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Comparison of taurine chloramine and taurine bromamine effects on rheumatoid arthritis synoviocytes

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Summary. Fibroblast-like synoviocytes (FLS) participate in rheumatoid arthritis (RA) chronic synovitis by producing pro-inflammatory cytokines (IL-6, IL-8), growth factors (VEGF) and other inflammatory mediators (PGE_2, NO). We have previously reported that Tau-Cl, generated by neutrophils, inhibits in vitro some of these pathogenic RA FLS functions. Taurine bromamine (Tau-Br) originates from eosinophils and neutrophils, and its immunoregulatory activities are poorly known. Therefore, we investigated the effects of Tau-Br on RA FLS functions and compared it to Tau-Cl anti-inflammatory action. When applied at noncytotoxic concentrations: (i) Tau-Br inhibited IL-6 and PGE_2 production with potency similar to Tau-Cl ($IC_{50} \approx 250\,\mu M$), (ii) Tau-Br failed to affect VEGF and IL-8 synthesis, while Tau-Cl exerted inhibitory effect ($IC_{50} \approx 400\,\mu M$), (iii) none of these compounds affected NO generation and iNOS expression. Thus, Tau-Cl is more effective than Tau-Br in normalization of pro-inflammatory RA FLS functions.

Keywords: Taurine chloramine – Taurine bromamine – Inflammation – Rheumatoid arthritis – Synoviocytes

Introduction

Leukocyte-derived peroxidases, such as neutrophil/monocyte myeloperoxidase (MPO) and eosinophil peroxidase, use hydrogen peroxide and halides (Cl^- and Br^-) to generate halogeneting intermediates: hypochlorous (HOCl) and hypobromous (HOBr) acids, that are highly reactive but unstable oxidants with strong microbicidal and cytotoxic activities (Schuller-Levis and Park, 2004; van Dalen and Kettle, 2001). At physiologic pH, both hypohalous acids react with amino acids and amino groups of proteins, leading to formation of chloramines and bromamines (Marcinkiewicz, 1997; Thomas et al., 1995). The major stable products of these reactions are taurine chloramine (Tau-Cl) and taurine bromamine (Tau-Br), because taurine is the most abundant free β-amino acid in leukocyte cytosol and the derivatives of α-amino acids are unstable (Cramer et al., 1981; Kanofsky, 1989; Learn et al., 1990; Thomas et al., 1995). Accumulating evidence show Tau-Cl to be a powerful regulator of inflammation with predominating anti-inflammatory effects (Kontny et al., 2003a; Mainnemare et al., 2004; Marcinkiewicz, 1997; Schuller-Levis and Park, 2004), but little is known about immunoregulatory potential of Tau-Br. Our recent findings suggest Tau-Br to exert similar anti-inflammatory effects as Tau-Cl, at least in mouse macrophages (Marcinkiewicz et al., 2005; Olszanecki and Marcinkiewicz, 2004). To extend these studies, present investigations were undertaken to compare Tau-Cl and Tau-Br effects on rheumatoid fibroblast-like synoviocytes (FLS). Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that leads to progressive destruction of joint cartilage and bone with resulting disability. Fibroblast-like synoviocytes participate in RA hallmarks: chronic synovitis, synovial membrane hyperplasia and tissue destruction (Kontny et al., 2003a; Lee et al., 2005). Therapeutic approaches to normalise aggresive behaviour of these cells are not satisfactory. We have previously reported that Tau-Cl inhibits in vitro some pro-inflammatory activities of RA FLS (Kontny et al., 1999, 2000, 2003a, b, 2006b). In the present study the effects of Tau-Br and Tau-Cl on select pathogenic functions of RA FLS: (i) the production of pro-inflammatory cytokines (IL-6, IL-8), and vascular endothelial growth factor (VEGF), (ii) the generation of inflammatory mediators, prostaglandin E_2 (PGE_2) and nitric oxide (NO), as well as (iii) the expression of enzymes, relevant to PGE_2

and NO synthesis, i.e., cyclooxygenase 1 and 2 (COX-1, COX-2), and inducible nitric oxide synthase (iNOS), were compared.

