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REVIEW ARTICLE

Taurine chloramine produced from taurine under inflammation provides anti-inflammatory and cytoprotective effects

Chaekyun Kim · Young-Nam Cha

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Abstract Taurine is one of the most abundant non-essential amino acid in mammals and has many physiological functions in the nervous, cardiovascular, renal, endocrine, and immune systems. Upon inflammation, taurine undergoes halogenation in phagocytes and is converted to taurine chloramine (TauCl) and taurine bromamine. In the activated neutrophils, TauCl is produced by reaction with hypochlorite (HOCl) generated by the halide-dependent myeloperoxidase system. TauCl is released from activated neutrophils following their apoptosis and inhibits the production of inflammatory mediators such as, superoxide anion, nitric oxide, tumor necrosis factor-α, interleukins, and prostaglandins in inflammatory cells at inflammatory tissues. Furthermore, TauCl increases the expressions of antioxidant proteins, such as heme oxygenase 1, peroxiredoxin, thioredoxin, glutathione peroxidase, and catalase in macrophages. Thus, a central role of TauCl produced by activated neutrophils is to trigger the resolution of inflammation and protect macrophages and surrounding tissues from being damaged by cytotoxic reactive oxygen metabolites overproduced during inflammation. This is achieved by attenuating further production of proinflammatory cytokines and reactive oxygen metabolites and also by increasing the levels of antioxidant proteins that are able to scavenge and diminish the production of cytotoxic oxygen metabolites. These findings suggest that TauCl released from activated neutrophils may be involved in the recovery processes of cells affected by inflammatory oxidative stresses and thus TauCl could be used as a potential physiological agent to control pathogenic symptoms of chronic inflammatory diseases.

Keywords Taurine · Taurine chloramine · Neutrophils · Inflammation · Antioxidant

C. Kim (✉) · Y.-N. Cha
Laboratory for Leukocyte Signaling Research, Department of Pharmacology and Toxicology, Inha University School of Medicine, 7-206, 3rd St, Shinheung-dong, Jung-gu, Incheon 400-712, Korea
e-mail: chaekyun@inha.ac.kr

Taurine is present in mammals

Taurine is one of the most abundant free amino acids, consisting of almost 0.1 % of body weight in most mammals, but is absent or present at extremely low levels if any in bacteria and plants. Taurine was first purified from ox bile (*Bos taurus*) in 1827 by German scientists Friedrich Tiedemann and Leopold Gmelin (Tiedemann and Gmelin 1827). Taurine was simply considered as an inert endpoint metabolite of sulfur-containing amino acids. In mammals, taurine is excreted either in unmodified form or in the form of bile salts like taurocholate. During last three decades, taurine has been found to have many physiological functions. For example, taurine is now known to be involved in osmoregulation, membrane stabilization, calcium mobilization, neurotransmission, reproduction and detoxification (Huxtable 1992; Schuller-Levis and Park 2003). In particular, taurine has been shown to provide anti-inflammatory effects and to protect cells from cytotoxic effects of inflammation (Marcinkiewicz and Kontny 2012).

Cysteine is an essential sulfur-containing amino acid and is involved in the maintenance of cellular redox balance. Within cells, cysteine is oxidized by cysteine dioxygenase forming cysteine sulfinic acid, which then undergoes decarboxylation to hypotaurine by cysteine sulfinate decarboxylase (CSD). Hypotaurine is then oxidized to taurine (2-aminoethane sulfonic acid; $SO_3HCH_2CH_2NH_2$)

which cannot be incorporated into proteins. Since taurine is a sulfonic amino acid with strong acidity and zwitterionic property ($pK_1 = 1.5$, $pK_2 = 8.8$), it is highly water soluble and poorly lipophilic over the physiological pH ranges. Thus, taurine cannot diffuse easily through the lipophilic cellular membrane, and this feature causes taurine to create steep concentration gradient across the cell membranes. For example, intracellular concentration of taurine ranges from 10 to 70 mM in human phagocytic cells but only 20–100 μM in extracellular fluid (Fukuda et al. 1982). Despite the low membrane permeability, taurine can be transported into cells by sodium-dependent taurine transporter (TauT). In support, TauT-null mice showed severely reduced taurine concentrations in variety of tissues (Heller-Stilb et al. 2002).

Taurine chloramine is produced endogenously by activated neutrophils

Neutrophils accumulate in the regions of inflammation or infected tissues and play a prominent first-line defense by engulfing the invading microorganisms and killing them with oxidants and microbicidal proteins. When neutrophils engulf invading microbes, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is activated and produces superoxide anion (O_2^-) by transferring electrons from NADPH to oxygen, a process called oxidative burst. Superoxide anion then undergoes dismutation quickly by being converted to hydrogen peroxide (H_2O_2). Although H_2O_2 has bactericidal properties, it is subsequently converted to hypochlorite ($HOCl/OCl^-$), an even more potent bactericidal oxidant, by the neutrophil myeloperoxidase (MPO). Taurine existing at more than 20 mM in resting neutrophils under normal conditions (Grisham et al. 1984) reacts with hypochlorite and acquires chloride to its N–H group, and the taurine is converted to taurine chloramine (TauCl, *N*-chlorotaurine) (Fig. 1). However, under an acidic microenviroment of inflammation, TauCl may convert to taurine dichloramine and taurine (Gottardi et al. 2005). While taurine reacts with hypochlorite, it cannot react with superoxide, peroxide, or hydroxyl radical in mammals (Aruoma et al. 1988).

