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Taurine chloramine modulates cytokine production by human peripheral blood mononuclear cells

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Summary. The effect of taurine (Tau) and taurine chloramine (Tau-Cl) on the production of TNF-α, IL-1β, and IL-6 by peripheral blood mononuclear cells of healthy volunteers was examined. Cells were stimulated with bacterial lipopolysaccharide (LPS) in the presence of either Tau or Tau-Cl. After 24 h culture the cytokine concentrations were measured in both culture supernatants (secreted) and cell lysates (cell-associated) using ELISA. In LPS-stimulated cells Tau-Cl inhibited both the secreted and cell-associated IL-1β and IL-6, while exerted dual effect on TNF-α production: raising it slightly at low and reducing at higher concentration. By contrast, Tau had no significant effect on the cytokine production. These results indicate that Tau-Cl modulates synthesis of pro-inflammatory cytokines, and therefore it may play a role in the initiation and propagation of immune response.

Keywords: Taurine chloramine – TNF-α – IL-1β – IL-6 – Peripheral blood mononuclear cells

Abbreviations: Tau, taurine; Tau-Cl, taurine chloramine; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1β; IL-6, interleukin 6; PBMC, peripheral blood mononuclear cells

Introduction

Pleiotropic cytokines, TNF-α, IL-1β, and IL-6, form a link between innate and acquired immune responses. These cytokines are produced by a variety of cells of hematopoietic origin and by somatic tissue. However, in the initial phase of inflammatory response TNF-α, IL-1β, and IL-6 originate primarily from activated macrophages. Then secreted cytokines act as growth factors for particular lymphocyte subpopulations engaged in the development of acquired immune response. Interleukin-1 is a comitogen for T lymphocytes (Auron, 1998). Tumor necrosis factor-α propagates T helper type 1 (Th1) cell-mediated immune response both by the up-regulation of IL-12 synthesis (O'Garra, 1998) and acting synergistically with IFN-γ (Paludan, 2000). Interleukin-6 is a growth factor for B lymphocytes (Taga and Kishimoto, 1997) and is implicated in the initiation and enhancement of T helper type 2 (Th2) humoral immune response (Rincon et al., 1997). Importantly, by triggering synthesis of the other pro-inflammatory cytokines (e.g. IL-8), numerous inflammatory mediators (e.g. NO, PGE_2), and tissue degrading enzymes (e.g. metalloproteinases) both TNF-α and IL-1β participate in the effector phase of inflammatory response (Carteron, 2000). By contrast, IL-6 does not possess such activities and is rather engaged in the down-regulation of inflammatory response. This cytokine was reported to inhibit TNF-α and IL-1β synthesis, to induce the synthesis of endogenous antagonists of TNF-α (TNF-α soluble receptor) and IL-1β (IL-1 receptor antagonist), as well as to up-regulate tissue inhibitors of metalloproteinases (Tilg et al., 1994; Lotz and Guerne, 1991). Despite these differences, TNF-α, IL-1β, and IL-6 are co-ordinately engaged in the development of systemic symptoms, like the acute-phase response, fever and anorexia (Koj, 1996; Gabay and Kushner, 1999). Accordingly, TNF-α and IL-1β are considered to be the prototypical pro-inflammatory cytokines while IL-6 represents cytokine that juxtaposes pro- and anti-inflammatory activities.

Neutrophils are active participants of acute inflammatory response (Smith, 1994). The major function of

these cells is to kill the invading micro-organisms by a variety of microbicidal agents, including the myeloperoxidase-produced oxidant, hypochlorous acid (HOCl) (Babior, 2000). However, the reactive oxidants generated by neutrophils inflict also the damage on nearby tissues. Taurine (Tau), the most abundant free amino acid in neutrophil cytosol, acts as a trap for HOCl, forming the long-lived, less reactive and less toxic oxidant taurine monochloramine (Tau-Cl) (reviewed by Marcinkiewicz, 1997). There is growing evidence that Tau-Cl exerts anti-inflammatory effect on murine neutrophils and macrophages (reviewed by Marcinkiewicz, 1997) and modulates the induction of antigen-specific acquired immune response (Marcinkiewicz et al., 1998a; Marcinkiewicz et al., 1999).

