well plates and treated as specified. Standards and samples were prepared according to kit instructions. Optical density was measured at 450 nm using a Thermo Multiskan FC microplate reader.

Studying the expression patterns of genes involved in neurogenesis

SH-SY5Y cells were seeded in a 6-well plate at 1×10^5 cells/well and incubated for 24 hr. They were then treated with taurine (0.5 and 1 mg/ml) and LPS (10 µg/ml) for another 24 hr. Total RNA was extracted using an RNeasy Kit (Favorgen, Taiwan), and cDNA was synthesized with the RT2 First Strand Kit (YTA, Austria; Cat. No: YT4500). Gene expression changes in 84 neurogenesis-related genes were assessed using the RT² Profiler™ PCR Array (Qiagen, Cat. No: PAHS-404Z) and Light Cycler 480 II (Roche). Data were analyzed with the comparative $2^{-\Delta\Delta CT}$ method and considered significant if changes exceeded ±2-fold with *P*-values <0.05.

Statistical analysis

All experiments in this study were performed in triplicate, and results from three separate trials are presented as mean ± standard deviation. Statistical comparisons were made using one-way ANOVA followed by Tukey's *post hoc* test. Data analysis was carried out using GraphPad Prism software (version 8.0.2). Gene expression levels were normalized using the $2^{\wedge-\Delta\Delta Cq}$ method, and a *P*-value below 0.05 was considered statistically significant.

Results

Evaluation of the toxicity effects of taurine and LPS on SH-SY5Y cells

To assess the survival rate of SH-SY5Y cells treated with taurine and LPS after 24 hr, cell viability was measured using the MTT assay. The results indicated that LPS (0.5 and 10 µg/ml) significantly decreased cell survival. However, when taurine was added at concentrations of 0.5 and 1 mg/ml to LPS-stimulated SH-SY5Y cells, it reduced LPS toxicity and improved cell viability (Figure 1).

Expression level of IL-1β and IL-6

The effects of taurine (0.5 and 1 mg/ml) on LPS-induced inflammatory responses were evaluated by measuring IL-1β and IL-6 expression levels in SH-SY5Y cells. Stimulation with LPS (0.5 and 10 µg/ml) significantly increased the expression of both IL-1β and IL-6 compared to the control group. Treatment with taurine markedly attenuated the LPS-induced up-regulation of these pro-inflammatory cytokines (Figure 2). The suppressive effect of taurine was significantly greater after 24 hr compared to 12 hr of treatment ($P<0.001$).

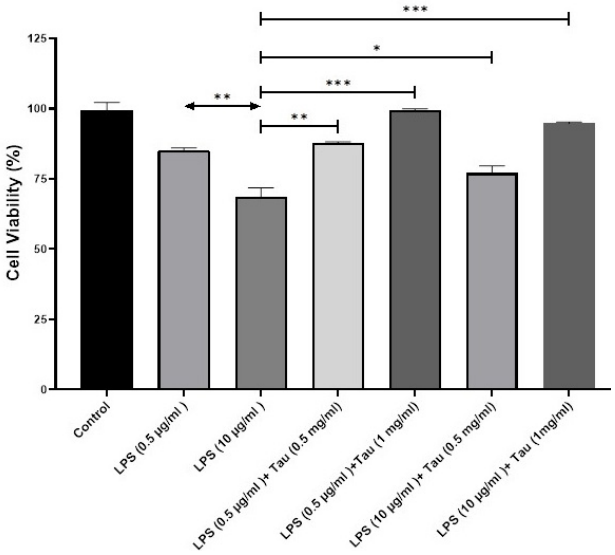

Figure 1. Comparison of SH-SY5Y cell viability after treatment with different concentrations of taurine and LPS relative to the control group
Statistical significance is denoted by **P*<0.05, ***P*<0.01, and ****P*<0.001.
Tau: Taurine; LPS: Lipopolysaccharide

