



The potential protective role of taurine against experimental allergic inflammation

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ABSTRACT

Aims: Taurine has been widely evaluated as a potential therapeutic agent in chronic inflammatory disorders and various infections. However, the potential role of taurine in regulating allergic inflammatory responses is currently unknown.

Materials and methods: The present study was designed to evaluate the in vitro effects of taurine on the levels of thymic stromal lymphopoietin (TSLP) and other pro-inflammatory cytokines and activation of caspase-1 and nuclear factor (NF)- κ B as well as the phosphorylations of c-Jun N-terminal kinase (JNK) and p38 in phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-triggered human mast cell line, HMC-1 cells. Furthermore, we assessed the therapeutic effects of taurine on ovalbumin (OVA)-induced allergic rhinitis (AR) animal models.

Key findings and significance: Here, the obtained results showed that taurine dose-dependently inhibited the production and mRNA expression of TSLP and pro-inflammatory cytokines in HMC-1 cells exposed to PMACI. Taurine attenuated the phosphorylation of JNK and p38 in activated HMC-1 cells. Moreover, taurine brought a significant inhibition of the activities of NF- κ B and caspase-1. In an OVA-induced AR animal model, the increased levels of nose rubbing, histamine, immunoglobulin E, TSLP, and interleukin IL-1 β were dramatically reduced by the administration of taurine. In summary, taurine could serve as potential novel remedy of allergic inflammatory disorders.

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1. Introduction

Mast cells are commonly found tissue-resident cells and have an integral role in various allergic inflammatory disorders [1]. Mast cells typically release tumor necrosis factor (TNF)- α and interleukin (IL)-6 as well as thymic stromal lymphopoietin (TSLP), when activated by specific antigen, immunoglobulin E (IgE), and many other stimuli [2–4]. TSLP, one of the major cytokine produced by mast cells, induced the pathological development of allergic inflammatory diseases like allergic rhinitis (AR), atopic dermatitis (AD), and asthma [5]. TSLP is involved in a number of mast cell biology, including development, growth, attachment, and survival, which accelerates allergic inflammatory reactions [6]. Several signal pathways such as caspase-1, nuclear factor (NF)- κ B, and mitogen-activated protein kinases (MAPKs) are involved in the TSLP production and mRNA expression in mast cells [7]. Therefore, TSLP-blocking has attracted much attention for preventing the allergic

inflammatory disorders. Several lines of reports showed that natural products with TSLP modulatory property ameliorate allergic immune responses [8–9].

Taurine is mostly present in most animal tissues in free-state and implicated in essential physiological functions [10]. Taurine levels are present between 3 and 40 mM in many tissues like skeletal muscle, heart, and brain [11,12]. Plasma concentration of taurine (0.02–0.1 mM) is much lower than tissues [12–14]. Taurine transporter plays an essential role in regulating the intracellular taurine contents [15]. TNF- α and IL-1 β increased the activities of taurine transporter in intestinal Caco-2 cells [15] and TNF- α increased the taurine uptake in rat astrocytes [16]. Taurine could resist oxidation, improve immunity, delay senility, reduce blood pressure, etc. [17–19]. Previous studies revealed the pharmacological activities of this natural substance and its derivatives in chronic inflammatory disorders and various infections [20,21]. In addition, taurine has been demonstrated to control pro-inflammatory cytokine production and possess antioxidant activities in humans and animals [22,23]. Despite emerging knowledge about the pharmacological effect of taurine, less is known about the pharmacological effect and possible regulatory mechanism of taurine on allergic inflammatory disorders. The present work was conducted to investigate the possible usefulness of the taurine and to elucidate its possible molecular

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Table 1
List of primers used for RT-PCR.

Primers	Sequence
TSLP forward	5'-TAT GAG TGG GAC CAA AAG TAC CG3'
TSLP reverse	5'-GGG ATT GAA GGT TAG GCT CTG G3'
IL-1 β forward	5'-CCG GAT CCA TGG CAC CTG TAC GAT CA-3'
IL-1 β reverse	5'-GGG GTA CCT TAG GAA GAC ACA AAT TG-3'
TNF- α forward	5'-CAC CAG CTG GTT ATC TCT CAG CTC-3'
TNF- α reverse	5'-CGG GAC GTG GAG CTG GCC GAG GAG-3'
IL-6 forward	5'-GAT GGATGC TTC CAATCT GGAT-3'
IL-6 reverse	5'-AGT TCT CCATAG AGA ACA ACA TA-3'
IL-8 forward	5'-CGA TGT CAG TGC ATA AAG ACA-3'
IL-8 reverse	5'-TGA ATT CTC AGC CCT CTT CAA AAA-3'
GAPDH forward	5'-CAA AAG GGT CAT CAT CTC TG-3'
GAPDH reverse	5'-CCT GCT TCA CCA CCT TCT TG-3'

mechanisms in phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-induced allergic inflammatory reaction and ovalbumin (OVA)-induced AR animal model.