These data prompted us to investigate the effect of Tau-Cl on the production of TNF-α, IL-1β and IL-6 by human peripheral blood mononuclear cells.

Materials and methods

Cell culture and treatment

The group of 10 healthy adult volunteers (3 men/7 women; mean age = 35.5 ± 11.4) was included in the study. Peripheral blood mononuclear cells were separated from heparinized blood on density gradient using Gradisol L (Polfa, Poland). Cells obtained from particular donor were suspended in RPMI 1640 medium supplemented with 10% foetal calf serum (Biochrom KG, Berlin, Germany), 2 mM L-glutamine, 100 units/ml penicillin, 10 μg/ml kanamycin and 100 μg/ml streptomycin, and were seeded at a density of 1×10^6 cells/ml/well in the 24-well flat-bottom culture plates (Nunc A/S, Roskilde, Denmark). Cells were stimulated with 5 μg/ml of lipopolysaccharide (LPS; *E. coli* 055:B5; Difco, Detroit, MI), in the presence or absence of either Tau or Tau-Cl. Both compounds were added together with the stimulus at the concentration 100–500 μM. Tested compounds were not cytotoxic, as estimated by the measurement of lactate dehydrogenase activity (LDH; Takara Shuzo Co, Otsu, Shiga, Japan) in culture supernatants.

Cytokine detection using enzyme-linked immunosorbent assay (ELISA)

Cytokine production was assayed after 24 h of cell culture. Culture supernatants were collected, clarified by centrifugation (400 × g for 10 minutes) and used to measure production of secreted forms of cytokines. The synthesis of cell-associated cytokines was determined in cell lysates, obtained by three cycles of freezing-thawing of cells resuspended in 1 ml of freshly added culture medium. The concentration of cytokines was measured in the samples collected from cell culture of particular donor (n = 10 or n = 8 for IL-1β and IL-6, or TNF-α determinations, respectively) using specific ELISA as previously described (Kontny et al., 1999). Briefly, goat polyclonal neutralising antibody (Ab) specific for human IL-6 and mouse monoclonal neutralising Ab specific for human IL-1β (both from R&D Systems, Minneapolis, MN) were used as the capture Abs. Cytokine specific rabbit polyclonal Abs were used as detection ones (both from Sigma, St. Louis, MO, USA), followed by horseradish peroxidase-conjugated goat anti-rabbit immunoglobulins and *o*-phenylenediamine dihydrochloride (from Sigma) as a substrate. Human recombinant cytokine standards for IL-1β and IL-6 were from R&D Systems. The concentration of TNF-α was estimated using Opt EIA™ SET (Pharmingen, San Diego, CA). Optical density was measured at 450 nm (for TNF-α) and 492 nm (for IL-1β and IL-6) using an automatic ELISA reader (LP 400, Diagnostics Pasteur, France). The detection limit was 15.6 pg/ml for TNF-α and 39 pg/ml for both IL-1β and IL-6.

Synthesis of Tau-Cl

Taurine monochloramine was prepared according to the method described previously (Marcinkiewicz et al., 1998b). Briefly, 5 ml of 20 mM NaOCl (Aldrich, Steinheim, Germany) solution in 0.2 M phosphate buffer (pH 7.4–7.5) was added dropwise to 5 ml of 24 mM Tau (Sigma) with vigorous stirring. Each preparation of Tau-Cl was monitored by ultraviolet absorption spectra (200–400 nm) to ensure the authenticity of Tau-Cl (252 nm) and the absence of dichloramine, NH_2Cl, and unreacted $HOCl/OCL^-$. The concentration of synthesised monochloramine was determined by the molar extinction coefficient 415 M^{-1} cm^{-1} with absorbance at a wavelength of 252 nm. Stock solutions of Tau and Tau-Cl (10 mM) were kept at 4°C for a maximum period of 3 days before use.

Statistical analysis

Repeated-measures analysis of variance (ANOVA) followed by Tukey's test were applied to evaluate the effect of stimulus and Tau/Tau-Cl. All data are expressed as the mean ± SD. *P* values less than 0.05 were considered to be statistically significantly.