Stimulation of normal human neutrophils and monocytes with phorbol 12-myristate 13-acetate (PMA) or opsonized zymosan induces TauCl production, and addition of exogenous taurine enhances TauCl production even further (Pero et al. 1996; Weiss et al. 1982; Witko et al. 1992). We investigated to see whether TauCl production requires the O_2^- derived from NADPH oxidase using fully differentiated neutrophil-like PLB-985 and X-PLB (NADPH oxidase $gp91^{phox}$-null) cells (Zhen et al. 1993), which are able and unable, respectively, to produce O_2^-. These cells were stimulated with PMA (100 μg/ml) in the presence of 1 mM taurine, and the production of TauCl was evaluated. The O_2^- producing PLB-985 but not the non-O_2^- producing X-PLB cells (2×10^6) produced about 100 μM of TauCl in 30 min (Fig. 2). Furthermore, neutrophils from patients with chronic granulomatous disease (CGD), who genetically lack the ability to produce O_2^-, are unable to produce TauCl (Witko et al. 1992). Thus, the fact that only the O_2^- producing PLB-985 cells, but not the X-PLB cells nor the neutrophils of CGD patients, possess the ability to produce TauCl demonstrate that O_2^- produced as a result of oxidative burst in activated neutrophils is an essential element for the production of TauCl. After the oxidative burst, neutrophils undergo apoptosis and release TauCl into inflammatory site where dendritic cells and macrophages infiltrate. These cells which phagocytose the TauCl-rich dying neutrophils are exposed to TauCl. In addition, it has also been reported that TauCl is transported actively into macrophages in sodium, temperature and energy-dependent manners (Kim et al. 1998; Park et al. 1993; Tallan et al. 1983), and suggested that TauCl uptake system may be separate and distinct from that of taurine (Park et al. 1993). The influence of temperature and pH on TauCl stability has been studied in vitro. TauCl exhibited stable thermal stability and lost only 10 % of its activity per year when kept at 2–4 °C (Gottardi and Nagl 2002). TauCl was unstable in acidic condition and degraded at a rate proportional to acidity (Gottardi et al. 2005). However,

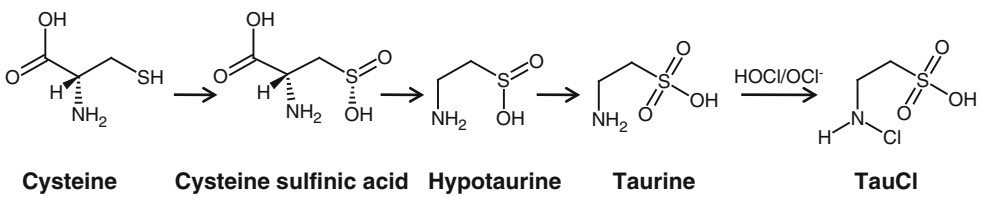

Fig. 1 Biosynthesis of TauCl. Cysteine is oxidized to cysteine sulfinic acid by cysteine dioxygenase. Cysteine sulfinic acid is then decarboxylated by cysteine sulfinate decarboxylase and forms hypotaurine which is further oxidized to taurine. In the activated neutrophils, taurine reacts with hypochlorite ($HOCl/OCl^-$) which is generated from H_2O_2 and chloride by neutrophil myeloperoxidase and forms taurine chloramine abbreviated as TauCl

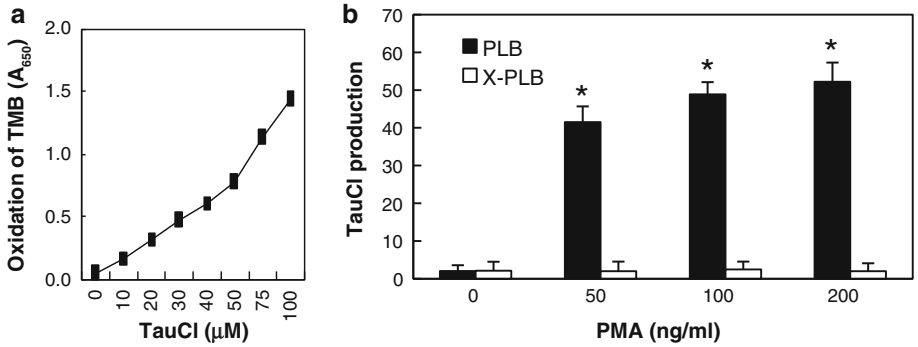

Fig. 2 Production of TauCl in neutrophils requires effective NADPH oxidase activity. **a** TauCl oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) was monitored at 650 nm. **b** Human myeloid cell lines, PLB-985 and X-PLB were grown in RPMI 1640 medium containing 10 % FBS, 100 U/ml penicillin and 100 μg/ml streptomycin at 37 °C in 5 % CO_2. To induce the differentiation of these cells into granulocytic cells, they were incubated with 0.5 % *N*,*N*-dimethylformamide for 5 days. Differentiated PLB-985 and X-PLB cells (2×10^6) were then stimulated with PMA for 30 min in the presence of 1 mM of taurine. TauCl production by these cells was determined by quantifying the oxidation of TMB. Data were compared by two-tailed Student's *t* test and the bar graph shows mean ± SD ($n = 3$), *$p < 0.01$ compared to control

the stability of TauCl under in vivo condition has not been reported and is considered quite unstable.