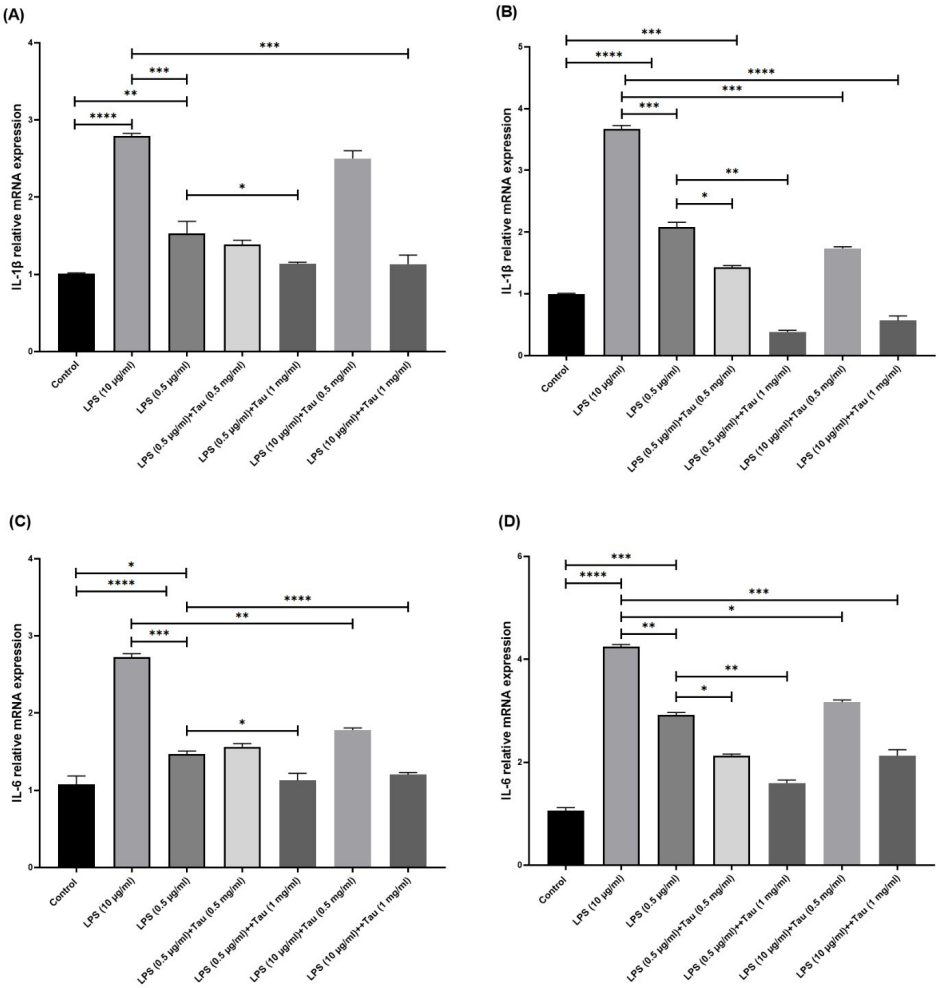

Figure 2. Effect of taurine on IL-1β and IL-6 expression levels in LPS-stimulated SH-SY5Y cells
IL-1β expression levels were measured after taurine and LPS treatment at (A) 12 and (B) 24 hr. IL-6 expression levels were assessed after (C) 12 and (D) 24 hr of treatment. Taurine significantly reduced IL-1β and IL-6 expression in LPS-stimulated SH-SY5Y cells in a time-dependent manner (*P<0.05, **P<0.01, ***P<0.001).
Tau: Taurine; LPS: Lipopolysaccharide

Measurement of matrix metalloproteinases-9, and angiotensin converting enzyme in the SH-SY5Y cell line

The ELISA data revealed that at an LPS concentration of 0.5 µg/ml, the level of ACE enzyme was statistically significant in SH-SY5Y cells compared to the control group (P<0.05), whereas the MMP-9 level did not show statistical significance (P>0.05). At a concentration of 10 µg/ml LPS, there was a statistically significant decrease in the levels of both ACE and MMP-9 enzymes in SH-SY5Y cells compared to the control group (P<0.01). The addition of taurine (1 mg/ml) resulted in a significant increase in the levels of ACE and MMP-9 enzymes in LPS-stimulated SH-SY5Y cells, which was statistically significant (P<0.01). The combination of taurine (0.5 mg/ml) showed a lower increase in the level of ACE and MMP-9 enzymes in LPS-stimulated SH-SY5Y cells, which was statistically significant (P<0.05) (Figure 3).

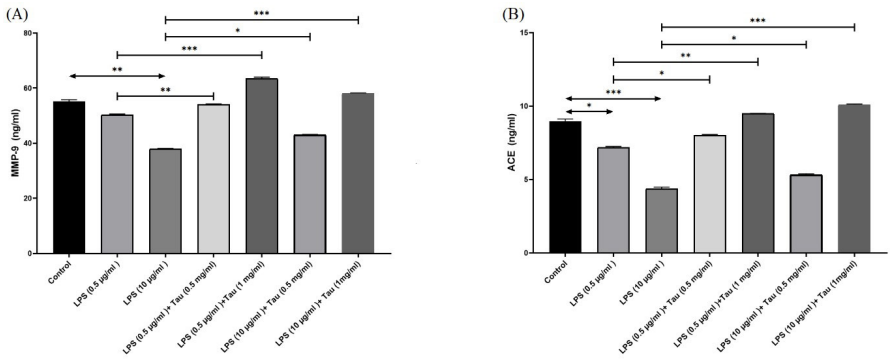

Figure 3. Levels of MMP-9 (A) and ACE (B) in SH-SY5Y cells were quantified using ELISA following treatment with LPS (0.5 and 10 µg/ml) and taurine (0.5 and 1 mg/ml)
Taurine treatment significantly increased the concentrations of MMP-9 and ACE in LPS-stimulated SH-SY5Y cells (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).
MMP: Matrix metalloproteinases; ACE: Angiotensin-converting enzyme; Tau, Taurine; LPS: Lipopolysaccharide

