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Effect of taurine on mRNA expression of thioredoxin interacting protein in Caco-2 cells

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ABSTRACT

Taurine (2-aminoethanesulfonic acid), a sulfur-containing β-amino acid, plays an important role in several essential biological processes; although, the underlying mechanisms for these regulatory functions remain to be elucidated, especially at the genetic level. We investigated the effects of taurine on the gene expression profile in Caco-2 cells using DNA microarray. Taurine increased the mRNA expression of thioredoxin interacting protein (TXNIP), which is involved in various metabolisms and diseases. β-Alanine or γ-aminobutyric acid (GABA), which are structurally or functionally related to taurine, did not increase TXNIP mRNA expression. These suggest the expression of TXNIP mRNA is induced specifically by taurine. β-Alanine is also known to be a substrate of taurine transporter (TAUT) and competitively inhibits taurine uptake. Inhibition of taurine uptake by β-alanine eliminated the up-regulation of TXNIP, which suggests TAUT is involved in inducing TXNIP mRNA expression. The up-regulation of TXNIP mRNA expression by taurine was also observed at the protein level. Furthermore, taurine significantly increased TXNIP promoter activity. Our present study demonstrated the taurine-specific phenomenon of TXNIP up-regulation, which sheds light on the physiological function of taurine.

1. Introduction

Taurine (2-aminoethanesulfonic acid), a sulfur-containing β-amino acid present at high concentrations in mammalian tissues, plays an important role in several essential biological processes such as detoxification, anti-oxidation, membrane stabilization, and osmoregulation [1]. Taurine is especially essential to the development of fetuses and newborns [2]. In mammals, the nutritional and physiological requirements for taurine are mainly supplied by dietary sources and partly by biosynthesis in several tissues such as the liver, kidneys, astrocytes, and testes [3]. Dietary taurine is absorbed into the small intestine, where taurine is present at a high concentration.

The Caco-2 cell line, derived from human colon carcinoma, has been mainly used as a model of intestinal epithelial cells [4,5]. We previously reported that taurine pretreatment prevents inflammatory damage of Caco-2 cells [6]. The taurine transporter (TAUT/SLC6A6) is expressed in most tissues, including the intestine, and is involved in taurine absorption. Negative regulation of TAUT expression in Caco-2 cells by the taurine pretreatment was also reported [7]. The underlying molecular mechanisms for these regulatory functions of taurine in intestinal epithelial cells, however, remain to be elucidated. There is little information available on the taurine-responsive genes or signal transduction pathways.

Recently, the concept of nutritional genomics, known as nutrigenomics, was developed. It aims to identify and understand the role of nutrients and food compounds in gene expression changes [8–10]. Nutrigenomic analysis of some food compounds, such as epicatechin [9] and conjugated linoleic acid [10], has been investigated in Caco-2 cells using DNA microarrays. This approach may also be useful for analyzing the molecular mechanisms of taurine in a variety of physiological phenomena.

The present study was undertaken to examine the effect of taurine on the gene expression profile in Caco-2 cells using DNA micorarray. We found for the first time that taurine induced a remarkable change in the expression of thioredoxin interaction protein (TXNIP) in Caco-2 cells. We then examined the taurine-specific induction of TXNIP up-regulation.

Abbreviations: TAUT, taurine transporter; DMEM, Dulbecco's modified Eagle's medium; FCS, fetal calf serum; NEAA, non-essential amino acids; GABA, γ-aminobutyric acid; TXNIP, thioredoxin interacting protein; MT1H, metallothionein 1H; SLC, solute carrier family; ATF, activating transcriptional factor; GLUT, glucose transporter; UC, ulcerative colitis; DSS, dextran sulfate sodium.