TauCl reacts with GSH and depletes cellular GSH

Glutathione (γ-L-glutamyl-L-cysteinylglycine; GSH) is one of the most abundant cellular antioxidant molecules that are involved in maintaining redox balance and prevents cells from oxidative damages caused by reactive oxygen species (ROS). GSH is oxidized easily and forms GSSG (oxidized glutathione). Overproduction of ROS increases the cellular level of GSSG at the expense of lowering the GSH level. As the TauCl is known to be a mild oxidant, we investigated whether the cellular GSH level is lowered or the GSSG level is increased in macrophages exposed to exogenous TauCl (Kim et al. 2010a). In RAW 264.7 macrophages treated with 0.7 mM TauCl, intracellular GSH level was decreased down to 30 % of control level within 30 min, and the decreased GSH level was recovered to the control level by 2 h (Kim et al. 2010a). This result suggests that the TauCl-derived depletion of GSH level may stimulate the expression of antioxidant enzyme genes to replenish the depleted GSH. Alternatively, when GSH was added directly to the test tube containing TauCl, the spectral absorption peak of TauCl was abolished in a dose-dependent manner of the added GSH (Fig. 3). In support of this, TauCl has also been shown to oxidize various other cellular components like glycine, methionine, tryptophan, and melatonin (Gottardi and Nagl 2002; Kanayama et al. 2002; Ximenes et al. 2010, 2011). This indicates that TauCl oxidizes cellular GSH and cysteine residues contained in various cellular proteins and further suggests that TauCl is unstable under in vivo conditions. The cysteine containing cellular proteins, after undergoing oxidation in

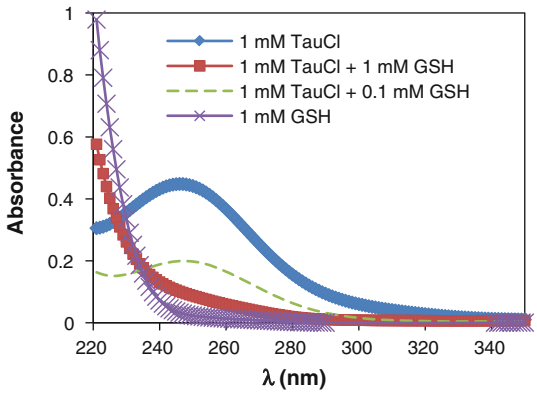

Fig. 3 Direct reaction between TauCl and GSH in vitro. To 1 mM TauCl, an equal volume of either 0.1 or 1 mM GSH was added in vitro, and the disappearance of the TauCl peak at 252 nm was monitored at a wavelength range of 220–350 nm

their cysteine residues by TauCl, may create intramolecular disulfide bonds or alter their three-dimensional structures so that their enzymatic activities are altered.

TauCl has microbicidal activity

In addition to the oxidizing effect on sulfhydryl (–SH) containing amino acids and proteins, TauCl has been shown to provide 'chlorine covers' (chlorination in the form of covalent N–Cl bonds) on the bacterial surface proteins that leads to loss of virulence and lag of bacterial regrowth (Gottardi and Nagl 2005). However, for killing of pathogens, penetration of TauCl into the cytosol as well as chlorination and oxidation of intracellular proteins is necessary (Gottardi and Nagl 2010). The chlorine transfer from TauCl to the amino groups on proteins of microbial membranes occurs without the need of catalysts, and this suggests that the lone pair of electrons on the

nitrogen atom of amino groups of bacterial proteins interacts with the chlorine atom of TauCl as an electrophilic chemical reaction. Therefore, the extent of chlorine transfer reaction and bactericidal effects of TauCl depend on the type of microorganism species, incubation time, pH, temperature, and the buffer system used (Gottardi and Nagl 2005).

Abundant amounts of TauCl and taurine bromamine (TauBr) are produced by neutrophils and eosinophils, respectively, upon microbial and parasite infections. Both TauCl and TauBr are known to be bactericidal, fungicidal and antiparasitic. For example, physiologic concentrations of TauCl (12.5–50 μM) are high enough to kill both gram-positive (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*) (Nagl et al. 2000). More recently, TauCl was shown to neutralize Shiga toxin of enterohemorrhagic *E. coli* by oxidizing the thiols and aromatic amino acids of the bacterial proteins (Eitzinger et al. 2012). TauCl is also known to kill fungi like *Candida* spp., *Aspergillus* spp., *Fusarium moniliforme* and *Polytrichum commune* (Gottardi and Nagl 2010), and inactivate viruses including type 1 and 2 human herpes simplex virus (HSV), adenovirus, human immunodeficiency virus (HIV)-1, and influenza viruses. In addition, TauCl and TauBr have been shown to kill the schistosomula of *Schistosoma mansoni* (Yazdanbakhsh et al. 1987). In fact, schistosomula can be eradicated completely by 1 mM TauCl or TauBr to nearly 40 % by 100 μM. TauCl has also been shown to be effective in killing Acanthamoebae, Leishmaniae and Trichomonas. These findings provide strong evidences that TauCl and TauBr generated endogenously during microbial and parasitic infections may play significant anti-microbial roles at physiological concentrations that are non-cytotoxic to host tissues. Thus, it has been suggested that 1 % TauCl (55 mM), which is a supra-physiologic but well-tolerated concentration by human tissue, can be used clinically for treatment of infections of the eye, skin, outer ear canal, nasal and paranasal sinuses, oral cavity, and urinary bladder, and suggested that it can be administered by instillation and inhalation. The therapeutic efficacy of TauCl has been proven at phase II clinical studies for the treatment of external otitis, crural ulcerations, and keratoconjunctivitis (Gottardi and Nagl 2010). In addition, synthetic stable TauCl derivatives like *N*-monochloro-2,2-dimethyltaurine and *N*-dichloro-2,2-dimethyltaurine have also been shown to have antimicrobial activity (Martini et al. 2012; Teuchner et al. 2012; Wang et al. 2011a).