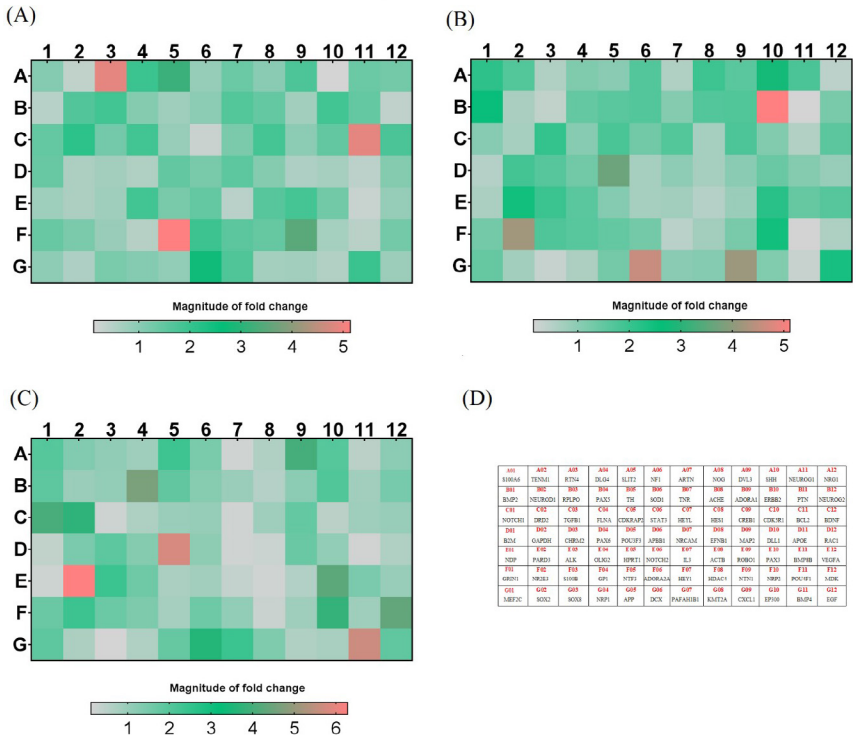

Figure 4. Heat map of human neurogenesis-associated genes in SH-SY5Y cells treated with (A) LPS (10 µg/ml), (B) LPS (10 µg/ml) + Taurine (0.5 mg/ml), and (C) LPS (10 µg/ml) + Taurine (1 mg/ml). (C) Lists the genes related to human neurogenesis examined in our study

Changes in the expression of genes involved in human neurogenesis

A PCR array was conducted on SH-SY5Y cells to evaluate the impact of LPS (10 µg/ml), LPS (10 µg/ml) + Taurine (0.5 mg/ml), and LPS (10 µg/ml) + Taurine (1 mg/ml) on the expression of Human Neurogenesis-associated genes (Figure 4). PCR array analysis showed that exposure to LPS and Taurine induces the expression of genes involved in neurogenesis in SH-SY5Y cells (Table 2). The results showed that when SH-SY5Y cells are exposed to taurine,

Table 2. PCR array analysis of human neurogenesis-associated genes exposed to lipopolysaccharide (LPS) and taurine

Gene	LPS (10 µg/ml)		LPS (10 µg/ml) + Taurine (0.5 mg/ml)		LPS (10 µg/ml) + Taurine (1 mg/ml)	
	*Fold change**	*P-value*	*Fold change**	*P-value*	*Fold change**	*P-value*
S100A6	1.07	0.45	2.13	0.004	1.98	0.005
TENM1	0.34	0.001	1.69	0.001	1.32	0.000
RTN4	4.87	0.001	0.58	0.26	1.12	0.002
DLG4	1.97	0.001	1.15	0.001	0.89	0.001
SLIT2	3.18	0.001	1.02	0.001	2.36	0.001
NF1	0.86	0.04	1.68	0.000	1.45	0.000
ARTN	1.37	0.001	0.57	0.005	0.18	0.001
NOG	1.02	0.05	1.94	0.000	0.67	0.05
DVL3	1.74	0.005	1.60	0.06	3.98	0.001
SIHH	0.12	0.01	2.78	0.000	1.98	0.001
NEUROG1	1.37	0.003	1.78	0.000	0.49	0.000
NRG1	1.28	0.001	0.42	0.005	1.19	0.000
BMP2	0.47	0.05	2.57	0.002	1.87	0.001
NEUROD1	1.69	0.71	0.64	0.001	0.97	0.000
RPLPO	1.87	0.08	0.36	0.000	1.06	0.001
PAX5	1.08	0.001	1.48	0.002	4.63	0.000
TH	0.74	0.25	1.59	0.001	1.81	0.001
SOD1	0.97	0.01	1.67	0.06	1.26	0.002
TNR	1.68	0.001	1.09	0.000	0.98	0.005
ACHE	1.47	0.003	1.68	0.000	0.58	0.000