Materials and methods

Patients, synovial samples, and synoviocyte cultures

Synovial tissues were obtained from the knee joints at the time of joint surgery, performed as a normal part of clinical care, from 32 patients (25F/7M), that fulfilled the American College of Rheumatology criteria for the diagnosis of RA stages III to IV (the means ± SEM of age and disease duration were 53 ± 2.3 and 11.5 ± 3.5, respectively). The study was approved by the local Ethics Committee. FLS were isolated and cultured as described previously (Kontny et al., 1999). Synoviocytes, obtained from different RA patients, were used for experiments between passages 3 and 6, showed fibroblast-like morphology, and 98.69 ± 0.035% of cells were positive for proline-4-hydroxylase, the fibroblast specific enzyme (Kontny et al., 2006b).

Cytokines, PGE_2 and NO determination

Recombinant human cytokines, IL-1β, IFN-γ and TNF-α (R & D Systems, Abingdon, UK), were used as the stimuli. Taurine bromamine, prepared as described previously (Olszanecki and Marcinkiewicz, 2004), and the sodium salt of N-chlorotaurine (Tau-Cl) (Gottardi and Nagl, 2002), were added to the cell cultures at physiologically relevant (50–300 μM and 200–500 μM, respectively) concentrations (Kim et al., 2006; Marcinkiewicz et al., 2005), together with the stimuli. The viability of cells was controlled by measurement of lactate dehydrogenase (LDH) activity in the culture supernatants, using LDH assay kit (Takara Shuzo Co, Otsu, Shiga, Japan). Concentrations of IL-6, IL-8 and VEGF were measured in the culture supernatants and cell lysates, collected after stimulation of the cells (4×10^4/ml) with 1 ng/ml IL-1β for 24 h or 48 h, respectively. Cell lysates were prepared as described previously (Chorazy et al., 2002). For determination of VEGF the DuoSet ELISA Development System (R & D Systems, Abingdon, UK) was applied, while ELISA specific for IL-6 and IL-8 were performed as previously described (Kontny et al., 1999). Concentration of PGE_2 was measured in the culture supernatants, after 24 h stimulation of the cells with 1 ng/ml IL-1β, using the competitive acetylcholinesterase enzyme immunoassay (PGE_2 EIA kit; Cayman Chemical, Ann Arbor, MI). To evaluate NO production, the culture supernatants were collected after 48 h treatment of the cells with cytokine mixture (1 ng/ml IL-1β, 10 ng/ml IFN-γ, 10 ng/ml TNF-α) and the concentration of total nitrite (NO_2^-) was measured, using the nitric oxide assay based on the Griess reaction (R & D Systems).

Analysis of COX and iNOS expression by Western blotting

Expression of COX isoforms and iNOS was analyzed by Western blotting after 24 and 48 h stimulation of the cells (4×10^5/10 ml) with either IL-1β or cytokine mixture, respectively. Total protein fraction was prepared as described previously (Kontny et al., 2006b). Samples containing 40 μg of protein were separated on 8% SDS-PAGE denaturating gel, transferred onto the PVDF membranes (Sigma, St. Louis, MO), and probed with monoclonal antibodies specific for human COX-1 or COX-2 isoenzymes (Cayman Chemical), iNOS (R&D Systems), or α-tubulin (Sigma). Detection was performed with peroxidase conjugated goat anti-mouse IgG and the chemiluminescence reagents (SuperSignal West Femto Maximum Sensitivity Substrate), both from Pierce Biotechnology, Rockford, IL.

Statistical analysis

The repeated-measures analysis of variance, followed by Tukey's test, was applied to evaluate the effect of the stimuli, Tau-Br and Tau-Cl. Results are expressed as the mean ± SEM. P values less than 0.05 were considered significant.

Results

Cytotoxicity of Tau-Cl and Tau-Br

During 24–48 h culture of the cells, neither Tau-Cl nor Tau-Br was cytotoxic when applied at 200–400 μM or 50–300 μM, respectively. However, at 500 μM concentration Tau-Cl exerted mild cytotoxicity (12.5 ± 3.1%), while Tau-Br affected cell viability more strongly and at 400 μM concentration triggered necrosis of 31.3 ± % cells. Cytokines, that were used as the stimuli, did not affect cell viability.