Results

Spontaneous production of all tested cytokines was low or undetectable (Fig. 1) and it was significantly affected neither by Tau-Cl nor Tau, although the latter compound showed tendency to up-regulate it slightly (data not shown). Lipopolysaccharide significantly raised the synthesis of every cytokine with the highest increase of IL-6, moderate of IL-1β and the lowest of TNF-α. The bulk of the cytokines was secreted outside the cells (Fig. 1).

Taurine had no significant effect on LPS-triggered production of either TNF-α (Fig. 2) or IL-1β (Fig. 3) or IL-6 (Fig. 4). By contrast, Tau-Cl affected the LPS-induced cytokine responses in a dose-dependent manner, and similarly influenced the secretion and the cell-associated cytokine synthesis (Fig. 2–4). Interestingly, this compound exerted dual effect on TNF-α production: raising it at low (100–200 μM) concentration, while reducing it at higher concentration (IC_{50} = 460 or 480 μM for secreted or cell-associated TNF-α, respectively) (Fig. 2). However, in the presence of Tau-Cl synthesis of the other cytokines was evidently down-regulated (Fig. 3 and Fig. 4). Moreover, the

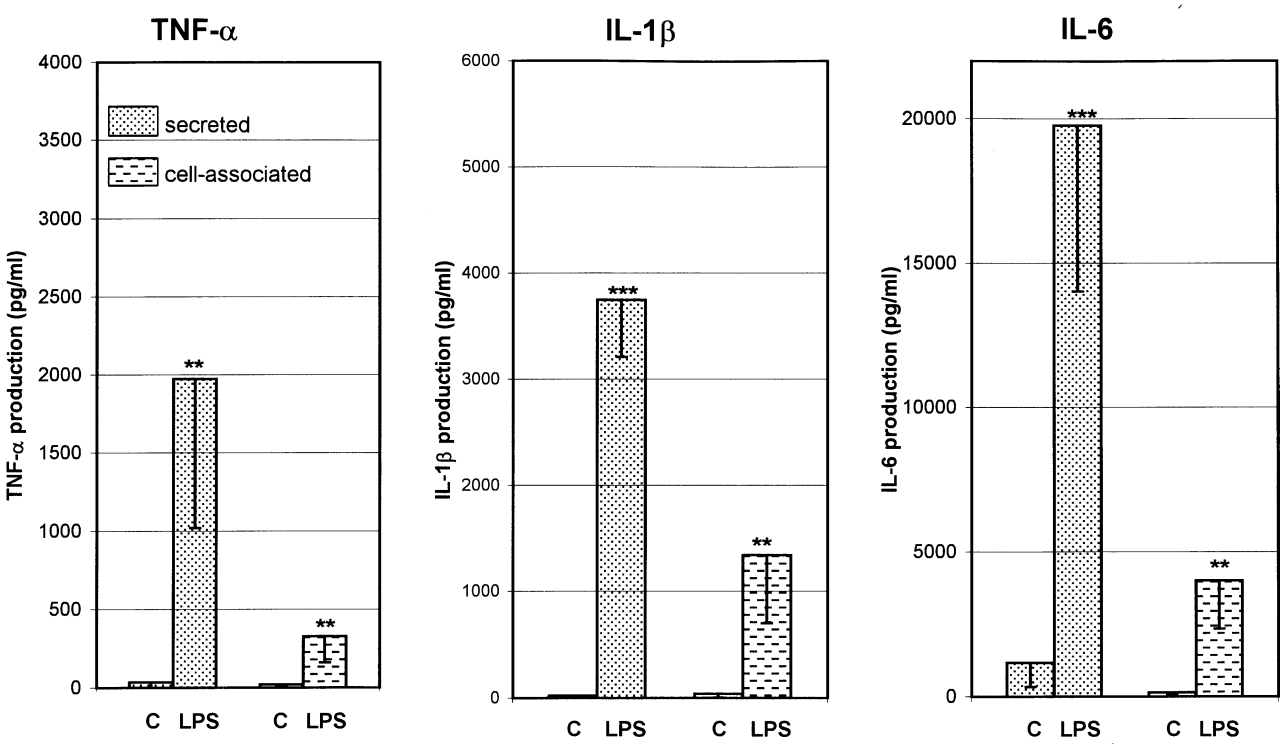
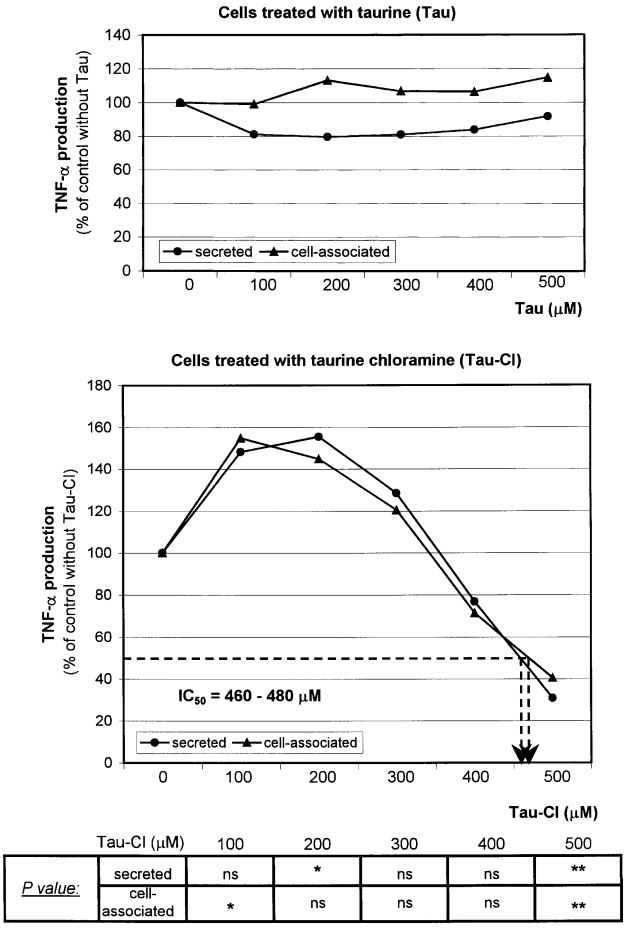