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2. Materials and methods

2.1. Materials

The following were obtained from the indicated sources. The Caco-2 cell line from the American Type Culture Collection (Rockville, MD, USA). Dulbecco's modified Eagle's medium (DMEM) from Wako (Osaka, Japan). Fetal calf serum (FCS), non-essential amino acids, and penicillin–streptomycin (10,000 U/ml and 10 mg/ml in 0.9% sodium chloride, respectively) from Gibco (Gaithersburg, MD, USA). Taurine, hypotaurine, β-alanine, and γ-aminobutyric acid (GABA) from Nacalai Tesque (Kyoto, Japan), Sigma (St. Louis, MO, USA), Wako, and Tokyo chemical industry (Tokyo, Japan), respectively.

2.2. Cell culture

Caco-2 cells were each-cultured in DMEM containing 10% FCS, 1% non-essential amino acids, 2% glutamine, and an appropriate amount of penicillin–streptomycin. The cells were incubated at 37 °C in a humidified atmosphere containing 5% CO_2 and 95% air. The Caco-2 cells were seeded in culture plates that had been precoated with collagen and further cultured for 14 days.

2.3. DNA microarray analysis

Caco-2 cells were treated with 50 mM taurine for 24 h. Control cells were not treated. Then, RNA was isolated from the cells using QIA shredder (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. First-strand cDNA was prepared from 5 μg of total RNA using the GeneChip expression 3′-amplification one-cycle cDNA synthesis kit (Affymetrix, CA, USA). Biotin-labeled cRNA was synthesized from the cDNA using GeneChip expression 3′-amplification reagents for IVT labeling (Affymetrix). The DNA microarray was hybridized at 45 °C for 16 h with a mixture of biotin-labeled cRNA. The microarray analysis was performed using a GeneChip (Human Genome U133 Plus 2.0; Affymetrix). Scanned images were analyzed with ArraySTAR (DNASTAR, WI, USA) software for gene expression ratios (taurine-treated vs control cells).

2.4. Real-time PCR

Total RNA was isolated from the Caco-2 cells using ISOGEN (Nippon Gene, Tokyo, Japan) according to the manufacturer's instructions. The RNA was reverse transcribed to cDNA using the Primescript™ RT reagent kit (TaKaRa, Shiga, Japan). First-strand cDNA was prepared from 0.5 μg of total RNA. Real-time PCR was performed with SYBR Green II (TaKaRa). After denaturing at 95 °C for 10 s, PCR was performed for 40 cycles of denaturing at 95 °C for 5 s, annealing at 60 °C for 20 s, and extension at 72 °C for 15 s. The PCR primers for β-actin (198 bp), thioredoxin interacting protein (TXNIP) (93 bp), metallothionein 1H (MT1H), solute carrier family 6A6 (SLC6A6) (137 bp), SLC7A11 (128 bp), activation of transcription factor 4 (ATF4) (106 bp), SLC2A3 (115 bp), and SLC2A1 (66 bp) are listed in the Supplementary Table. Taurine treatment did not have a significant effect on β-actin mRNA expression at any stage, indicating that β-actin could be used as a stable housekeeping gene throughout the experiment.

2.5. Western blotting

A cell extract was prepared using Lysis buffer (50 mM Tris–HCl, pH 7.2, 250 mM NaCl, 2 mM EDTA, 0.1% NP-40, 10% glycerol, 0.1% of an inhibitor cocktail) and Western Blotting was performed as previously described [11]. The primary antibody was the mouse anti-TXNIP antibody (Medical and Biological Laboratories, Nagoya, Japan) or the mouse anti-β-actin antibody (Amersham Bioscience, Buckinghamshire, UK); while, the goat anti-mouse IgG antibody linked to horseradish peroxidase (Amersham Biosciences) was the secondary antibody.

2.6. Preparation of reporter gene construct

The human TXNIP full length promoter region including −1299 bp upstream of the transcription start site was cloned from human genomic DNA by PCR. It was inserted into the pGL4-Basic vector (Promega, Madison, WI, USA) by digesting with *Kpn*I and *Hind*III, which were introduced with following primer set: 5′-CCGGTACCCCAACAAGAATGAAGAGAG-3′ (forward primer) and 5′-GCAAGCTTCTCCAAATCGAGGAAACCG-3′ (reverse primer).