Continued Table 2.

ADORA1	0.72	0.05	1.71	0.005	1.19	0.000
ERBB2	1.89	0.001	5.12	0.001	2.07	0.003
PTN	1.47	0.01	0.14	0.001	0.87	0.001
NEUROG2	0.37	0.00	1.23	0.000	1.49	0.05
NOTCH1	1.47	0.002	1.06	0.000	4.02	0.000
DRD2	2.14	0.001	0.67	0.002	3.71	0.003
TGFB1	1.29	0.001	2.06	0.003	0.23	0.000
FLNA	1.87	0.001	1.06	0.000	0.68	0.000
CDK5RAP2	0.84	0.05	1.81	0.000	0.97	0.002
STAT3	0.24	0.01	1.33	0.000	1.03	0.056
HEYL	1.19	0.57	1.69	0.005	0.19	0.05
HES1	1.85	0.001	0.68	0.05	0.89	0.000
CREB1	0.97	0.03	1.76	0.000	1.78	0.002
CDK5R1	1.49	0.001	1.12	0.000	0.49	0.005
BCL2	4.87	0.000	0.53	0.25	0.89	0.001
BDNF	1.78	0.001	1.58	0.000	1.02	0.005
B2M	1.44	0.05	0.51	0.002	0.39	0.003
GAPDH	0.59	0.00	1.87	0.000	1.42	0.000
CHRM2	0.71	0.001	1.63	0.000	1.89	0.001
PAX6	0.56	0.002	1.31	0.001	1.30	0.000
POU3F3	1.48	0.005	3.67	0.001	5.78	0.003
APBB1	1.23	0.000	0.68	0.001	1.16	0.001
NRCAM	1.56	0.001	0.97	0.05	0.18	0.000
EFNB1	1.09	0.001	0.69	0.26	0.26	0.01
MAP2	0.58	0.5	1.03	0.000	1.67	0.000
DLL1	0.67	0.001	1.41	0.003	1.09	0.001
APOE	0.41	0.000	1.09	0.000	0.17	0.05
RAC1	1.09	0.001	0.87	0.05	0.63	0.003
NDP	0.77	0.003	0.63	0.01	0.22	0.005
PARD3	0.59	0.51	2.47	0.002	6.28	0.000
ALK	0.74	0.04	1.98	0.001	2.39	0.002
OLIG2	1.88	0.003	1.59	0.000	1.62	0.000
HPRT1	1.23	0.005	1.08	0.056	0.73	0.003
NOTCH2	1.47	0.000	0.67	0.04	0.87	0.001
IL3	0.44	0.01	0.74	0.001	0.36	0.005
ACTB	1.62	0.001	0.51	0.51	0.19	0.23
ROBO1	1.85	0.000	0.83	0.002	0.62	0.11
PAX3	1.32	0.005	2.18	0.001	4.28	0.000
BMP8B	0.26	0.01	1.47	0.000	1.42	0.000
VEGFA	0.87	0.06	1.62	0.001	1.02	0.000
GRIN1	1.42	0.001	1.29	0.000	1.67	0.001
NR2E3	1.19	0.001	4.18	0.002	2.37	0.005
S100B	0.83	0.000	1.73	0.001	1.66	0.26
GP1	0.48	0.005	1.61	0.000	1.41	0.000
NTF3	5.14	0.003	1.48	0.001	0.79	0.000
ADORA2A	1.96	0.000	1.29	0.26	1.65	0.003
HEY1	1.57	0.000	0.46	0.051	1.09	0.000
HDAC1	1.46	0.001	0.72	0.000	0.28	0.001
NTN1	3.48	0.002	1.23	0.3	0.89	0.001
NRP2	0.68	0.002	2.47	0.001	3.78	0.000
POU4F1	0.43	0.054	0.16	0.01	0.89	0.05
MDK	1.28	0.001	0.59	0.000	4.37	0.001
MEF2C	0.95	0.000	1.47	0.000	1.87	0.001
SOX2	0.58	0.005	0.73	0.002	0.69	0.000
SOX8	1.21	0.003	0.32	0.000	0.12	0.51
NRP1	1.07	0.000	0.61	0.05	0.63	0.06

Continued Table 2.