Fig. 1. Production of cytokines by peripheral blood mononuclear cells (PBMC). Cells were cultured in medium alone (control, *C*) or in the presence of 5 μg/ml of lipopolysaccharide (*LPS*). Concentrations of tested cytokines were measured in the culture supernatants secreted) and in the cell lysates (cell-associated) by ELISA specific to particular cytokine (see *Material and methods* for details). Results represent cytokine production by cells isolated from peripheral blood of 10 healthy volunteers. Bars show the mean and SD. $^{**}0.001 > P > 0.0001$; $^{***}P < 0.0001$ versus control

production of IL-1β was inhibited more potently (IC_{50} = 250 or 300 μM for secreted or cell-associated IL-1β, respectively) (Fig. 3) than the production of IL-6 (IC_{50} = 400 or 425 μM for cell-associated or secreted IL-6, respectively) (Fig. 4).

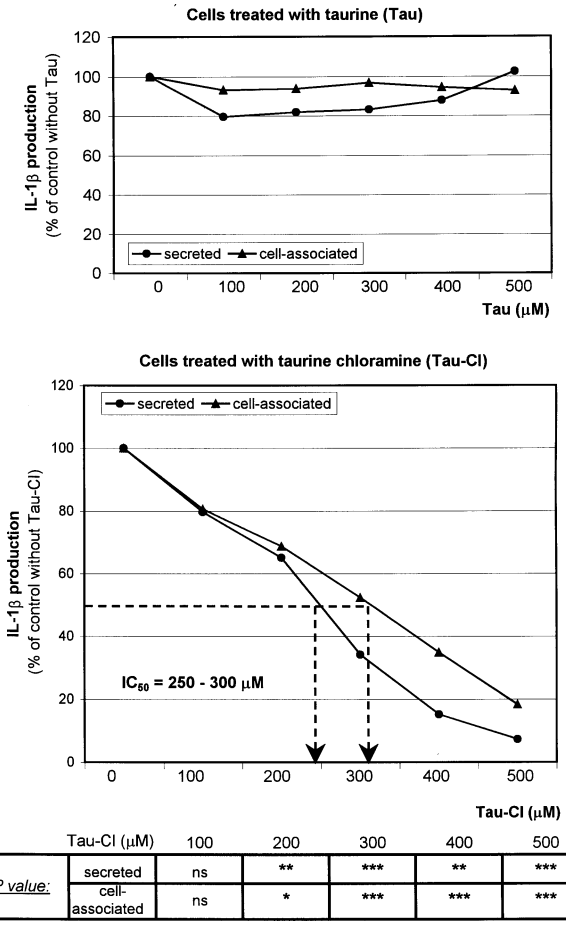
Discussion

The results of present study show that in human PBMC Tau-Cl dose-dependently modulates LPS-triggered synthesis of the key pro-inflammatory cytokines. Therefore this compound may represent an important immunoregulatory loop. Neutrophils are frequently the first cells recruited into the site of inflammatory response (Smith, 1994). It is well documented that activated neutrophils utilize the hydrogen peroxide-myeloperoxidase-chloride system to chlorinate Tau with resulting generation of Tau-Cl (Weiss et al., 1982). The physiologic concentrations of Tau-Cl are not yet known. However, Tau, a precursor of Tau-Cl, is a dominant free amino acid present in most mammalian tissues and human blood cells at 10–20 mM concentrations. In the plasma and other physiologic fluids concentration of Tau is lower, reaching the range of 50–100 μM (Learn et al., 1990). Importantly, *in vitro* activated human neutrophils can generate 200 nmol HOCl/10^6 cells/2 hr with resulting