TauCl inhibits superoxide production in activated neutrophils

We and others have demonstrated that TauCl inhibits O_2^- overproduction in murine and human neutrophils (Kim et al. 1996; Marcinkiewicz et al. 1998a; Park et al. 1998; Witko et al. 1992). Upon phagocytosis of bacterial components, neutrophils produce massive amounts of O_2^- and this is catalyzed by NADPH oxidase (phox) present in the phargosomal membrane. Upon stimulation, the cytosolic subunits ($p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and Rac GTPase) of NADPH oxidase associate with membrane cytochrome b_{558} ($gp91^{phox}$ and $p22^{phox}$) to form a functional NADPH oxidase complex and begin to catalyze O_2^- production via heme-dependent electron transfer from NADPH to molecular oxygen (Babior 1999; Dinauer 2003; Groemping and Rittinger 2005; Nauseef 2004). The serine residues in cytosolic $p47^{phox}$ are phosphorylated, and this signals other cytosolic components of phox to migrate to the phagosomal membrane. TauCl inhibited the PMA-induced phosphorylation of $p47^{phox}$ and the translocation of cytosolic $p47^{phox}$ and $p67^{phox}$ to membrane cytochrome b_{558}, thus prevented the assembly of functional NADPH oxidase in neutrophils (Choi et al. 2006). Although O_2^-, H_2O_2 and HOCl in phagosomes are essential for killing the phagocytosed bacteria, overproduction of O_2^-, H_2O_2, and HOCl may also cause considerable damage to phagosomal membrane and promote the leakage of ROS into the cytoplasm causing oxidative stress in neutrophils that result in apoptosis and necrosis.

TauCl produced and released from the activated neutrophils may inhibit the overproduction of O_2^- and thereby protect neutrophils from self-imposed cytotoxicity of ROS and oxidative stress. In this connection, TauCl and other monochloramines (R–NHCl) produced by interaction between HOCl and free amines in cytosol were shown to inhibit the overproduction of O_2^- in activated neutrophils and eosinophils (Ogino et al. 1997). These results suggest that such inhibition of O_2^- production by TauCl in stimulated phagocytic cells like neutrophils and macrophages may result from its inhibitory effect on $p47^{phox}$ phosphorylation and assembly of functional NADPH oxidase which may then serve as a self-limiting protective mechanism. Consequently, production of TauCl appears to play an important role in protecting phagocytic cells from this self-imposed oxidative injury under inflammatory conditions by inhibiting further production of ROS and HOCl.

TauCl inhibits production of pro-inflammatory mediators

It has been well documented that TauCl inhibits the overproduction of inflammatory mediators like nitric oxide (NO), tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-12, macrophage inflammatory protein-2 (MIP-2), and monocyte chemo-attractant protein (MCP)-1 and -2 (Table 1). NO is produced from L-arginine by members of the heme-containing nitric oxide synthase (NOS) family and serves