2. Materials and methods

2.1. Materials

Taurine (minimum 99% pure), phorbol 12-myristate 13-acetate (PMA, protein kinase C activator), calcium ionophore (A23187), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), OVA, lipopolysaccharide (LPS), O-phthalaldehyde (OPA), ethidium bromide (EtBr), and avidin peroxidase were purchased from Sigma Chemical Co. (St Louis, MO, USA). Anti-human IL-6/IL-8/TNF- α antibodies (Ab), biotinylated anti-human IL-6/IL-8/TNF- α Ab, recombinant human IL-6/IL-8/TNF- α , anti-mouse immunoglobulin E (IgE) Ab, biotinylated anti-mouse IgE Ab, and mouse recombinant IgE were purchased from BD Biosciences Pharmingen (San Diego, CA, USA). Anti-human TSLP/IL-1 β Ab, biotinylated anti-human TSLP/IL-1 β Ab, human recombinant TSLP/IL-1 β , anti-mouse TSLP/IL-1 β Ab, biotinylated anti-mouse TSLP/IL-1 β , and mouse recombinant TSLP and IL-1 β were obtained from R&D Systems (Minneapolis, MN, USA).

2.2. Cell culture and stimulation

Human mast cell lines, namely, HMC-1 cells were grown in an Isocove's Modified Dulbecco's Medium (Gibco, USA) containing 100 μ g/mL streptomycin, 100 U/mL penicillin, 10% heat-inactivated fetal bovine serum, and 10 μ M monothioglycerol at 37 °C and 5% CO₂. Taurine was dissolved in distilled water. Cells were treated with taurine for 1 h before PMACI stimulation and incubated at 37 °C for various times.

2.3. MTT assay

HMC-1 cell suspension (3×10^5 cells) was seeded into 24-well plates for 24 h after treatment by each concentration of taurine. MTT solution at 5 mg/ml was added to each well and the cells were incubated at 37 °C for 4 h. The insoluble formazan product was dissolved in dimethyl sulfoxide (Sigma Chemical Co., St Louis, MO, USA). Absorbance was measured using an ELISA reader at 540 nm.

2.4. Enzyme-linked immunosorbent assay (ELISA)

Cytokine levels of cell supernatant and serum were measured by an ELISA according to the manufacturer's protocol (BD Bioscience and Pharmingen). Absorption of the avidin-peroxidase color reaction was measured at 405 nm and compared with serial dilutions of human recombinant proteins as a standard.

$$\% \text{Inhibition} = (a - b) \times 100/a$$

where 'a' is cytokine release without taurine and 'b' is cytokine release with taurine.

2.5. Reverse transcription-polymerase chain reaction (RT-PCR)

The total RNA extracted by easy-BLUE RNA extraction kit (iNtRON Biotechnology, Kyunggi-do, Korea) was reverse transcribed into cDNA by a cDNA synthesis kit (Bioneer Corporation, Daejeon, Republic of Korea) according to the manufacturers' instructions. Primers for PCR are shown in Table 1. The annealing temperature was 62 °C for human TSLP, 50 °C for human, IL-6, IL-1 β , TNF- α , and IL-8, and 60 °C for