APP	0.91	0.004	1.28	0.001	1.76	0.000
DCX	2.74	0.000	4.57	0.002	3.57	0.001
PAFAH1B1	1.73	0.000	1.03	0.005	2.39	0.001
KMT2A	0.69	0.002	1.08	0.003	1.37	0.005
CXCL1	0.72	0.002	4.12	0.000	0.67	0.001
EP300	0.51	0.056	1.13	0.003	0.77	0.000
BMP4	1.98	0.003	0.29	0.026	5.64	0.000
EGF	0.87	0.000	2.41	0.005	1.83	0.002

genes involved in cell adhesion (NRP2 and SLIT2), genes involved in synaptic function (DCX, ERBB2, PAFAH1B1, S100A6, and DRD2), genes related to growth factors and cytokines (BMP2, BMP4, EGF, S100A6, and TGFB1), genes involved in cell differentiation including (PAFAH1B1, PAX3, and PAX5), genes related to cell cycle (MDK and PARD3), genes involved in signal transmission (BMP2, BMP4, CXCL1, DVL3, NOTCH1, and SHH) and genes involved in transcription and cofactors (NR2E3, PAX3, PAX5, and POU3F3) had a significant increase (Table 2). The results showed that when SH-SY5Y cells are exposed to LPS, gene apoptosis (BCL2 and NTN1), cell migration (NTN1, NTF3, RTN4, and SLIT2), and synaptic function (DCX and DRD2) had a significant increase (Table 2). Our findings suggest that taurine can modulate or inhibit the effects of LPS on the target genes.

Discussion

The present study aimed to explore the neuroprotective effects of taurine on SH-SY5Y cells, particularly focusing on its influence on MMP-9 and ACE, as well as its impact on neurogenesis-related genes. The significance of taurine, a sulfonic acid abundantly present in the brain, has been increasingly recognized in the context of neuroprotection, particularly in mitigating neurodegenerative processes. Given the growing body of evidence suggesting taurine's involvement in neuroprotective mechanisms, this study sought to delve deeper into its effects on SH-SY5Y cells, a widely used human-derived cell line for neurobiological studies.

Taurine, being a naturally occurring amino acid, is generally considered to have minimal adverse effects on the body. Toxicity assessments indicate that taurine lacks genotoxicity and has not been classified as carcinogenic or teratogenic (26, 27). Furthermore, treatment with specific concentrations of taurine did not result in significant toxicity to SH-SY5Y cells (18). Also, previous studies have demonstrated that taurine provides protective effects against rotenone-induced toxicity in the SH-SY5Y cell line (28, 29). The results from the MTT assay provided initial insights into taurine's protective role, demonstrating that taurine at concentrations of 0.5 and 1 mg/ml effectively reduced LPS-induced toxicity in SH-SY5Y cells. This reduction in toxicity suggests that taurine enhances cell viability under inflammatory conditions, which is crucial for understanding its potential therapeutic effects in neurodegenerative diseases. The ability of taurine to mitigate LPS-induced toxicity highlights its role as a protective agent against inflammatory damage, which is a significant contributor to neurodegenerative conditions such as AD.

Earlier studies have emphasized the pharmacological benefits of taurine and its derivatives in the treatment of chronic inflammatory diseases and diverse infections (30, 31). Moreover, taurine has demonstrated the ability to modulate the production of pro-inflammatory cytokines and to act as an antioxidant in both human and animal models (32). Almohaimeed *et al.* (18) reported a reduction in cytokine expression levels in SH-SY5Y cells exposed to LPS after taurine treatment. Further investigation into the inflammatory response revealed that taurine treatment significantly lowered the expression levels of pro-inflammatory cytokines IL-1β and IL-6 in LPS-exposed SH-SY5Y cells. These finding underscores taurine's anti-inflammatory properties, which are vital in the context of neuroprotection, as chronic inflammation is a well-documented factor in the progression of neurodegenerative diseases. The suppression of these cytokines suggests that taurine can modulate the inflammatory milieu within the brain, potentially slowing down or preventing the neurodegenerative process.