Effects of Tau-Br on pro-inflammatory cytokine production, PGE_2 secretion and COX expression

Unstimulated control cells produced little amount of IL-6, IL-8, and PGE_2 (191 ± 62 pg/ml), while upon stimulation with IL-1β production of both pro-inflammatory cytokines and PGE_2 (5797 ± 1274 pg/ml; $P = 0.0001$) rose significantly (Fig. 1A–C). Consistently, the expression of COX-2, weakly detectable in control FLS, was markedly up-regulated in IL-1β stimulated cells. By contrast, expression of COX-1 in RA FLS was constitutive and did not change upon cell treatment (Fig. 1D). Tau-Br did not affect IL-8 production but in a dose-dependent manner inhibited IL-1β-triggered production of IL-6, with the 50% inhibition concentration (IC_{50} value) ≈ 250 μM for both secreted and cell-asociated form of the cytokine. Similarly, Tau-Br significantly inhibited IL-1β-triggered PGE_2 production ($IC_{50} \approx 250$ μM), but had no effect on either COX-1 or COX-2 expression.

Effects of Tau-Cl and Tau-Br on VEGF production, NO generation, and iNOS expression

As shown in Fig. 2A, FLS produced VEGF spontaneously, but in the presence of IL-1β the concentration of both secreted and cell-associated form of VEGF was markedly elevated. Tau-Cl significantly and in a dose-dependent way inibited IL-1β-triggered production of VEGF with IC_{50} value ≈ 400 μM and 350 μM for secreted and cell-associated form of this growth factor, respectively. By contrast, Tau-Br did not affect VEGF production. On