Table 1 Effect of TauCl on the production of inflammatory mediators

Inflammatory Mediator	Cell and Tissue	Stimuli	Concentrations (mM)	References
IL-1β	h-PBMC	LPS	~0.4	Park et al. (2002), Chorazy et al. (2002), Chorazy-Massalska et al. (2004)
	h-adipose tissue	LPS	0.5	Marcinkiewicz and Kontny (2012)
IL-2	Spleen cell, $CD4^+$ T cell, DO-11-10 cell	Ovalbumin	~0.3	Marcinkiewicz et al. (1998b)
	m-DC, m-T cell	LPS and INF-γ	~0.5	Marcinkiewicz et al. (1999)
	h-PBMC	PHA	~0.4	Park et al. (2002)
IL-6	m-MP	INF-γ; LPS and INF-γ	~0.6; ~0.3	Marcinkiewicz et al. (1995, 2005)
	h-PMN	LPS	~0.4	Park et al. (1998)
	m-PMN	LPS and INF-γ	0.3	Marcinkiewicz et al. (1998a)
	m-DC	LPS and INF-γ	~0.5	Marcinkiewicz et al. (1999)
	h-FLS	IL-1β, TNF-α, IL-17; IL-1β; IL-1β; IL-1β	~0.45; ~0.5; ~0.5; ~0.225	Kontny et al. (1999, 2000, 2002, 2003a)
	h-PBMC	LPS	~0.5	Chorazy et al. (2002), Chorazy-Massalska et al. (2004)
	h-PBMC	LPS, PHA	~0.4	Park et al. (2002)
	h-adipose tissue	LPS	0.5	Marcinkiewicz and Kontny (2012)
IL-8	h-PMN	LPS	~ 0.4	Park et al. (1998)
	h-FLS	IL-1β, TNF-α, IL-17; IL-1β; IL-1β	~0.45; ~0.5; 0.25–0.5	Kontny et al. (1999, 2000, 2002)
	h-PBMC	LPS, PHA	~0.4	Park et al. (2002)
	h-adipose tissue	LPS	0.5	Marcinkiewicz and Kontny (2012)
IL-10	m-DC	LPS and INF-γ	~0.5	Marcinkiewicz et al. (1999)
	h-adipose tissue	LPS	0.5	Marcinkiewicz and Kontny (2012)
IL-12	m-DC	LPS and INF-γ	~0.5	Marcinkiewicz et al. (1999)
MCP-1 and MIP-2	C6 glioma cell	LPS, TNF-α, INF-γ	~2.0	Liu et al. (1999)
	NR8383	LPS and INF-γ	~2.0; ~1.0	Liu and Quinn (2002), Quinn et al. (2003)
MMPs	m-MP	LPS	~1.0	Park et al. (2000b)
	h-FLS	IL-1β; IL-1β, Adiponectin	~0.8; ~0.6	Kim et al. (2007, 2010b)
Neopterin and IFN-γ	h-PBMC	PHA, ConA	~1.1	Wirleitner et al. (2004)
NO (iNOS)	RAW 264.7	LPS and INF-γ; H37Ra LAM and INF-γ; LPS and INF-γ; LPS and INF-γ, Taxol, LAM, IL-2; Zymosan and INF-γ; INF-γ and CpG ODN	~1.0; ~1.0; ~0.8; ~1.0; ~0.8; ~0.8	Park et al. (1993, 1995, 1997), (Schuller-Levis et al. 1994), Kim et al. (2011, 2013)
	m-MP, J774.2, MME	INF-γ, TNF-α, LPS	~0.6	Marcinkiewicz et al. (1995)
	m-MP	LPS and INF-γ	~1.0	Kim et al. (1996)
	C6 glioma cell	LPS, INF-γ and TNF-α	~2.0	Liu et al. (1998)
	m-PMN; m-DC	LPS and INF-γ	~0.3; ~0.5	Marcinkiewicz et al. (1998a, 1999)
	m-MP	LPS and INF-γ	~0.3	Marcinkiewicz et al. (2005)
	m-MP	LPS, LAM, INF-β, INF-γ	~1.0	Park et al. (2000a)
	NR8383, rat MP;NR8383	LPS and INF-γ; LPS and INF-γ	~2.0; ~1.0	Barua et al. (2001), Quinn et al. (2003)
	RAW 264.7	LPS	~1.0	Kim and Kim (2005)

Table 1 continued

Inflammatory Mediator	Cell and Tissue	Stimuli	Concentrations (mM)	References
O_2^-/H_2O_2	m-PMN	PMA	~1.0	Kim et al. (1996)
	h-PMN	PMA	~0.4	Park et al. (1998)
	m-PMN, m-MP	LPS, INF-γ, Zymosan	~1.0	Marcinkiewicz et al. (2000)
	h-PMN, PLB-985	PMA	~1.5	Choi et al. (2006)
	h-eosinophil	fMLP, PMA, Zymosan	~1.0	Martinez-Losa et al. (2009)
PGE_2 (COX2)	m-MP	INF-γ	~0.6	Marcinkiewicz et al. (1995)
	RAW 264.7	LPS and INF-γ	~1.0	Quinn et al. (1996)
	C6 glioma cell	LPS, INF-γ and TNFα	~2.0	Liu et al. (1998)
	m-PMN	LPS and INF-γ	0.3	Marcinkiewicz et al. (1998a)
	m-DC	LPS and INF-γ	~0.5	Marcinkiewicz et al. (1999)
	h-FLS	IL-1β	~0.5	Kontny et al. (2003b)
	J774.2	LPS and INF-γ	~0.4	Olszanecki et al. (2008)
TNF-α	RAW 264.7	LPS and INF-γ; H37Ra LAM and INF-γ; LPS and INF-γ; Zymosan and INF-γ; -γ; INF-γ and CpG ODN	~1.0; ~1.0; 0.8; 0.8; ~0.8	Park et al. (1993, 1995), Schuller-Levis et al. (1994), Kim et al. (2011, 2013)
	m-MP	INF-γ; LPS and INF-γ; LPS and INF-γ	~0.6; ~0.5; ~0.3	Marcinkiewicz et al. (1995, 2000, 2005)
	m-MP	LPS and INF-γ; LAM and INF-β, LAM and INF-γ	~1.0; ~1.0	Kim et al. (1996), Levis et al. (2003)
	m-PMN	LPS and INF-γ	0.3	Marcinkiewicz et al. (1998a)
	m-DC	LPS and INF-γ	~0.5	Marcinkiewicz et al. (1999)
	NR8383, rat MP; NR8383	LPS and INF-γ; LPS and INF-γ	~1.5; ~1.0	Barua et al. (2001), Quinn et al. (2003)
	m-PBMC	LPS	~0.4	Chorazy et al. (2002), Chorazy-Massalska et al. (2004)
	h-adipose tissue	LPS	0.5	Marcinkiewicz and Kontny (2012)

h human, *m* mouse, *ConA* concanavalin A, *CpG ODN* CpG oligodeoxynucleotide, *DC* dendritic cells, *FLS* fibroblast-like cells, *H37Ra* virulent mycobacterium H37Ra, *LAM* lipoarabinomannan, *LPS* lipopolysaccharide, *MCP-1* monocyte chemo-attractant protein 1, *MIP-2* macrophage inflammatory protein 2, *MME* murine microvascular endothelial cells, *MMPs* matrix metalloproteinases, *MP*: macrophages, *PBMC* peripheral blood mononuclear cells, *PMN* polymorpho nuclear cells, *PHA* phytohemagglutinin