2.7. Transfection and reporter assay

Caco-2 cells grown in a 24-well plate to 80% confluency were transiently transfected with 1 μg of the indicated reporter construct and 0.05 μg of pRL-CMV using Lipofectamine and Plus Reagent (Invitrogen, CA, USA). Cells treated with or without 100 mM taurine for 24 h were washed with PBS and lysed with Passive Lysis Buffer (Promega). The luciferase activity was measured using the Dual-Luciferase Reporter assay (Promega) and an LB9507 Lumet luminometer (Berthold Technologies).

2.8. Statistical analysis

Data are expressed as the mean ± SEM. Data were analyzed by Dunnett's test, Student's *t*-test, or Tukey's test for variable comparison. A P value of less than 0.05 is considered significant.

3. Results

3.1. Effects of taurine on the gene expression profile in Caco-2 cells

We first investigated the effect of taurine on the gene expression profile in Caco-2 cells using DNA microarray analysis and real-time PCR. Seven of many genes affected by taurine were listed in Table 1, which have interesting physiological functions. The up-regulated genes included TXNIP and MT1H; whereas, SLC6A6/TAUT, SLC7A11/xCT, ATF4, SLC2A3/GLUT3, and SLC2A1/GLUT1 were down-regulated.

3.2. Taurine-induced up-regulation of TXNIP mRNA and protein in Caco-2 cells

We focused on taurine-induced up-regulation of TXNIP mRNA in Caco-2 cells. A real-time PCR experiment showed taurine increased the expression level of TXNIP mRNA in a dose-dependent manner (Fig. 1A). TXNIP mRNA expression significantly increased when cells were treated with 25 mM or higher taurine at for 48 h. We next examined the effect of taurine on TXNIP protein expression using western blotting. As shown in Fig. 1B, taurine increased the TXNIP protein in a dose-dependent manner. Compared to non-treated cells, there was an approximately 5.2-fold increase in TXNIP protein in cells treated with 100 mM taurine for 72 h.

3.3. The effect of other amino acids on the expression level of TXNIP mRNA

To determine whether up-regulation of TXNIP mRNA is specific for taurine treatment, we examined the effect of other amino acids, which are structurally or functionally related to taurine, on the

Table 1
DNA microarray results and confirmation by real-time PCR.

Accession number	Gene symbol	Gene title	Fold change (DNA microarray)	Fold change[a] (real-time PCR)
NM_006472	TXNIP	Thioredoxin interacting protein	9.91	14.6 ± 0.54
NM_005951	MT1H	Metallothionein 1H	1.69	3.43 ± 0.11
NM_001134367, NM_001134368, NM_003043	SLC6A6	Solute carrier family 6 (neurotransmitter transporter, taurine), member 6	0.24	0.27 ± 0.02
NM_014331	SLC7A11	Solute carrier family 7, (cationic amino acid transporter, y + system) member 11	0.42	0.42 ± 0.02
NM_001675, NM_182810	ATF4	Activating transcription factor 4 (tax-responsive enhancer element B67)	0.58	0.57 ± 0.03
NM_006931	SLC2A3	Solute carrier family 2 (facilitated glucose transporter), member 3	0.65	0.39 ± 0.10
NM_006516.1	SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	0.58	0.54 ± 0.07

DNA microarray and real-time PCR were performed as described in Section 2.
[a] Each value is the mean ± SEM ($n = 3$).