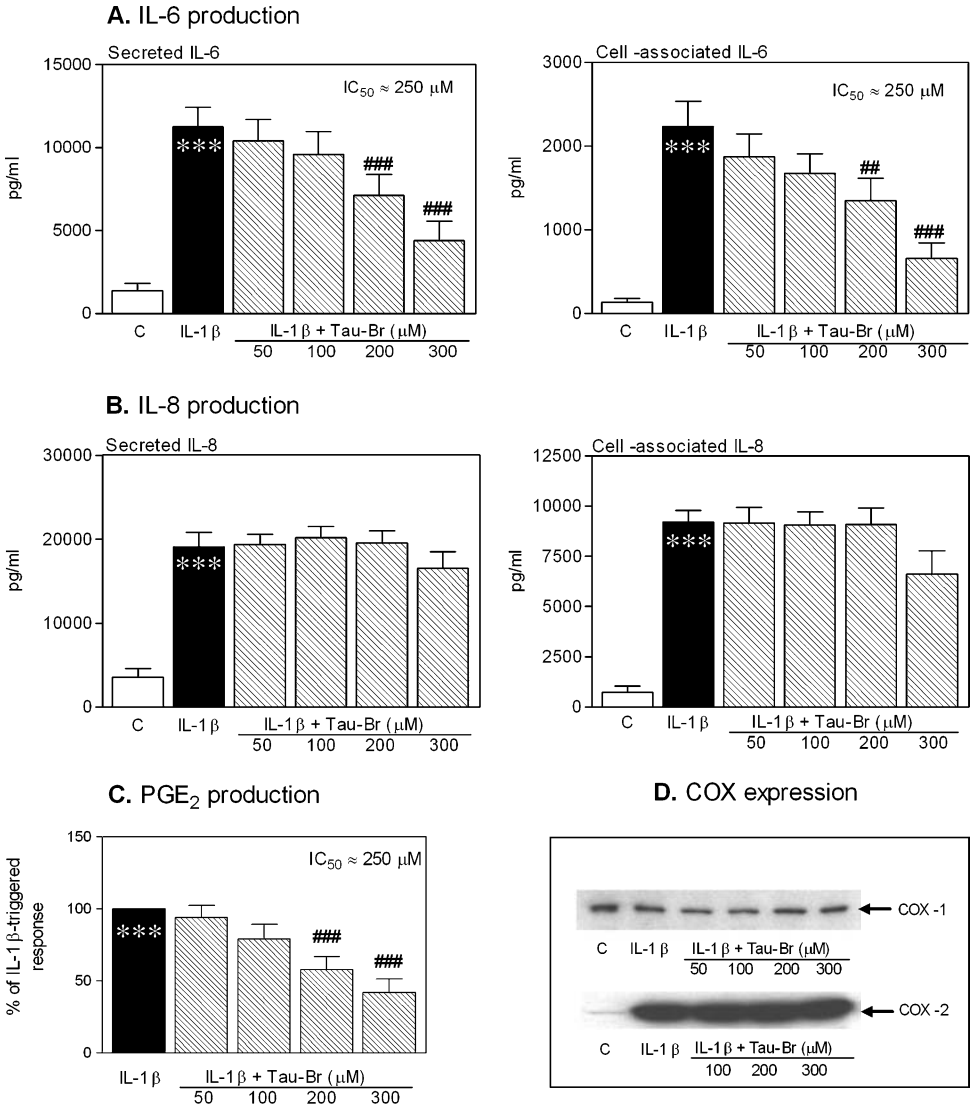

Fig. 1. Effects of Tau-Br on pro-inflammatory cytokine production, PGE_2 secretion and COX expression. Cells were cultured for 24 h in culture medium (control – *C*) or in medium supplemented with 1 ng/ml of IL-1β in the presence or absence of taurine bromamine (Tau-Br). Measurement of IL-6 (**A**), IL-8 (**B**) and PGE_2 (**C**) concentrations, as well as evaluation of COX isoenzymes expression were performed as described in Materials and methods. **A–C** Values are the mean and SEM of 10 experiments in which FLS from 10 different RA patients were used. The patients group was the same in **A** and **B**, while in **C** and **D** the other group of patients was included. $^{***}P = 0.001$–0.0001 for untreated versus IL-1β-stimulated cells. $^{\#\#}P = 0.01$–0.001 and $^{\#\#\#}P = 0.001$–0.0001 for IL-1β-stimulated versus IL-1β + Tau-Br-treated cells. IC_{50} – concentration of Tau-Br that causes 50% inhibition of IL-1β-triggered response. **D** Representative Western blot of 8 performed, showing COX-1 and COX-2 isoenzymes in the same protein samples

the contrary to pro-inflammatory cytokines and VEGF, spontaneous generation of NO by untreated control cells was high (532 ± 69 μM) and did not change upon stimulation of the cells with cytokine mixture alone or in the presence of Tau-Cl or Tau-Br (Fig. 2B). Consistently, the expression of iNOS was also similar in control, cytokine-stimulated and Tau-Cl- or Tau-Br-treated cells. Expression of α-tubulin, evaluated to verify equivalent protein contents in samples, did not differ between untreated and treated cells (Fig. 2C).

Discussion

Taurine chloramine exerts in vitro potent anti-inflammatory effects in many cell types (Kontny et al., 2003a; Mainnemare et al., 2004; Marcinkiewicz, 1997; Schuller-Levis and Park, 2004) and is protective in animal models of both acute and chronic inflammatory diseases (Kim et al., 2006; Kwasny-Krochin et al., 2002). Similarly, Tau-Br inhibits cytokine (TNF-α, IL-6, IL-10, IL-12p40) and NO production, as well as up-regulates the expression