as a gaseous signal molecule for many cellular functions. Although the small amounts of NO produced by constitutively expressed eNOS and nNOS serve in many physiological events, the overproduced NO catalyzed by oxidative stress-induced inducible NOS (iNOS) typically seen in stimulated macrophages can damage surrounding tissues (Ignarro 1996). The excessive NO produced by iNOS reacts with O_2^- and generates even more toxic $ONOO^-$ which plays a central role in many patho-physiological processes mediated by inflammatory cells, particularly activated macrophages. TNF-α is another prominent pro-inflammatory mediator produced by activated immune cells that induce further productions of several other pro-inflammatory mediators such as, NO, IL-6, IL-8, prostaglandins (PGs) and TNF-α itself. Thus, the ability of TauCl to inhibit overproduction of NO and TNF-α suggests that TauCl can be used as a physiological non-toxic biomolecule for blocking cellular damages caused by chronic inflammatory disease conditions.

TauCl appears to inhibit NO overproduction by several different mechanisms; depressing iNOS expression at mRNA and protein levels and also inhibiting the iNOS enzyme activity (Park et al. 1993, 1995). The inhibitory effect of TauCl on iNOS activity was determined in a cell-free cytosolic system obtained from lipopolysaccharide (LPS) and interferon (IFN)-γ-activated RAW 264.7 cells (Park et al. 1993). TauCl inhibited the catalytic activity of iNOS directly by targeting the enzyme protein rather than by interfering with the interaction of cofactors with iNOS. TauCl also inhibited the expressions of TNF-α and cyclooxygenase (COX)-2, and the production of TNF-α and PGE_2 (Marcinkiewicz et al. 1995; Park et al. 1995). Since the transcriptional regulation of genes coding for enzymes producing these proinflammatory

mediators, such as iNOS, TNF-α and COX-2 is mediated largely by activation of NF-κB, these results suggested that Tau-Cl may inhibit NF-κB activation.

TauCl inhibits NF-κB activation

NF-κB is a hetero- or homodimeric transcription factor involved in the synthesis of enzymes and cytokines that produce proinflammatory mediators and is comprised of subunits of Rel family members. In resting cells, NF-κB is bound by its inhibitor kappa B protein (IκB) and is sequestered in the cytoplasm. When cells are stimulated, the IκB-α bound to NF-κB is phosphorylated at its serine residues 32 and 36 by the redox-sensitive IκB kinase (IKK) and then the phosphorylated IκB-α is ubiquitinated and degraded by proteosome. This degradation of IκB-α then unmasks the nuclear localization motif of NF-κB and the activated NF-κB then translocates into the nucleus where it binds to specific DNA sequences in the promoter region of several genes involved in the synthesis of proinflammatory mediators including iNOS, TNF-α and COX-2, and stimulates their transcription.

TauCl inactivates IKK enzymatic activity and inhibits the phosphorylation of serine 32 of IκB-α and thus prevents IκB-α from degradation. In the activated NR8383 macrophage cells stimulated by LPS and IFN-γ and treated with TauCl, NF-κB remained in association with IκB in the cytoplasm and its nuclear migration was prevented (Barua et al. 2001). However, in Jurkat T cells activated by TNF-α, TauCl was shown to inhibit the TNF-α-derived NF-κB activation by oxidizing the methionine 45 in IκB-α but not by inhibiting the phosphorylation of serine 32/36 of IκB-α (Kanayama et al. 2002). Similarly in fibroblast-like synoviocytes (FLS) isolated from rheumatoid arthritis (RA) patients, TauCl was shown to diminish the IL-1β-derived NF-κB DNA binding activity (Kontny et al. 2000). Alternatively in the LPS-stimulated macrophages, we found that TauCl inhibits NF-κB DNA binding activity by inhibiting the LPS-induced activation of extracellular signal-regulated kinase (ERK), a key signaling kinase that regulates NF-κB activation by preventing Ras small GTPase without interrupting the activation of activator protein (AP)-1 (Kim and Kim 2005). Although it remains to be further clarified, our results strongly suggest that inhibition of NF-κB-dependent production of pro-inflammatory mediators by TauCl is attributed at least in part to the inhibitory effect on LPS-derived ERK activation in macrophages.

TauCl increases nuclear translocation of Nrf2

In resting cells, a redox-sensitive nuclear factor E2-related factor (Nrf2) exists in cytoplasm in an inactive state by being bound to Kelch-like ECH-associated protein 1 (Keap1). When cells are stimulated by various oxidants, cysteine thiol residues of Keap1 undergo oxidative modification and Keap1 is no longer able to bind Nrf2 (Dinkova-Kostova et al. 2002). Some of the cysteines in Keap1 are targeted by electrophiles and free radical oxidants and such modification of Keap1 promotes the dissociation of Nrf2 from Keap1 (Holland et al. 2008). Nrf2 released from Keap1 migrates into the nucleus where it binds to the DNA sequences known as anti-oxidant element (ARE) located in the promoter region of many anti-oxidant enzyme genes. ARE is the master regulator of the entire antioxidant system and when Nrf2 binds to ARE, transcription of various antioxidant enzyme genes like heme oxygenase-1 (HO-1), NADPH:quinone oxidoreductase (NQO-1), glutathione peroxidase (GPx), peroxiredoxin (Prx), and thioredoxin (Trx) is stimulated (Huie and Padmaja 1993; Motterlini et al. 2002). In addition to the increases in the expression of the antioxidant enzymes, we noticed that TauCl could rapidly increase nuclear translocation of Nrf2 and its binding to ARE beginning at 20 min and sustained the Nrf2–ARE binding effect for 1 h in RAW 264.7 macrophages (Kim et al. 2010a; Sun Jang et al. 2009). Furthermore, TauCl increased the cytosolic level of Nrf2 (Kim et al. 2010a; Sun Jang et al. 2009). Although TauCl increases cellular level of Nrf2 and activates its nuclear translocation, whether it is through modification of cysteine residues on Keap1 remains to be characterized.