In both early- and late-onset AD, the clearance of Aβ peptides from the brain is impaired. The removal of Aβ involves enzymatic degradation as well as transport mechanisms (33). Studies using animal models of AD have demonstrated that up-regulating ACE expression can reduce brain Aβ levels. For example, bone marrow-derived myeloid cells engineered to overexpress the ACE gene effectively cleared both soluble and insoluble forms of Aβ42 when administered to APP/PS1 mice (34). Furthermore, a meta-analysis revealed that individuals using ACE inhibitors have a lower likelihood of developing AD compared to those who do not receive these drugs (35). In transgenic AD mouse models, increased expression of matrix metalloproteinases MMP-2 and MMP-9 has been observed in cerebral capillaries and astrocytes surrounding amyloid plaques. Similarly, elevated levels of MMP-2, MMP-3, MMP-9, and MT1-MMP have been detected in the brains of AD patients (33). In APP/PS1 mice, knocking out MMP-2 or MMP-9, as well as pharmacologically inhibiting these MMPs in Tg2576 (APPSw) mice, led to an increase in brain Aβ levels (36). The ELISA results provided additional evidence supporting taurine's neuroprotective role by showing an increase in the secretion of MMP-9 and ACE, enzymes known for their involvement in the degradation of Aβ proteins. This increase is particularly noteworthy as the accumulation of Aβ plaques is a hallmark of AD pathology. By enhancing the activity of enzymes that break down Aβ, taurine may contribute to reducing the toxic burden of Aβ in the brain, thereby offering a therapeutic avenue for AD management.

Moreover, the study's analysis of gene expression related to neurogenesis revealed that taurine exposure led to a significant up-regulation of genes involved in various critical processes, including cell adhesion, synaptic function, growth

factors, and signal transmission. These findings suggest that taurine not only protects against inflammatory and toxic insults but also promotes the regenerative and functional capacity of neurons. The up-regulation of neurogenesis-related genes indicates that taurine could enhance neural repair and plasticity, which are essential for recovering from neurodegenerative damage.

Interestingly, some genes, like S100A6, exhibited higher expression at the lower taurine level (0.5 mg/ml) than at the higher level (1 mg/ml). This indicates a non-linear, hormetic dose–response rather than random experimental variation. Taurine seems to function as a physiological homeostatic regulator: at moderate concentrations, it partially reduces LPS-induced cellular stress while still allowing activation of adaptive pathways, especially Ca^{2+}-dependent transcription and stress responses. In these conditions, protective genes such as S100A6 are up-regulated. Conversely, at higher concentrations, taurine's antioxidant and anti-inflammatory effects are stronger, leading to more complete suppression of upstream stress signals. This better restores cellular balance, reducing the need for adaptive gene activation and thus lowering their expression levels. Overall, this biphasic response suggests taurine acts as a homeostatic neuromodulator rather than a straightforward dose-dependent transcriptional activator, with similar patterns observed for other stress-response genes in this study. These findings pave the way for future research to explore taurine's efficacy in clinical settings and its possible applications in treating conditions like AD.

Limitation of the study

Despite the promising findings, this study has several limitations. First, the use of SH-SY5Y neuroblastoma cells provides a simplified *in vitro* model that may not fully replicate the complex cellular and molecular interactions of the human brain *in vivo*. It is important to note that the LPS-induced inflammatory model used in this study represents a simplified approximation of AD pathology. While LPS stimulation mimics certain aspects of neuroinflammation, which is strongly implicated in AD progression, it does not reproduce the full spectrum of AD-related mechanisms, such as amyloid-β oligomer accumulation or tau hyperphosphorylation. Therefore, our findings should be interpreted primarily within the context of neuroinflammatory stress rather than as a comprehensive AD model. Future studies are warranted to validate these results using more disease-specific models. Second, while the observed changes in Aβ-degrading enzymes suggest a potential modulatory effect of taurine, future studies including direct quantification of Aβ40/42 are warranted to confirm its impact on Aβ metabolism. Third, while taurine showed regulatory effects on gene expression and inflammatory markers, the exact underlying molecular mechanisms remain unclear and warrant further investigation. Fourth, the study did not assess functional outcomes such as neuronal differentiation, neurite outgrowth, or synaptic activity, which are important to confirm neurogenesis. Lastly, the absence of animal model data limits the translational value of the findings to clinical contexts. Future studies involving *in vivo* models and additional functional assays are necessary to confirm and expand upon these results.

Conclusion

The outcomes of this study highlight taurine's possible neuroprotective influence on SH-SY5Y cells. Treatment with various concentrations of taurine effectively reduced the toxicity induced by LPS, as evidenced by the MTT assay results. Moreover, taurine exhibited significant enhancing effects on MMP-9 and ACE, enzymes involved in Aβ degradation, indicating a potential role in mitigating neurodegenerative processes. The observed down-regulation of IL-1β and IL-6 expression further suggests taurine's anti-inflammatory properties, which could contribute to its neuroprotective effects. Additionally, our findings revealed a significant up-regulation of genes associated with neurogenesis upon taurine treatment, underscoring its potential to promote neuronal regeneration and repair. Further studies are warranted to elucidate the underlying mechanisms and validate its efficacy *in vivo* and in clinical settings.