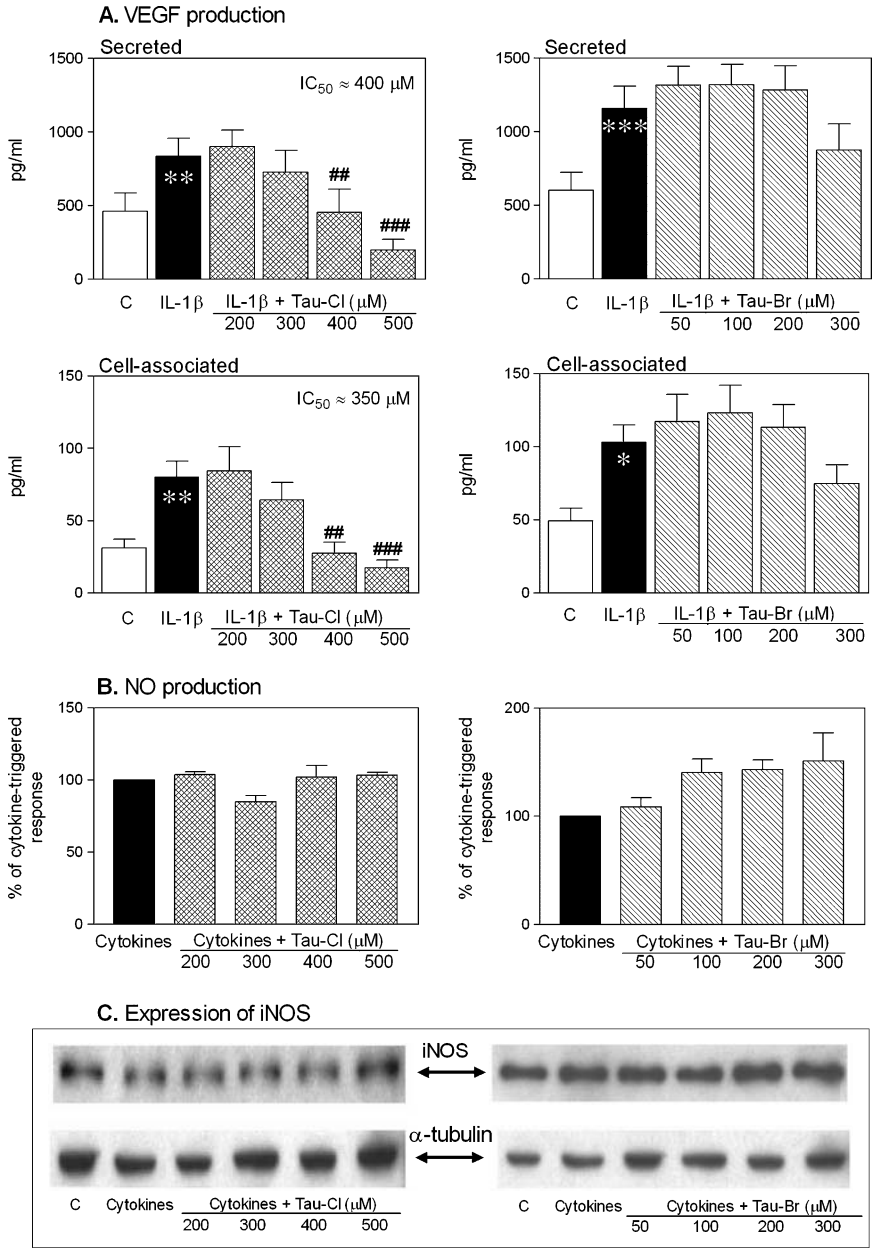

Fig. 2. Comparison of Tau-Cl and Tau-Br effects on VEGF production, NO generation, and iNOS expression. Cells were cultured for 48 h in culture medium (control – *C*) or in medium supplemented either with 1 ng/ml of IL-1β (**A**) or with cytokine mixture (1 ng/ml IL-1β, 10 ng/ml IFN-γ, 10 ng/ml TNF-α) (**B**), in the presence or absence of either taurine chloramine (Tau-Cl) or taurine bromamine (Tau-Br). Measurement of VEGF (**A**) and total (NO_2^-) concentrations (**B**), as well as evaluation of iNOS and α-tubulin expression (**C**) were performed as described in Materials and methods. Values (**A**, **B**) are the mean and SEM of 10–12 experiments in which FLS from different RA patients were used. The patients group in **B** and **C** was the same as in Fig. 1C and **D**, while in **A** the other group of patients was included. $^{*}P = 0.05$–0.01, $^{**}P = 0.01$–0.001 and $^{***}P = 0.001$–0.0001 for untreated versus IL-1β-stimulated cells. $^{\#\#}P = 0.01$–0.001 and $^{\#\#\#}P = 0.001$–0.0001 for IL-1β-stimulated versus IL-1β + Tau-Cl-treated cells. IC_{50} – concentration of Tau-Cl that causes 50% inhibition of IL-1β-triggered response. **C** Representative Western blot of 7 performed, showing iNOS (upper blot). To verify equivalent protein loading, the same membrane was reprobed with antibody specific for α-tubulin (lower blot)

of anti-inflammatory heme oxygenase-1 in mouse macrophages (Marcinkiewicz et al., 2005; Olszanecki and Marcinkiewicz, 2004). Thus, it is likely that conversion of inflammation from acute into chronic phase is facilitated by the impaired generation of these anti-inflammatory compounds by leukocytes. At physiologic plasma concentrations of halide (100 mM chloride >20–100 μM bromide), chloride and bromide are assumed to be the preferential substrates for neutrophil MPO and eosiophil peroxidase, respectively (Thomas et al., 1995). Despite

this, neutrophil MPO produces both chlorinating and brominating oxidants (Gaut et al., 2001; Thomas et al., 1995).