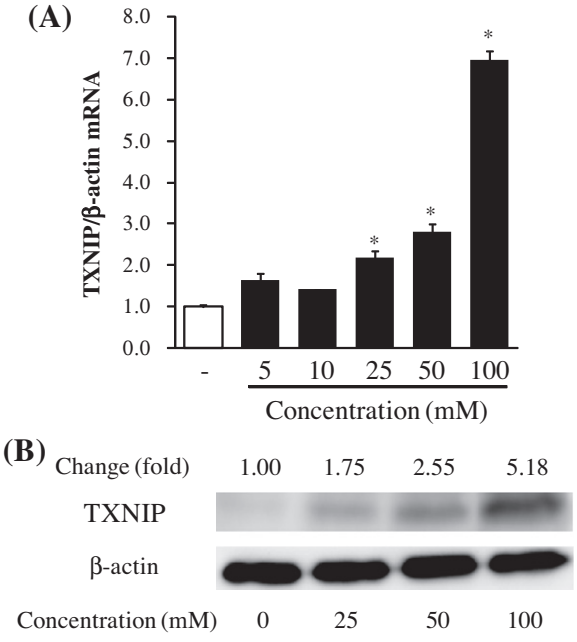

Fig. 1. Taurine-induced up-regulation of TXNIP mRNA and protein. (A) Total RNA was extracted from cells after treatment with 5, 10, 25, 50, or 100 mM taurine for 48 h. Real-time PCR was performed as described in Section 2. First-strand cDNA was prepared from 0.5 μg of total RNA. Each value is the mean ± SEM ($n = 3$), $^{*}P < 0.05$ using Dunnet's test. (B) The induction of TXNIP protein by taurine. Caco-2 cells were treated with 25, 50, or 100 mM taurine for 72 h. Western blotting was performed as described in Section 2.

expression of TXNIP mRNA in Caco-2 cells. We found hypotaurine increased TXNIP mRNA, but much less than taurine did (Fig. 2A); while, neither β-alanine nor GABA increased TXNIP mRNA expression. These results suggest the expression of TXNIP mRNA is induced specifically by taurine.

β-Alanine is known to be a substrate of TAUT and competitively inhibits taurine uptake in Caco-2 cells [12]. Therefore, we investigated whether β-alanine could interfere with the taurine-induced up-regulation of TXNIP mRNA expression. The marked increase in TXNIP mRNA expression by 25 mM taurine treatment was suppressed to the control level in the presence of 100 mM β-alanine (Fig. 2B), suggesting TAUT is involved in the increase in the TXNIP mRNA expression by taurine.

3.4. The effect of taurine on the transcriptional activity of the 5′-flanking region of the TXNIP promoter

To determine whether the up-regulation of TXNIP expression by taurine was due to activation of the TXNIP promoter, we investigated the effect of taurine on the transcriptional activity of TXNIP promoter in Caco-2 cells using a reporter assay. As shown in Fig. 3, taurine significantly increased the promoter activity in a dose-dependent manner. This result suggests that taurine induces the expression of TXNIP at the transcriptional level.

4. Discussion

In the present study, we investigated taurine-induced gene expression changes in Caco-2 cells. Using a DNA microarray, we showed taurine increased TXNIP and MT1H mRNA expression and decreased mRNA levels of TAUT, xCT, ATF4, GLUT3, and GLUT1 (Table 1). MT1H belongs to a super family of intracellular metal-binding proteins, which exert protective functions such as regeneration, anti-inflammation, anti-oxidation, and anti-apoptosis [13,14]. Therefore, the anti-inflammatory [6] and anti-oxidative effects of taurine may partly be due to up-regulation of MT1H mRNA expression. The xCT protein couples to the subunit SLC3A2/4F2hc, forming a heterodimeric amino acid transporter, which transports cystine in exchange for glutamate. It is reported that suppression of this transporter is therapeutic in cancer and other diseases [15,16]. The transcriptional factor ATF4 induces xCT mRNA expression [17]; thus, the decrease in xCT mRNA by taurine may be due to down-regulation of ATF4 mRNA. Although the identification of taurine-responsive genes using DNA microarray was reported in HepG2 cells as a hepatic model [18], our results did not correspond with those. It may be due to the difference of the property of cell lines or experimental conditions.