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Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval

Not applicable.

Consent to Publication

The authors affirm that they have contributed to the research and hereby give their consent for its publication.

Authors' Contributions

P P and F R conceived the study. P P, F S, and S S provided methodology. P P, F S, and S S contributed to software analysis and visualization. P P, F S, S S, and F R provided formal analysis. F S, S S, and F R performed investigation. P P, F S, S S, and F R prepared the original draft. F S, S S, and F R edited the manuscript. F R supervised the study. F R submitted the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Declaration

We acknowledge the use of ChatGPT by OpenAI to assist in language editing, paraphrasing, and literature organization of this manuscript. All generated content was carefully reviewed, revised, and validated by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the final manuscript.

References

1. Si ZZ, Zou CJ, Mei X, Li XF, Luo H, Shen Y, *et al.* Targeting neuroinflammation in Alzheimer's disease: From mechanisms to clinical applications. Neural Regen Res 2023; 18: 708-715.
2. Xu J, Liu B, Shang G, Feng Z, Yang H, Chen Y, *et al.* Efficacy

and safety of bilateral deep brain stimulation (DBS) for severe Alzheimer's disease: A comparative analysis of fornix versus basal ganglia of meynert. CNS Neurosci Ther 2025; 31: e70285.
3. Zhang J, Kong G, Yang J, Pang L, Li X. Pathological mechanisms and treatment progression of Alzheimer's disease. Eur J Med Res 2025; 30:625.
4. Krawczuk D, Kulczyńska-Przybik A, Mroczko B. The potential regulators of amyloidogenic pathway of APP processing in Alzheimer's disease. Biomedicines. 2025; 13: 1513.
5. Ullah R, Lee EJ. Advances in amyloid-β clearance in the brain and periphery: Implications for neurodegenerative diseases. Exp Neurobiol 2023; 32: 216.
6. Cheng Y, Tian DY, Wang YJ. Peripheral clearance of brain-derived Aβ in Alzheimer's disease: Pathophysiology and therapeutic perspectives. Transl Neurodegener 2020; 9: 1-1.
7. Eckman EA, Watson M, Marlow L, Sambamurti K, Eckman CB. Alzheimer's disease β-amyloid peptide is increased in mice deficient in endothelin-converting enzyme. J Biol Chem 2003; 278: 2081-2084.
8. Miners S, Ashby E, Baig S, Harrison R, Tayler H, Speedy E, *et al.* Angiotensin-converting enzyme levels and activity in Alzheimer's disease: Differences in brain and CSF ACE and association with ACE1 genotypes. Am J Transl Res 2009; 1: 163.
9. Loeffler DA. Experimental approaches for altering the expression of Abeta-degrading enzymes. J Neurochem 2023;164: 725-763.
10. Hofer HR, Tuan RS. Secreted trophic factors of mesenchymal stem cells support neurovascular and musculoskeletal therapies. Stem Cell Res Ther 2016; 7:131.
11. Vardy ER, Catto AJ, Hooper NM. Proteolytic mechanisms in amyloid-β metabolism: Therapeutic implications for Alzheimer's disease. Trends Mol Med 2005; 11: 464-472.
12. Sung PS, Lin PY, Liu CH, Su HC, Tsai KJ. Neuroinflammation and neurogenesis in Alzheimer's disease and potential therapeutic approaches. Int J Mol Sci 2020; 21:701.
13. Gonzalez R, Reinberg D. The Notch pathway: A guardian of cell fate during neurogenesis. Curr Opin Cell Biol 2025; 95: 102543.
14. Tutukova S, Tarabykin V, Hernandez-Miranda LR. The role of neurod genes in brain development, function, and disease. Front Mol Neurosci 2021; 14: 662774.
15. Shademan B, Yousefi H, Sharafkhani R, Nourazarian A. LPS-induced neuroinflammation disrupts brain-derived neurotrophic factor and kinase pathways in Alzheimer's disease cell models. Cell Mol Neurobiol 2025; 45: 102.
16. Ara Z, Rastogi D, Khan AA, Waliullah S. Beneficial effects: A review article. Acta Sci Med Sci 2022; 6: 95.