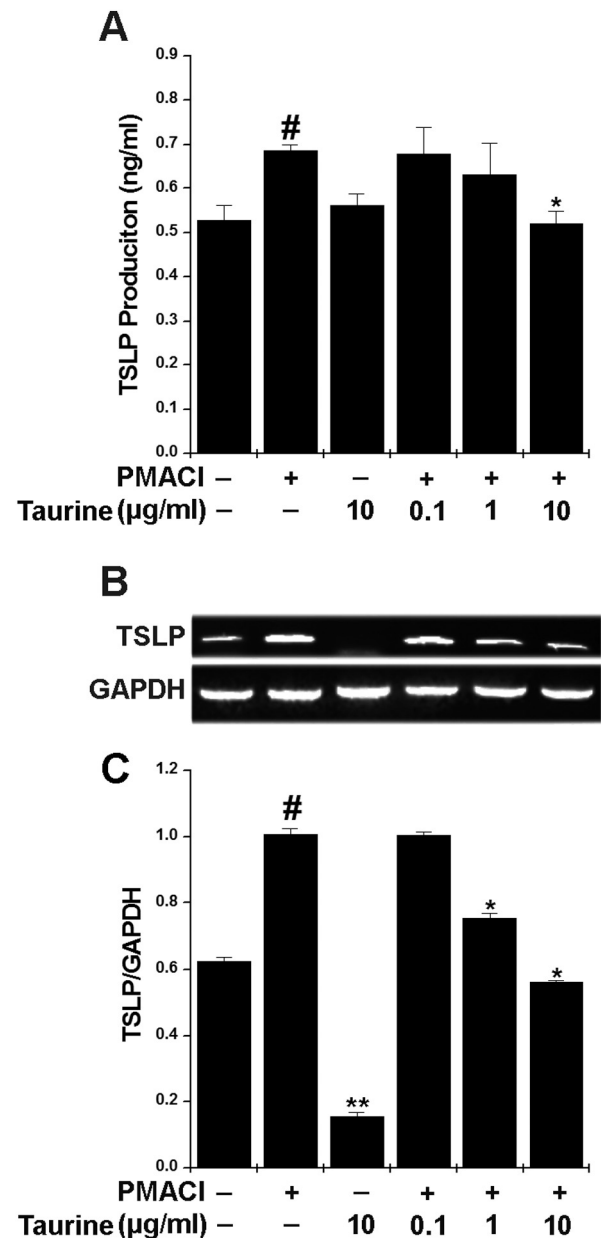


Fig. 1. Effect of taurine on the production and mRNA expression of TSLP in HMC-1 cells. (A) HMC-1 cells (3×10^5) were treated with taurine (0.1, 1, or 10 μ g/ml) for 1 h, and then stimulated by PMACI for 8 h. The levels of TSLP in the supernatant were measured with the ELISA method. (B) HMC-1 cells (3×10^5) were treated with taurine (0.1, 1, or 10 μ g/ml) for 1 h, and then stimulated by PMACI for 5 h. The mRNA was measured with the RT-PCR method. (C) The TSLP mRNA expression levels were quantitated by densitometry. Each datum represents the mean $\pm$ S.E.M. of three independent experiments. [#] $P < 0.05$; significantly different from the unstimulated cells. ^{*} $P < 0.05$; significantly different from the PMACI-stimulated cells. ^{**} $P < 0.05$; significantly different from the unstimulated cells. PMACI, PMA plus A23187.

human GAPDH, respectively. Products were electrophoresed on 1–1.5% agarose gel and visualized by staining with EtBr.

2.6. Caspase-1 assay

Caspase-1 activities were measured according to the manufacturer's specifications using a caspase-1 colorimetric assay kit (R&D Systems, Inc.).

2.7. Western blot analysis

Total protein was prepared by a detergent lysis procedure. Protein samples (100 µg aliquots) were resolved by 12% SDS-polyacrylamide gel electrophoresis and were electrotransferred to nitrocellulose membranes in 25 mM Tris, pH 8.5, 200 mM glycerol, and 20% methanol at 20 V. The membrane was blocked for at least 2 h with 5% with bovine serum albumin at room temperature. Thereafter, the membrane was incubated for 1 h at room temperature with primary antibodies for p38, phosphorylated (p)-p38, c-Jun N-terminal kinase (JNK), p-JNK, extracellular signal-regulated protein kinase (ERK), p-ERK, poly (ADP-ribose) polymerase (PARP), NF-κB, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA). The membrane was developed by peroxidase-conjugated secondary antibodies (Santa Cruz, CA, USA) and proteins were visualized by enhanced chemiluminescence procedures (GE Healthcare, Piscataway, NJ, U.S.A.).

2.8. OVA-induced AR animal model

Female 4-week-old BALB/c (Dae-Han Experimental Animal Center, Eumsung, Republic of Korea) mice were maintained under pathogen-free conditions. Mouse care and experimental procedures were performed with the approval of the animal care committee of Kyung Hee University [No. KHUASP(SE)-15-118]. Sensitization was performed three times (at 1, 5, and 14 days) by an intraperitoneally (ip) injecting of OVA (100 µg) in 100 µl phosphate-buffered saline (PBS) containing 20 mg aluminum hydroxide (Sigma Chemical Co, St. Louis, MO, USA).

Thereafter, local immunization was performed daily with 1.5 mg of OVA in 2 µl PBS for another 10 days. In addition, negative controls were challenged intranasally with saline for another 10 days. Taurine (10 mg/kg) treated mice including normal and OVA-induced AR mice were administrated orally before the local immunization, while normal and OVA-induced AR groups were received distilled water alone instead of taurine on the same schedule. The frequencies of nose rubbing were determined for 10 min after final OVA challenge at 10 days, by a trained observer blinded to the experimental treatments. Five mice were allocated to each group.

2.9. Histamine assay

The levels of histamine from the serum of mice were measured by the OPA spectrofluorometric procedure [24]. The fluorescent intensity was measured at 460 nm (excitation at 355 nm) using a spectrofluorometer.

2.10. Statistical analysis

The experiments shown are a summary of the data from at least three independent experiments (each with duplicate) and statistical analyses were performed using SPSS statistical software (SPSS 11.5, USA). Treatment effects were analyzed by one-way ANOVA, offered by Tukey's multiple range tests, and differences with $P < 0.05$ were considered statistically significant.

3. Results

3.1. Effect of taurine on the production and mRNA expression of TSLP in HMC-1 cells

The detection with MTT assay showed that taurine did not affect the viability of HMC-1 cells up to 10 µg/ml dose (data not shown). Based on these results, 0.1 µg/ml to 10 µg/ml taurine was chosen for the subsequent experiments. First, the inhibitory influence of taurine on PMACI-induced TSLP production was assessed according to ELISA method.