The DNA microarray analysis demonstrated that the expression of TXNIP mRNA was most markedly increased by taurine. This increase was confirmed by real-time PCR and taurine also induced TXNIP protein expression (Table 1 and Fig. 1). TXNIP is a multifunctional protein [19]. TXNIP knockout mice were unable to respond properly to energy deprivation [20–24]. Deficiency of TXNIP is also associated with reduced fatty acid utilization [20], hyperlipidemia [23,25], hypoglycemia, and other metabolic abnormalities [21,22]. In addition, TXNIP plays a role in hepatic glucose production [26] and its genetic variation is associated with diabetes and hypertension [25,27]. TXNIP also controls cardiac hypertrophy [28]. Takahashi et al. reported that TXNIP mRNA expression decreased in the inflamed colonic mucosa of patients with ulcerative colitis (UC), a type of chronic inflammatory bowel diseases [29]. They

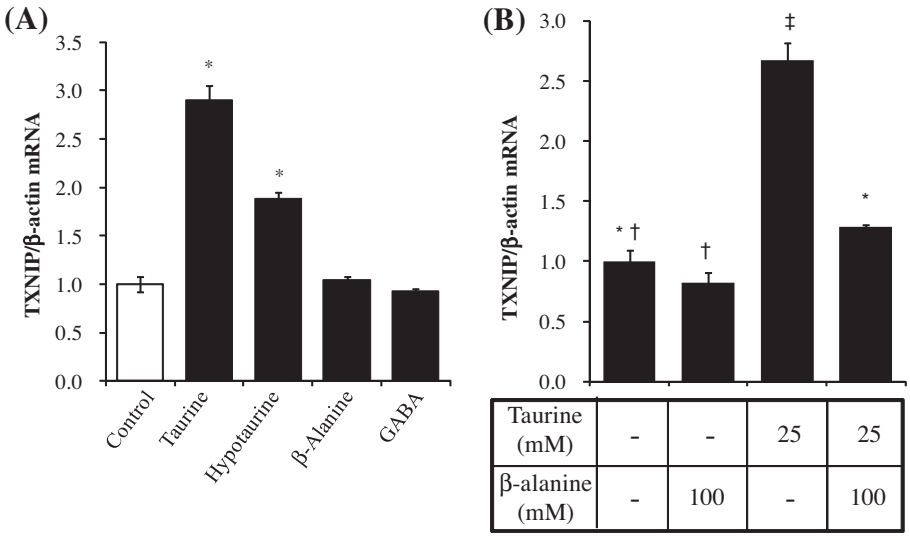

Fig. 2. The effect of other amino acids on the induction of TXNIP mRNA. (A) Caco-2 cells were treated with 100 mM taurine, hypotaurine, β-alanine, or GABA for 48 h. Real-time PCR was performed as described in Section 2. Each value is the mean ± SEM ($n = 3$), $^{*}P < 0.05$ using Student's t-test. (B) Caco-2 cells were treated with 25 mM taurine with or without 100 mM β-alanine for 48 h. Real-time PCR was performed as described in Section 2. Each value is the mean ± SEM ($n = 3$).*, †, and ‡: Values with different symbols are significantly different from each other, $P < 0.05$ using Tukey's test.

suggested that down-regulation of TXNIP was partly involved in the pathogenesis of UC. We previously reported that taurine had an anti-inflammatory effect on dextran sulfate sodium (DSS)-induced colitis [6]. This may be related to the taurine induced up-regulation of TXNIP. We also observed decreased expression of the mRNAs of glucose transporters, such as GLUT1/GLUT3, in the present study (Table 1). Yu et al. [30] and Patwari et al. [31] reported that TXNIP played a role in cellular glucose uptake. The modulating effects of taurine in various metabolic reactions and disease prevention may be attributed to a beneficial physiology of taurine that arises from the induction of TXNIP.