TauCl protects cells from oxidative stresses via induction of anti-oxidant enzyme, HO-1

As mentioned above, TauCl increases the expression of many anti-oxidant enzymes, among which HO-1 induction is highly significant (Sun Jang et al. 2009). HO activity is responsible for catalyzing oxidative degradation of free heme released from heme-containing proteins upon oxidative stress to yield ferrous iron, CO, and biliverdin/bilirubin. Of the three known isoforms of HO, inducible HO-1 is the subset expressed upon exposure to either free heme or oxidative stress. Free heme is detrimental to ROS producing cells because it catalyzes production of highly reactive and toxic hydroxyl radical ($HO^{\bullet}$) from H_2O_2 via Fenton reaction (Balla et al. 1991; Kumar and Bandyopadhyay 2005). While free heme is detrimental to cells, the products of its degradation, biliverdin/bilirubin and CO are beneficial to the cells by serving as potent antioxidant and anti-inflammatory mediator, respectively (Tenhunen et al. 1968). Therefore, it is necessary for the cells undergoing oxidative stress to eliminate free heme by increasing the HO activity.

TauCl elevated the expression of HO-1 in macrophages both at mRNA and protein levels, and increased its

enzymatic activity by TauCl alone or in combination with LPS (Kang and Kim 2013; Kim et al. 2010a; Olszanecki and Marcinkiewicz 2004; Sun Jang et al. 2009). This TauCl-induced upregulation of HO-1 expression appeared to be mediated by activation of Nrf2–ARE system. This was evidenced by the results that TauCl-derived induction of HO-1 was reduced in RAW 264.7 cells transfected with Nrf2 siRNA (Kim et al. 2010a). Therefore, the role of TauCl in inducing the expression of HO-1 and increasing the HO activity is physiologically important because the elevated HO activity removes free heme and provides bilirubin and CO, which, respectively, eliminates toxic hydroxyl radicals and also prevents additional ROS production by blocking the cytochrome catalyzed electron transfer to oxygen.

Oxidative stress causes activation of NF-κB and induction of iNOS which then produces NO and subsequently peroxynitrite ($ONOO^-$). The $ONOO^-$ modifies Keap1 and activates Nrf2 and then induces HO-1 expression to increase the HO activity which leads to an overproduction of CO. The CO generated as a product of heme degradation binds to the heme enzymes like NADPH oxidase and iNOS and suppresses further additional production of O_2^- and NO, respectively, (Srisook and Cha 2004). Thus, TauCl may act as a signal molecule to promote cellular homeostasis from inflammation-derived oxidative stress. This reaction cycle can be explained by the following results: (1) production of TauCl is initiated in neutrophils by inflammatory ROS, (2) TauCl induces HO-1 and elevates CO production, (3) the elevated CO then suppresses the inflammation-derived overproduction of O_2^- and NO by inhibiting NADPH oxidase and iNOS, respectively. In this regard, the TauCl produced and released from activated neutrophils may play an important auto-regulatory role to allow the cells to survive from oxidative injuries that can be caused by chronic inflammation.

TauCl prevents cell death caused by oxidative stresses

Phagocytes experience oxidative burst with immediate production of a large amount of O_2^- during phagocytosis of bacterial components. Although the production of O_2^- and H_2O_2 is essential for killing the phagocytosed bacteria, excessive amounts of these oxidative burst products can cause death of phagocytes as well as surrounding cells. In the presence of free heme, H_2O_2 converts to highly toxic $HO^\bullet$ radical that causes destruction of cellular membranes and necrosis. Our study revealed that nearly 50 % of RAW 264.7 cells died after 1 h exposure to 1 mM H_2O_2 and more than 30 % of this cell death resulted from necrosis (Sun Jang et al. 2009), and with 0.5 mM H_2O_2, 14 % of cells underwent apoptosis after exposure for 1 h (Piao et al. 2011). However, the cells pretreated with 0.5 mM TauCl for 12 h were effectively protected from cell death induced by H_2O_2 (Piao et al. 2011; Sun Jang et al. 2009). In contrast to our studies, treatment of FL5.12 pro-B cells with 1 mM TauCl activated apoptotic pathway involving activation of Bax and caspase-9 (Emerson et al. 2005). TauCl also caused apoptosis of human B lymphoma cells through mitochondrial damage via decreases in mitochondrial transmembrane potential (Klamt and Shacter 2005). HOCl also caused the death of human B lymphoma cells largely by apoptosis, and this was claimed to be mediated by chloramines like TauCl generated from HOCl in culture media (Englert and Shacter 2002). In support, TauCl was also reported to induce apoptosis in human osteosarcoma cell lines (Pilz et al. 2012). Taken together, while it appears that TauCl promotes death of cancer cells by inducing apoptosis, TauCl prevents phagocytic cells from death caused by the overproduced O_2^- and H_2O_2 in an inflammatory milieu.