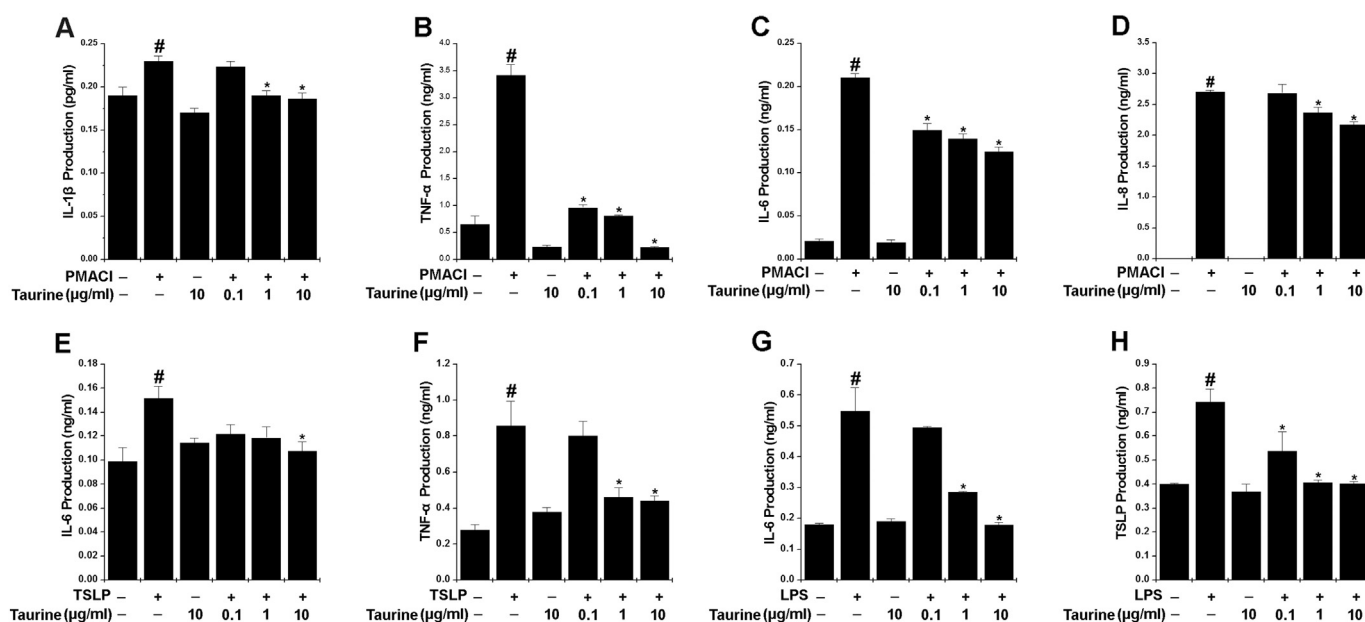


Fig. 2. Taurine inhibited the production of pro-inflammatory cytokines in HMC-1 cells. (A–D) HMC-1 cells (3×10^5) were treated with taurine (0.1, 1, or 10 µg/ml) for 1 h and then stimulated by PMACI for 8 h. The production of cytokines in the supernatant was measured by an ELISA method. (E–F) HMC-1 cells (3×10^5) were treated with taurine (0.1, 1, or 10 µg/ml) for 1 h and then stimulated by TSLP (20 ng/ml) for 8 h. The production of cytokines in the supernatant was measured by an ELISA method. (G–H) HMC-1 cells (3×10^5) were treated with taurine (0.1, 1, or 10 µg/ml) for 1 h and then stimulated by LPS (100 ng/ml) for 8 h. The production of cytokines in the supernatant was measured by an ELISA method. Each datum represents the mean $\pm$ S.E.M. of three independent experiments. [#] $P < 0.05$; significantly different from the unstimulated cells. ^{*} $P < 0.05$; significantly different from the PMACI-stimulated cells. PMACI, PMA plus A23187.