The concentrations of taurine used in this study (25, 50, or 100 mM) are relatively high and may be considered unpractical or non-physiological. However, the concentration of taurine in certain shellfishes and cephalopoda is higher than 100 mM, and dietary supplements sometimes contain 240 mM, indicating the concentration of taurine in the stomach and upper intestines will reach 25–100 mM. Considering that intestinal epithelial cells are exposed to the gastrointestinal contents, the concentrations of taurine used in this experiment with Caco-2 cells are relevant, as observed in a previous study on gastric cells [32].

To analyze the specificity of taurine in the regulation of TXNIP mRNA expression, we investigated the effect of other amino acids on TXNIP mRNA expression. The amino acids tested are known substrates of TAUT [12] and are transported into the cells. The increased expression of TXNIP was observed when cells were treated with hypotaurine, the precursor of taurine, but not β-alanine and GABA (Fig. 2A). Taurine differs structurally from β-alanine, which has a carboxyl residue instead of a sulfate residue. Thus, the sulfate in the taurine molecule may be important in regulating TXNIP mRNA expression. The inability of 100 mM β-alanine to induce the up-regulation of TXNIP also indicates the up-regulation by taurine is not caused by extracellular hyperosmolality.

As shown in Fig. 2B, inhibition of taurine uptake by β-alanine eliminated the up-regulation of TXNIP, which suggests TAUT is involved in inducing TXNIP mRNA expression. Thus, intracellular taurine may be responsible for this regulation. Previous studies have shown that taurine acts on GABA-A and glycine receptors [33] and is a weak agonist of these receptors [34,35] in several brain areas. However, these receptors are expressed in the plasma membrane [36] and are also activated by β-alanine [33]; therefore, they may not be involved in this regulation. Additionally, the expression of these receptors has been observed only in neural tissues, not in Caco-2 cells. These findings suggest the existence of an intracellular taurine-selective receptor.

Although the taurine receptor has not yet been identified, the present study demonstrated that a taurine response element may exist in the TXNIP promoter region (Fig. 3). The TXNIP promoter region (−1299/+256) includes some sequences that can be recognized by certain transcriptional factors [30,37], suggesting that one of those transcriptional factors is specifically activated by taurine.

The present study on taurine functions was initially based on the concept of nutrigenomics using Caco-2 cells. The results have demonstrated that taurine may have new physiological functions through its regulation of gene expression for various proteins, including TXNIP. The induction of TXNIP by taurine is likely a

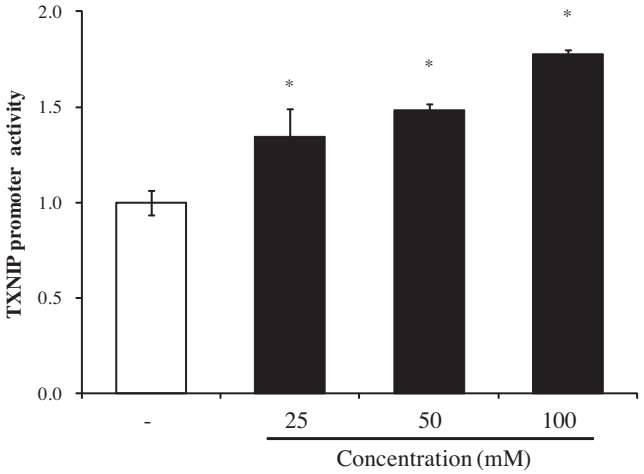

Fig. 3. Effect of taurine on the transcriptional activity of the 5′-flanking region of TXNIP promoter. Caco-2 cells were treated with 25, 50, 100 mM taurine for 24 h. The transcriptional activity was estimated by a luciferase assay as described in Section 2. Each value is the mean ± SEM ($n = 3$). *corresponds to $P < 0.05$ using Dunnett's test.

specific phenomenon and thus a valuable finding because the functions previously reported for taurine, including suppression of TAUT [12] and the activation of GABA-A and glycine receptors [33], are not specific but caused also by β-alanine. Our present study demonstrates the taurine-specific induction of TXNIP up-regulation and sheds light on the mechanism of the physiological functions of taurine.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.08.116.

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