TauCl prevents the development of chronic inflammatory diseases

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic inflammation of joints and progressive erosion of cartilage and bone (Gabriel 2001). RA symptoms are accompanied by accumulation of inflammatory cells and FLS in joints and this contributes to the onset of chronic synovitis and synovial membrane hyperplasia. Anti-arthritic effect of TauCl has been observed in various experimental animal models (Kwasny-Krochin et al. 2002; Verdrengh and Tarkowski 2005; Wojtecka-Lukasik et al. 2005), and lack of TauCl production was suggested to promote the development of RA. In support of this hypothesis, neutrophils isolated from synovial fluid samples obtained from RA patients generated less TauCl than those from healthy volunteers (Kontny et al. 2002). In a murine septic arthritis model induced by intravenous injection of *S. aureus*, intra-articular injection of TauCl inhibited the development of arthritis and suppressed the bone and cartilage damages (Kwasny-Krochin et al. 2002; Verdrengh and Tarkowski 2005; Wojtecka-Lukasik et al. 2005). In support, we found that repeated subcutaneous injections of TauCl in the DBA1/J mice with collagen-induced arthritis (CIA) reduced the severity of paw swelling, arthritic scores, cartilage damage, synovial inflammation and bone erosion (Wang et al. 2011b). In addition, splenocyte proliferation and osteoclast differentiation in CIA mice were also inhibited by the TauCl treatment. Alternatively, when mice were pretreated with TauCl prior to induction of CIA by collagen injection, the

onset of CIA was delayed and the incidence of CIA was diminished apparently (Kwasny-Krochin et al. 2002) by direct inhibition of collagenase activity (Davies et al. 1994). Taken together, these findings suggest that TauCl inhibits synovial inflammation and collagenase activity and minimizes the damage to cartilaginous joint structures in RA perhaps by inhibiting the NF-κB activation.

The mechanisms by which TauCl exerts anti-arthritic effects have not been well characterized. Because the neutrophils accumulating in the affected joints with RA symptoms produce excessive amounts of ROS and reactive nitrogen species (RNS) that are toxic to surrounding cells, the TauCl-derived inhibition of ROS and RNS overproduction may provide at least part of the mechanism. Alternatively, TauCl has been reported to inhibit the production of pro-inflammatory cytokines (IL-6, IL-8, and PGE_2) in the FLS and RA-associated adipose tissues isolated from RA patients (Kontny et al. 1999, 2000, 2003b; Marcinkiewicz and Kontny 2012). TauCl inhibited the proliferation of FLS by triggering p53-dependent cell-cycle arrest (Kontny et al. 1999). In our study, TauCl inhibited production of matrix metalloproteinase (MMP) in FLS as well (Kim et al. 2007, 2010b). Thus, it is likely that abundant production of TauCl in the inflamed synovial joints may inhibit the proliferation of FLS as well as the functions of FLS (e.g. production of inflammatory mediators) that are associated with pathogenesis of RA.

Although weak, taurine has been shown to have anti-inflammatory effect as manifested in many chronic inflammatory diseases models such as carrageenan-induced rat paw edema, rat inflammatory bowel disease (IBD), and hamster lung fibrosis models (Bhattacharya and Sarkar 1986; Son et al. 1996, 1998; Wang et al. 1992). Compared to taurine, TauCl has far more effective anti-inflammatory effects as reported in many in vivo studies using diverse experimental animal species such as acute otitis externa in man, arthritis in mice, and acute streptococcal lower airway inflammation in pigs (Neher et al. 2004, 2007; Schwienbacher et al. 2011; Verdrengh and Tarkowski 2005; Wang et al. 2011b; Wojtecka-Lukasik et al. 2005). As taurine by itself alone has not revealed any specific anti-inflammatory effect in vitro, it is speculated that the weak anti-inflammatory effects shown in vivo with taurine may be mediated by the taurine haloamines (TauCl and TauBr) which are readily detected in neutrophils and eosinophils infiltrating the inflammatory sites.

Conclusions

TauCl is produced endogenously in neutrophils under inflammatory conditions. The generation and release of TauCl by activated neutrophils confers important impacts on many nearby cells in several respects.

First, TauCl is formed upon elimination of toxic hypochlorite and thus its formation protects neutrophils from the toxic effects of hypochlorite.

Second, TauCl is microbicidal by transferring its Cl^- to amine components of bacteria, fungi, and viruses (Gottardi and Nagl 2010) and thus, may contribute to intracellular killing of pathogens by neutrophils.

Third, TauCl inhibits production of pro-inflammatory mediators, such as NO, TNF-α, PGs, and pro-inflammatory interleukins in those inflammatory cells that infiltrate into the inflamed tissues, and it prevents the development of chronic inflammation.

Forth, TauCl also inhibits further overproduction of O_2^-, thus diminishing additional oxidative stress in cells at the inflammatory site.

Fifth, TauCl promotes recovery of redox balance in diverse cells at the inflammatory site by increasing the expression of many antioxidant enzymes, such as HO-1, Prx, Trx, GPx, and catalase and thus protects these cells from the cytotoxicity of reactive oxygen metabolites.

These diverse properties of TauCl could provide important physiological anti-inflammatory effects and prevent the development of pathogenic symptoms of chronic inflammatory diseases.

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Conflict of interest The authors declare that they have no conflict of interest.

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