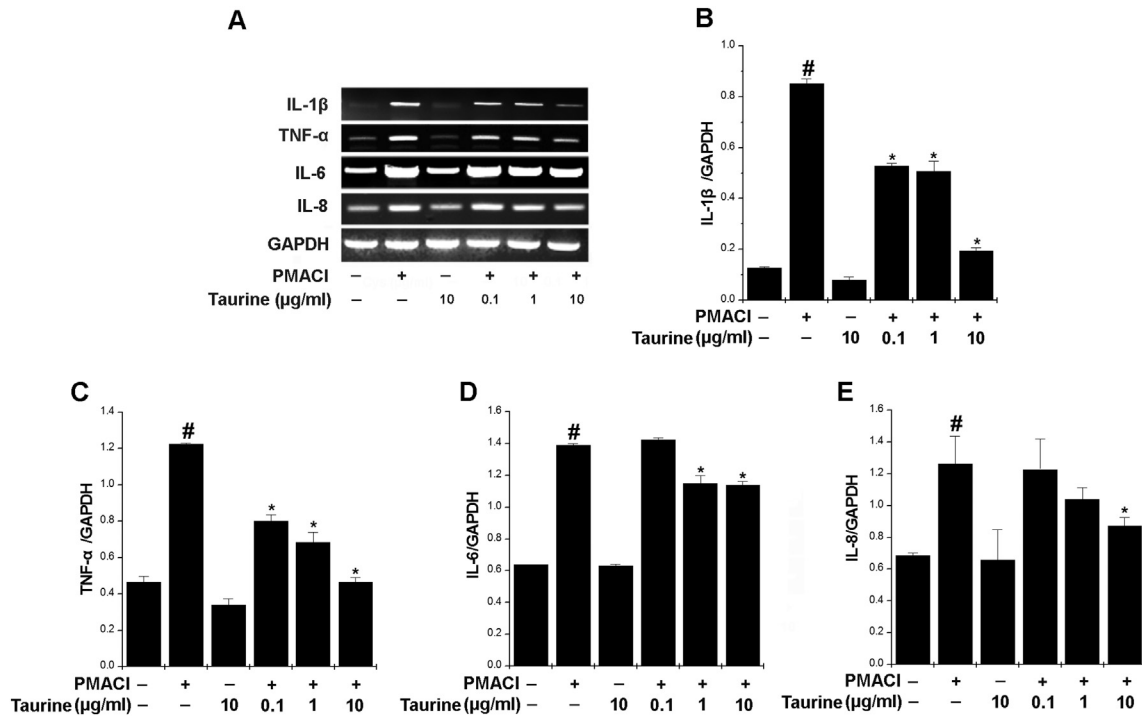


Fig. 3. Taurine inhibited the mRNA expression of pro-inflammatory cytokines. (A) HMC-1 cells (3×10^6) were treated with taurine (0.1, 1, or 10 μg/ml) for 1 h and then stimulated by PMACI for 5 h. IL-1β, TNF-α, IL-6, and IL-8 mRNA expressions were analyzed by a RT-PCR method. (B) The relative intensities were quantified by densitometry means IL-1β/GAPDH, TNF-α/GAPDH, IL-6/GAPDH, and IL-8/GAPDH. Each datum represents the mean $\pm$ S.E.M. of three independent experiments. # $P < 0.05$; significantly different from the unstimulated cells. * $P < 0.05$; significantly different from the PMACI-stimulated cells. PMACI, PMA plus A23187.

Exposure of HMC-1 cells to PMACI increased the TSLP production ($P < 0.05$; Fig. 1A). In contrast, the presence of taurine reduced the PMACI-induced TSLP production in a dose-dependent manner ($P < 0.05$; Fig. 1A). At a concentration of taurine 10 μg/ml, TSLP levels were similar to that of the untreated cells (Fig. 1A). No obvious change was observed when HMC-1 cells were treated with taurine alone.

In addition, we further detected the TSLP gene expression at the transcriptional levels in PMACI-triggered HMC-1 cells. As revealed by a RT-PCR in Fig. 1B and C, TSLP transcript levels were considerably up-regulated in HMC-1 cells in response to PMACI ($P < 0.05$). Coincident with the change in TSLP production, the PMACI-induced TSLP transcript levels were progressively decreased after the addition of taurine ($P <$

0.05; Fig. 1B and C). Levels of TSLP transcript were faintly expressed in unstimulated HMC-1 cells. Approximately 88% of the PMACI-induced TSLP production was inhibited by 10 μg/ml taurine. In addition, taurine alone significantly reduced the transcript levels of TSLP ($P < 0.05$; Fig. 1B and C). These results indicate that taurine exhibited strong anti-allergic inflammatory effects.

3.2. Effect of taurine on the production and mRNA expression of pro-inflammatory cytokines in HMC-1 cells

The efficacy of taurine on the production of the pro-inflammatory cytokines by PMACI-triggered HMC-1 cells was examined using ELISA

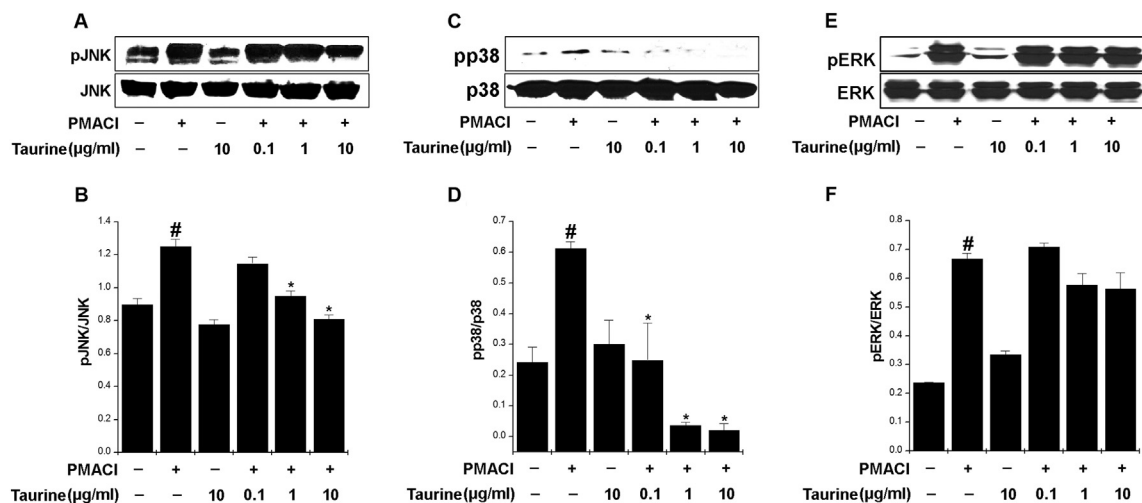


Fig. 4. Effect of taurine on the activation of MAPKs. (A, C, E) HMC-1 cells (3×10^6) were treated with taurine (0.1, 1, or 10 μg/ml) for 1 h and then stimulated by PMACI for 30 min. The p-JNK, p-p38, and p-ERK were determined by Western blotting. (B, D, F) The relative densities were quantified by densitometry means p-JNK/JNK, p-p38/p38, and p-ERK/ERK. Each datum represents the mean $\pm$ S.E.M. of three independent experiments. # $P < 0.05$; significantly different from the unstimulated cells. * $P < 0.05$; significantly different from the PMACI-stimulated cells. PMACI, PMA plus A23187.

method. Pro-inflammatory cytokines were not detected in the culture medium of non-triggered HMC-1 cells (Fig. 2). The release of pro-inflammatory cytokines including IL-1 β , TNF- α , IL-6, and IL-8 was increased by PMACI in HMC-1 cells (to 0.23 pg/ml for IL-1 β , 3.41 ng/ml for TNF- α , 0.21 ng/ml for IL-6, 2.70 ng/ml for IL-8, respectively) ($P < 0.05$; Fig. 2A–D). However, taurine significantly inhibited the amount of these cytokines increased by PMACI in a dose-dependent manner ($P < 0.05$; Fig. 2A–D). Inhibition rates at 10 μ g/ml taurine were about 108.3% for IL-1 β , 115.4% for TNF- α , 45.5% for IL-6, and 19.7% for IL-8 (Fig. 2A–D).

