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# 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)-κB 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-κB and caspase-1. In an OVA-induced AR animal model, the increased levels of nose rubbing, histamine, immunoglobulin E, TSLP, and interleukin IL-1β were dramatically reduced by the administration of taurine. In summary, taurine could serve as potential novel remedy of allergic inflammatory disorders.



## 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)-κB, 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 likes 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-1β 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-1β forward | 5′-CCG GAT CCA TGG CAC CTG TAC GAT CA-3′ |
| IL-1β 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*-phthaldialdehyde (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-1β Ab, biotinylated anti-human TSLP/IL-1β Ab, human recombinant TSLP/IL-1β, anti-mouse TSLP/IL-1β Ab, biotinylated anti-mouse TSLP/IL-1β, and mouse recombinant TSLP and IL-1β 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 μg/mL streptomycin, 100 U/mL penicillin, 10% heat-inactivated fetal bovine serum, and 10 μM monothioglycerol at 37 °C and 5% $CO_2$. 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 ($3 \times 10^5$ 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-1β, TNF-α, and IL-8, and 60 °C for

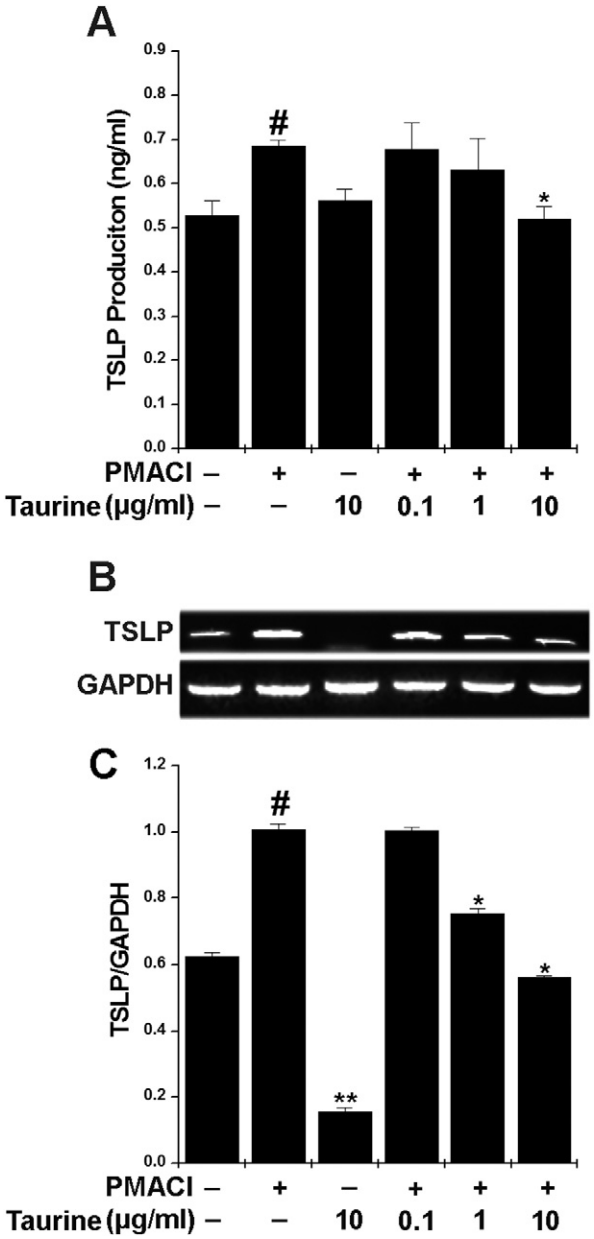


**Fig. 1.** Effect of taurine on the production and mRNA expression of TSLP in HMC-1 cells. (A) HMC-1 cells ($3 \times 10^5$) were treated with taurine (0.1, 1, or 10 μg/ml) for 1 h, and then stimulated by PMACI for 8 h. The levels of TSLP in the supernatant were measured with the ELISA method. (B) HMC-1 cells ($3 \times 10^6$) were treated with taurine (0.1, 1, or 10 μg/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 ± 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.