17. Rossato RC, Granato AE, de Oliveira Moraes CD, Salles GN, Soares CP. Neuroprotective effects of taurine on SH-SY5Y cells under hydrocortisone induced stress. Res Soc Dev 2021; 10: e55510918426.
18. Almohaimeed HM, Almars AI, Alsulaimani F, Basri AM, Althobaiti NA, Albalaw AE, *et al.* Investigating the potential neuroprotective benefits of taurine and Dihydrotestosterone and Hydroxyprogesterone levels in SH-SY5Y cells. Front Aging Neurosci 2024; 16: 1379431.
19. Baliou S, Adamaki M, Ioannou P, Pappa A, Panayiotidis MI, Spandidos DA, *et al.* Protective role of taurine against oxidative stress. Mol Med Rep 2021; 24: 1-9.
20. Sharma S, Sahoo BM, Banik BK. Biological effects and mechanisms of taurine in various therapeutics. Curr Drug Discov Technol 2023; 20: 60-78.
21. Li X, Bao X, Wang R. Neurogenesis-based epigenetic therapeutics for Alzheimer's disease. Mol Med Rep 2016; 14: 1043-53.
22. Subramanian VS, Teafatiller T, Agrawal A, Kitazawa M, Marchant JS. Effect of lipopolysaccharide and TNFα on neuronal ascorbic acid uptake. Mediators Inflamm 2021; 2021: 4157132.
23. Hasanpour M, Rahbarghazi R, Nourazarian A, Khaki-Khatibi F, Avci ÇB, Hassanpour M, *et al.* Conditioned medium from amniotic fluid mesenchymal stem cells could modulate Alzheimer's disease-like changes in human neuroblastoma cell line SY-SY5Y in a paracrine manner. Tissue Cell 2022; 76: 101808.
24. Althobaiti NA, Alsharif I, Alhasani RH, Albalawi AE, Alshahrani MY, Almars AI, *et al.* Taurine and neuroprotection: A potential shield against methylglyoxal-induced toxicity in SH-SY5Y cells. J Biochem Mol Toxicol 2025; 39: e70343.
25. Al-Attabi A, Mukhlif BA, Al-Shami KR, Merza MS, Alkubaisy SA, Abdulhadi MA. Evaluation of the effect of taurine on the matrix metalloproteinase-9 and the expression changes of miRNA-21 and miRNA-146a in the SH-SY5Y cell line. Horm Mol Biol Clin Investig 2024; 45: 165-170.
26. Su Y, Fan W, Ma Z, Wen X, Wang W, Wu Q, *et al.* Taurine improves functional and histological outcomes and reduces inflammation in traumatic brain injury. Neuroscience 2014; 266: 56-65.
27. Ni H, Han Y, Jin X. Celastrol inhibits colon cancer cell proliferation by downregulating miR-21 and PI3K/AKT/GSK-3β pathway. Int J Clin Exp Pathol 2019; 12: 808.
28. Jong CJ, Azuma J, Schaffer S. Mechanism underlying the antioxidant activity of taurine: prevention of mitochondrial oxidant production. Amino Acids 2012; 42: 2223-2232.
29. Alkholifi FK, Albers DS. Attenuation of rotenone toxicity in SY5Y cells by taurine and N-acetyl cysteine alone or in combination. Brain Res 2015; 1622: 409-413.
30. Erdem AY, Sevgili AM, Akbiyik F, Atilla PE, Cakar N, Balkanci ZD, *et al.* The effect of taurine on mesenteric blood flow and organ injury in sepsis. Amino Acids 2008; 35: 403-410.
31. Nagl M, Hess MW, Pfaller K, Hengster P, Gottardi W. Bactericidal activity of micromolar N-chlorotaurine: evidence for its antimicrobial function in the human defense system. Antimicrob Agents Chemother 2000; 44: 2507-2513.
32. Nam SY, Kim HM, Jeong HJ. The potential protective role of taurine against experimental allergic inflammation. Life Sci 2017; 184: 18-24.
33. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, *et al.* Clearance systems in the brain—implications for Alzheimer disease. Nat Rev Neurol 2015;11:457.
34. Koronyo-Hamaoui M, Sheyn J, Hayden EY, Li S, Fuchs DT, Regis GC, *et al.* Peripherally derived angiotensin converting enzyme-enhanced macrophages alleviate Alzheimer-related disease. Brain 2020; 143: 336-358.
35. Zhuang S, Wang HF, Wang X, Li J, Xing CM. The association of renin-angiotensin system blockade use with the risks of cognitive impairment of aging and Alzheimer's disease: A meta-analysis. J Clin Neurosci 2016; 33: 32-38.
36. Yin KJ, Cirrito JR, Yan P, Hu X, Xiao Q, Pan X, *et al.* Matrix metalloproteinases expressed by astrocytes mediate extracellular amyloid-β peptide catabolism. J Neurosci 2006; 26: 10939-10948.