TSLP induced the release of inflammatory cytokines from mast cells [25]. Thus, we investigated the effect of taurine on the release of inflammatory cytokines induced by TSLP. The results revealed that the amounts of IL-6 and TNF- α were significantly elevated by TSLP ($P < 0.05$; Fig. 2E–F). However, taurine treatment exhibited a significant decrease in the amounts of IL-6 and TNF- α elevated by TSLP ($P < 0.05$; Fig. 2E–F). Next, we investigated the effect of taurine on the release of inflammatory cytokines induced by LPS to determine that taurine is able to affect more physiological type of immune activation. Taurine exhibited a significant decrease in the amounts of IL-6 and TSLP induced by LPS ($P < 0.05$; Fig. 2G–H).

Further investigation revealed that the mRNA expression of pro-inflammatory cytokines was also upregulated in PMACI-triggered HMC-1 cells (Fig. 3). These increases in the expression of mRNA were significantly decreased by treatment with taurine (Fig. 3). No significant changes were detected with taurine alone. Altogether, these results indicate that taurine exhibited anti-inflammatory effects via inhibition of inflammatory cytokine production.

3.3. Effect of taurine on the activation of MAPKs

To find out the role of MAPKs on the TSLP expression, we investigated activation of MAPKs members (ERK, JNK, and p38). The amounts of p-JNK and p-p38 were markedly increased in response to PMACI, whereas the addition of taurine exhibited significant attenuation of p-JNK and p-p38, relative to those in PMACI stimulation ($P < 0.05$; Fig. 4A–D). However, treatment with taurine had no additional effect on the phosphorylation of ERK (Fig. 4E and F). Collectively, these results suggest that taurine affects the JNK and p38 MAPKs pathway in PMACI-triggered HMC-1 cells.

3.4. Effect of taurine on the activation of NF- κ B

Next, we examined the impact of NF- κ B whose expression is highly susceptible to cytokine transcription. The results showed a substantial increase of the accumulation of NF- κ B in the nucleus after the addition of PMACI to HMC-1 cells relative to untreated controls ($P < 0.05$; Fig. 5A). In addition, co-incubation with taurine (1 and 10 μ g/ml) followed by PMACI stimulation was found to suppress the nuclear accumulation of NF- κ B triggered by PMACI ($P < 0.05$; Fig. 5A). Furthermore, phosphorylation of I κ B- α was studied. In response to PMACI, I κ B- α phosphorylation was drastically enhanced, which was obviously inhibited by incubation of cultures with taurine ($P < 0.05$; Fig. 5B). These findings imply that taurine suppressed cytokine transcript levels via regulation of NF- κ B activation in PMACI-triggered HMC-1 cells.

3.5. Effect of taurine on the activation of caspase-1

To further understand the mechanism of taurine on the inhibition of cytokine production, we elucidated the impact of taurine on activation of caspase-1 pathway. Treatment with taurine alone resulted in no change in caspase-1 activity, whereas the PMACI treatment of cells drastically increased the caspase-1 activity ($P < 0.05$; Fig. 5C). Pre-treatment of cells with taurine attenuated the PMACI-induced caspase-1 activity ($P < 0.05$; Fig. 5C). These results suggest that taurine inhibits the cytokine production by down-regulating caspase-1 activities.

3.6. Effect of taurine on the OVA-induced AR animal model

Finally, we determined the beneficial effect of taurine in the AR in vivo model. Frequencies of nasal rubbing for 10 min in mice with OVA intranasal challenge were significantly elevated ($P < 0.05$; Fig. 6A), and taurine treatment group (10 mg/kg) showed lower frequencies of nasal rubbing compared with the OVA-sensitized AR group ($P < 0.05$; Fig. 6A). Furthermore, no significant alteration of nasal rubbing frequencies was found in taurine treatment group (10 mg/kg) compared with the normal group (Fig. 6A). Significant elevation of histamine, IgE, TSLP, and IL-1 β levels in the serum from the OVA-sensitized AR group were found compared with those from untreated normal group ($P < 0.05$; Fig. 6B–E). Taurine treatment resulted in the reduction of histamine, IgE, TSLP, and IL-1 β in the serum compared with the OVA-sensitized AR group ($P < 0.05$; Fig. 6B–E).