release of $\approx$100 nmol of Tau-Cl (Weiss et al., 1982; Weiss, 1989). Under these conditions the majority of Tau-Cl is found extracellularly (Weiss et al., 1989). It is proposed that Tau-Cl may be synthesized within the vacuolar space and then diffused out of the cells. However, because activated neutrophils release H_2O_2 and myeloperoxidase outside the cell, Tau-Cl may also be generated extracellularly (Weiss et al., 1989; Marquez and Dunford, 1994). *In vivo*, a large interstitial inflammatory site may contain as many as 25 $\times$ 10^6 neutrophils/ml (Weiss, 1989). Moreover, Tau-Cl is a long-lived oxidant, undergoing less than 5% decomposition/h (Grisham et al., 1984). Consequently, it is conceivable that with the progression of inflammatory response there is gradual accumulation of Tau-Cl that may finally reach high local concentrations of the mM range.



Tau-Cl (μM)		100	200	300	400	500
P value:	secreted	ns	*	ns	ns	**
	cell-associated	*	ns	ns	ns	**

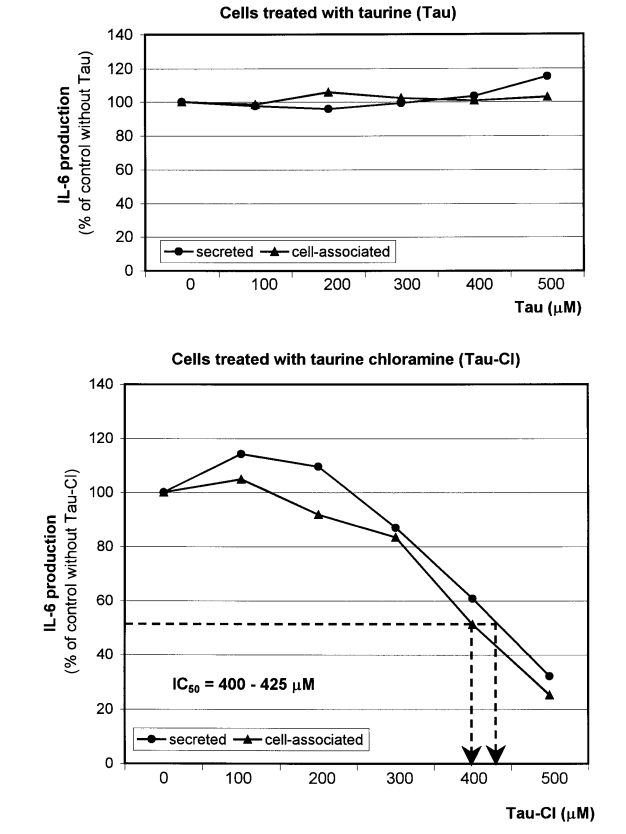
Fig. 2. Effects of taurine (*Tau*) or taurine chloramine (*Tau-Cl*) on the production of TNF-α by PBMC. Cells were stimulated with LPS (5 μg/ml) alone or in the presence of different concentrations of Tau or Tau-Cl. Concentration of TNF-α was measured by specific ELISA. Results are expressed as a percentage of the responses noted in the control cell cultures, which were treated with LPS alone. Values are the mean of 8 experiments. Differences between the cells treated with Tau and control cells were not significant. The arrows indicate the concentrations of Tau-Cl that caused 50% inhibition of either TNF-α secretion (IC_{50} = 460 μM) or the cell-associated synthesis of this cytokine (IC_{50} = 480 μM). *$0.05 > P > 0.01$; **$0.01 > P > 0.001$ for Tau-Cl-treated versus control cells. *ns* = not significant (see Fig. 1 for other definitions)