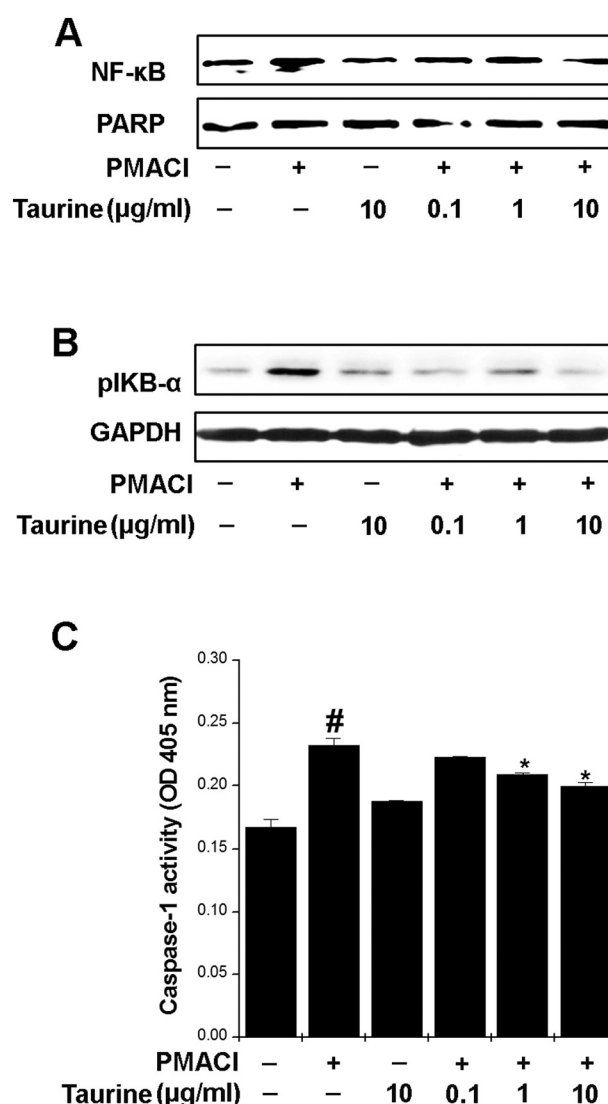


Fig. 5. Effect of taurine on the activation of NF- κ B and caspase-1. HMC-1 cells (3×10^6) were treated with taurine (0.1, 1, or 10 μ g/ml) for 1 h and then stimulated by PMACI for 2 h. (A) NF- κ B and (B) p-I κ B- α were determined by Western blotting. (C) Caspase-1 activity was measured using a caspase-1 assay kit. The data of caspase-1 activity represents the mean $\pm$ S.E.M. of three independent experiments. ^{*} $P < 0.05$; significantly different from the unstimulated cells. [#] $P < 0.05$; significantly different from the PMACI-stimulated cells. PMACI, PMA plus A23187.

4. Discussion

The important findings of this work are that taurine has efficacy in ameliorating the allergic inflammatory reactions by inhibiting the production of TSLP and other pro-inflammatory cytokines. In the present study, we found that these mediators were suppressed due to the prevention of phosphorylation of JNK and p38 and activation of NF- κ B and caspase-1 in PMACI-triggered HMC-1 cells. In addition, taurine reduced the OVA-induced AR reaction.

The cytokine TSLP is reported to be a main switch for Th2-cytokine-driven pro-inflammatory responses, such as asthma, AD, and AR [25–28]. TSLP is rapidly secreted from mast cells and keratinocytes responded to the diverse factors, such as physical injury, inflammatory cytokines, or microbial products [29]. There is copious evidence supporting the causative role of TSLP in allergic inflammatory severity, evidenced by the accumulation of abnormal amounts of TSLP in patients with AR, in lesional skin of AD patients and in bronchoalveolar lavage samples from asthmatic patients [27,30–32]. Moreover, prior studies identified that TSLP serves in generation of clinical symptoms in AD and asthma mice [33,34]. TSLP-induced Th2 cytokines (IL-1 β , IL-4, IL-6, and IL-13) exaggerate allergic inflammatory diseases [8]. On that basis, TSLP in allergic inflammatory diseases is viewed as essentially pro-inflammatory mediator. Mizuno et al., [35] reported that TSLP targeting biologic agent has improved allergic inflammatory disease, such as atopic dermatitis. The present study also revealed that taurine suppressed the TSLP production and mRNA expression in PMACI-triggered HMC-1 cells. In addition, taurine suppressed the TSLP or LPS-induced proinflammatory cytokine production. These findings indicate that taurine plays a prominent role in the pathophysiology of allergic inflammation via regulation of TSLP and inflammatory cytokines.

In the search for other pathways potentially involved in pro-inflammatory cytokines expression, we first focused on the phosphorylation of MAPKs in PMACI-triggered HMC-1 cells. Most studies showed that the production and expression of inflammatory cytokines are controlled by the activation of MAPKs [36]. MAPKs family member, JNK cascade appear to be involved in inflammatory reactions, whereas the p38 kinase

is required to a variety of cytokine production. PMACI triggered the activation of MAPKs [37]. So, suppressing JNK and p38 resulted in the reduction of pro-inflammatory cytokines [37,38]. A number of studies have also demonstrated that the widely distributed NF- κ B has a role in the TSLP and pro-inflammatory cytokines mRNA expressions in a variety of cells like mast cells, keratinocytes, fibroblasts, and epithelial cells [9,39–42]. Although, inhibition of NF- κ B may induce systemic inflammatory aberration, many inhibitors of NF- κ B have frequently been used to treat inflammatory diseases [9,15,24,25,37]. Caspase-1 induces the secretion of cytokines via cleavage of immature cytokine [7,43]. A published report showed that level of caspase-1 in AR animal model was higher than normal control mice [44]. Furthermore, another study has shown that overexpression of caspase-1 in mice increased serum histamine and IgE levels [45]. In addition, the concentrations of caspase-1 in patients with allergy are also higher than those in healthy people [44]. The current study showed that taurine attenuated the PMACI-triggered phosphorylation of JNK and p38 but not of ERK. Moreover, we also showed that taurine attenuated the phosphorylation of I κ B- α , nuclear accumulation of NF- κ B, and activation of caspase-1 on PMACI-triggered HMC-1 cells. Based on these finding, we can assume that the anti-allergic inflammatory effect of taurine depends at least in part on modulation of JNK/p38/NF- κ B/caspase-1 pathways.

Additionally, we examined whether taurine really works in limiting allergic inflammation. AR is characterized by nasal congestion, itchy nose, sneezing, and lacrimation rhinorrhea [46]. These symptoms are mainly triggered by a variety of inflammatory mediators, including histamine, proteases, growth factors, and cytokines [47]. Histamine is a key organic compound of mast cells since it causes nasal obstruction, rhinorrhea, and sneezing [48]. Akhalaya et al. [49] reported that taurine blocked the production of histamine by PMACI in rat peritoneal mast cells. Taurine also significantly repressed the damage to Caco-2 cells caused by TNF- α [15]. Previous study showed that the levels of serum taurine were decreased in AD group compared to healthy control [50]. The present study showed that taurine suppressed the clinical symptoms of AR and the amounts of inflammatory mediators, including IgE, histamine, TSLP, and IL-1 β in the AR animal model. These findings

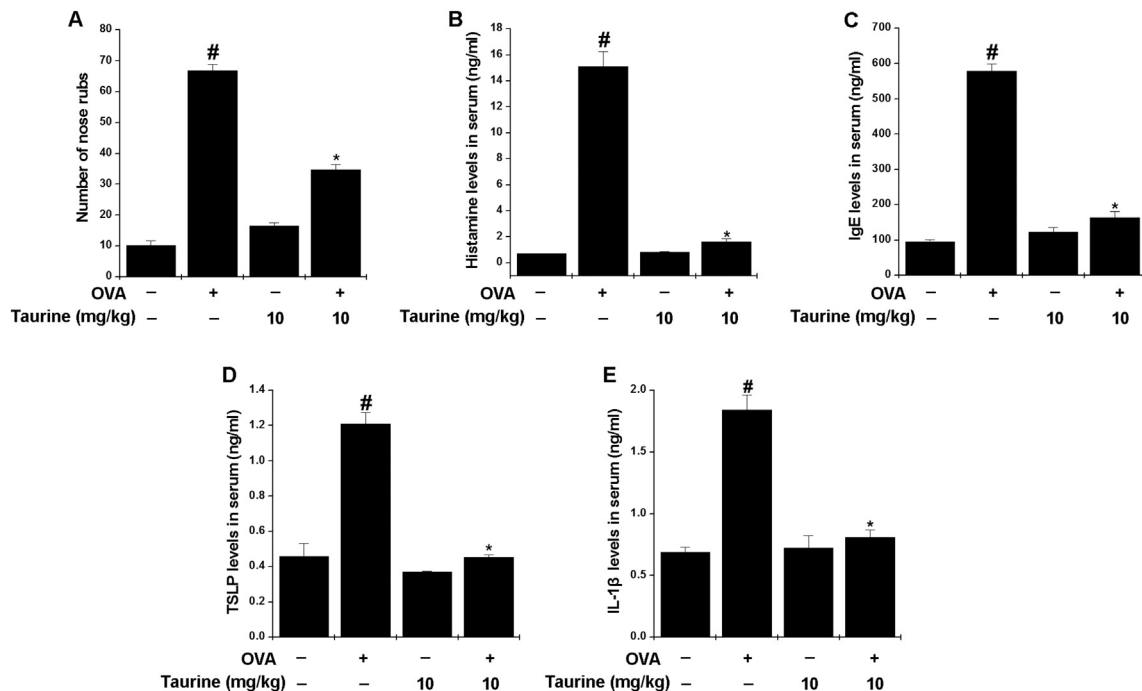


Fig. 6. Effects of taurine in the AR mice. We sensitized mice on days 1, 5, 14 by ip injections of 100 μ g OVA emulsified in 20 mg of aluminum hydroxide and we challenged mice with 1.5 mg OVA. Mice received orally taurine before the intranasal OVA challenge for 10 days. (A) The number of the nasal rubs that occurred in the 10 min after the OVA intranasal provocation. (B) Serum was isolated from blood and then assayed about histamine. Levels of (C) IgE (D) TSLP and (E) IL-1 β in the serum were measured by the ELISA method. [#] $P < 0.05$; significantly different from the OVA-unsensitized mice. ^{*} $P < 0.05$; significantly different from the OVA-sensitized mice, $n = 5$.

indicate that taurine has an anti-allergic inflammatory activity on allergic inflammation.

In summary, we showed that taurine can regulate the allergic inflammatory responses by affecting the caspase-1/NF- κ B/JNK/p38 pathways. In addition, taurine suppressed the AR responses. Therefore, our data suggest that taurine is a promising agent of therapeutic potential in allergic inflammatory disorders.

Conflict of interests

None to declare.

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