Tau-Cl (μM)		100	200	300	400	500
P value:	secreted	ns	**	***	**	***
	cell-associated	ns	*	***	***	***

Fig. 3. Effects of Tau or Tau-Cl on the production of IL-1β by PBMC. Values are the mean of 10 experiments. Differences between the cells treated with Tau and control cells were not significant. The arrows indicate the concentrations of Tau-Cl that caused 50% inhibition of either IL-1β secretion (IC_{50} = 250 μM) or the cell-associated synthesis of this cytokine (IC_{50} = 300 μM). *$0.05 > P > 0.01$; **$0.01 > P > 0.001$; ***$P < 0.0001$ for Tau-Cl-treated versus control cells. ns = not significant (see Fig. 2 for explanations)

Present finding that Tau-Cl exerts bimodal effect on TNF-α synthesis seems to be of particular importance. It is well known that the effector functions of TNF-α are numerous and that virtually every step in the inflammatory process could be dependent on this cytokine (Beutler, 1999). However, the generation of TNF-deficient mice (TNF$-/-$) allows to define the most critical function of this cytokine (reviewed by Sedgwick et al., 2000). It is proposed that haematopoietically derived TNF triggers synthesis of chemokines by TNF receptor-expressing resident tissue cells and thus this cytokine regulates leukocyte movement during inflammatory response. Moreover, it seems to be necessary for the target organ to respond to TNF for inflammation to develop normally in tissues. Recent data also show that the initial low level of TNF-α and IL-1β synthesis triggered in myeloid cells (macrophages, neutrophils) via pattern recognition receptors (PRRs) promotes elimination of bacterial infection (Aderem and Ulevitch, 2000), while further amplification of these cytokine synthesis mediated by TREM-1 (triggering receptor expressed on myeloid cells) can lead to excessive inflammation, tissue damage and septic shock (Bouchon et al., 2001). Accordingly, it has been suggested that antigen activated T cells stimulate monocytes to produce TNF-α that is



Tau-Cl (μM)		100	200	300	400	500
P value:	secreted	ns	ns	ns	**	***
	cell-associated	ns	ns	ns	***	***

Fig. 4. Effects of Tau or Tau-Cl on the production of IL-6 by PBMC. Values are the mean of 10 experiments. Differences between the cells treated with Tau and control cell were not significant. The arrows indicate the concentrations of Tau-Cl that caused 50% inhibition of either IL-6 secretion (IC_{50} = 425 μM) or the cell-associated synthesis of this cytokine (IC_{50} = 400 μM). **$0.01 > P > 0.001$; ***$P < 0.0001$ for Tau-Cl-treated versus control cells. ns = not significant (see Fig. 2 for explanations)

important for the resolution of innate and adaptive immune response ("immune" TNF-α), while cytokine activated bystander T cells trigger in monocytes unrestrained synthesis of this cytokine leading to chronic inflammatory disease like rheumatoid arthritis (RA) (Foxwell et al., 2000; Feldmann et al., 2001). Altogether, these data show that adequate level of TNF-α is critical for the initiation of protective immune response, while over-expression of this cytokine leads to pathogenic chronic inflammation. Accordingly, present results allow to speculate that in the initial phase of immune response Tau-Cl (present at low concentration) may favour the resolution of protective inflammation by supporting synthesis of TNF-α. Then, with the progression of inflammatory process accompanied by local accumulation of Tau-Cl, this compound could prevent perpetuation of chronic inflammation by gradual down-regulation of pro-inflammatory cytokine (IL-1β > IL-6 > TNF-α) synthesis. Although this suggestion is based on our present *in vitro* study, there are results of experiments performed *in vivo* supporting this suggestion. For example, Tau treatment has beneficial effects in various animal models of inflammation, where Tau acts mostly by preventing the oxygen free radicals tissue injury (Schuller-Levis et al., 1994; Gurujeyalakshmi et al., 2000; Ahn et al., 2001; Waters et al., 2001). However, in some (Schuller-Levis et al., 1994; Gurujeyalakshmi et al., 2000) of these animal models Tau treatment resulted in attenuation of pro-inflammatory cytokine (TNF-α, IL-1, IL-6, TGF-β) synthesis in the inflammed tissue but had no effect on the serum cytokine (TNF-α, IL-1β) concentration (Ahn et al., 2001). Importantly, in Tau-treated animals the inhibition of local pro-inflammatory cytokine synthesis was accompanied by inhibition of NFκB activation (Gurujeyalakshmi et al., 2000). Moreover, it has been proposed that in rat model, Tau may protect the lung from oxidant injury via formation of Tau-Cl, that in turn inhibits production of nitrite and the release of TNF-α (Schuller-Levis et al., 1994). Therefore, it is very likely that at least some anti-inflammatory effects of Tau are mediated via Tau-Cl generation and regulation of pro-inflammatory cytokine synthesis. However, further studies are necessary to confirm the existence of Tau-Cl mediated regulatory loop *in vivo*.

Taurine chloramine is hydrophilic and therefore membrane-impermeable, but this compound is actively transported into the various types of cells (Park et al., 1993; Cantin 1994; Vile et al., 2000). In the RAW 264.7 macrophage cell line the uptake system for Tau-Cl is energy, temperature and Na^+ dependent and distinct from that for Tau (Park et al., 1993). Thus, it is very likely that similar mechanism is responsible for Tau-Cl uptake by human PBMC. Interestingly, present results clearly show that Tau-Cl similarly modulates both the secretion and the intracellular levels of tested cytokines, suggesting that this compound interferes with the signalling pathways responsible for pro-inflammatory cytokine production. The mechanism of this Tau-Cl action is not fully understood. However, we have previously shown that LPS-triggered synthesis of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) by human monocytes is dependent on the activation of protein kinase C (PKC)

(Kontny et al., 1999) and reported that the synthesis of particular cytokine differs in the requirements for particular PKC isozyme and transcription factor (AP-1, NFκB) activities (Kontny et al., 2000a). Interestingly, membrane-permeable monochloramine NH_2Cl has been shown to inhibit PKC activation and suppress PKC-mediated cellular response (IL-2 receptor expression in Jurkat cells and neutrophil respiratory burst) (Ogino et al., 1997). Moreover, we found that in fibroblast-like synoviocytes of RA patients Tau-Cl inhibits more potently the activity of NFκB and IL-6 transcription ($IC_{50} \approx 225\ \mu M$) than the activity of AP-1 and IL-8 transcription ($IC_{50} \approx 450\ \mu M$) (Kontny et al., 2000b). Consistently, in rat alveolar macrophages Tau-Cl has been shown to inhibit production of TNF-α through the mechanism that involves reduction of IκB kinase activity, and stabilization of cytoplasmic IκB-α inhibitor with resulting inhibition of NFκB activation (Barua et al., 2001). Altogether these data suggest that Tau-Cl and other oxidizing chloramines may indeed interfere with signalling pathways that trigger transcription of cytokine genes. However, the interference of Tau-Cl with the post-transcriptional events (e.g. for TNF-α synthesis) could also be considered (Park et al., 1995). Finally, it seems that numerous signalling events whose combination result in the initiation of particular cytokine synthesis differ in their sensitivity to Tau-Cl. In this context, it is not surprising that different concentrations of Tau-Cl are required for effective inhibition of tested pro-inflammatory cytokine synthesis.

In summary, the results of present work suggest that Tau-Cl acts as an important immunoregulatory factor that tunes the synthesis of pro-inflammatory cytokines.

Acknowledgments

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