Chronic, self-perpetuating synovitis is the characteristic feature of RA. In the peripheral blood of RA patients both neutrophils and eosinophils show signs of activation (Torsteinsdottir et al., 1999). However, eosinophils are seemingly absent from inflamed synovium (Tetlow and Woolley, 1996), while neutrophils represent dominant subpopulation of cells ($20–25 \times 10^6$/ml) accumulating in synovial fluid (Davies et al., 1990). Thus, neutrophils are likely to be the major source of Tau-Cl and Tau-Br generated in rheumatoid joints. Fibroblast-like synoviocytes are located in the joint intimal lining of RA synovial membrane and are in a direct contact with synovial fluid, enriched in neutrophils. By producing numerous cytokines and mediators RA FLS participate in both: (i) joint inflammation (e.g. VEGF, IL-8 and IL-6 recruit immune cells; VEGF and IL-8 trigger angiogenesis; PGE_2 mediates vascular phase of inflammatory response; IL-6 supports growth and differentiation of lymphocytes, and participates in systemic symptoms), and (ii) tissue destruction process (e.g. PGE_2 stimulates osteoclastic bone resorption; NO promotes both cartilage degradation and bone resorption) (Lee et al., 2005; Lopez, 2003; Robinson, 2003). We have previously found that in RA FLS Tau-Cl inhibits synthesis of IL-6 ($IC_{50} \approx 250\,\mu M$), acting at the transcriptional level (Kontny et al., 2000). Present results show that Tau-Br exerts similar inhibitory effect, and likely acts through the same mechanism, because both secreted and cell-associated IL-6 concentrations were reduced by this compound with the same potency ($IC_{50} \approx 250\,\mu M$; Fig. 1A). Moreover, we have found Tau-Br to be as potent an inhibitor of PGE_2 generation ($IC_{50} \approx 250\,\mu M$; Fig. 1C) as Tau-Cl ($IC_{50} \approx 300\,\mu M$) (Kontny et al., 2003b). However, by contrast to selective down-regulation of COX-2 by Tau-Cl (Kontny et al., 2003b), present results failed to show any effect of Tau-Br on either COX-2 or COX-1 expression (Fig. 1D), suggesting different mechanisms of these compounds actions. Thus, it is possible that Tau-Br affects other events implicated in PGE_2 generation, e.g. the enzymatic activity of COX or PGE_2 stability, but further studies are required to resolve this question. Another difference between activity of tested compounds concerns their effects on IL-8 and VEGF production. According to our previous report, Tau-Cl inhibits IL-8 production by RA FLS with $IC_{50} \approx 450\,\mu M$ (Kontny et al., 2000). Present results reveal similar potency of Tau-Cl to inhibit VEGF synthesis ($IC_{50} \approx 350\,\mu M$ and $\approx 400\,\mu M$ for cell-associated and secreted VEGF, respectively; Fig. 2A). On the contrary, Tau-Br was without any significant effect on these FLS responses (Fig. 1B and 2A). The above differences may result from higher sensitivity of RA FLS to Tau-Br than Tau-Cl cytotoxicity (Kontny et al., 2006a). Surprisingly, Tau-Cl and Tau-Br failed to affect NO formation (Fig. 2B), suggesting both compounds to be ineffective in protection of RA joint from NO-mediated destruction. This is in contrast to inhibitory effects on NO synthesis stated in another cell types (Olszanecki and Marcinkiewicz, 2004; Quinn et al., 2003a, b; Serban et al., 2003). Supposedly, the atypical metabolism of RA FLS contributes to this, because RA FLS generated spontaneously a large amount of NO, and addition of known NO inducers (IL-1β + TNF-α + IFN-γ) (Grabowski et al., 1996; Quinn et al., 2003a, b) did not raise the cell response further (see Results). Moreover, Tau-Cl exerts weaker inhibitory effect on spontaneous than stimulated RA FLS responses (Kontny et al., 1999).

In summary, by showing Tau-Cl inhibition of VEGF production by RA FLS, the present results add more information concerning the anti-inflammatory effects of this compound, related to RA pathology. We also report for the first time that although Tau-Cl and Tau-Br reduce IL-6 and PGE_2 production with similar potency, Tau-Br is less effective in normalisation of other pro-inflammatory RA FLS functions (IL-8 and VEGF production), while none of tested compound affect generation of NO.

Since in vitro Tau-Cl potently inhibits pathogenic functions of RA FLS (Kontny et al., 2003a, 2006b), and in vivo gives protection in collagen-induced arthritis (Kwasny-Krochin et al., 2002), we suggest that supplementation of Tau-Cl may represent a new supportive therapeutic approach in RA. Interestingly, taurine supplementation, accompanied by local formation of Tau-Cl in mM concentration range, has recently been show to ameliorate TNBS-induced colitis in rats (Kim et al., 2006). By contrast to this animal model, it is likely that in RA supplementation of taurine would be less effective than Tau-Cl, because for synovial fluid neutrophils both reduced basal activity of enzymes critical for Tau-Cl synthesis (MPO and NADPH-oxidase) (Davies et al., 1990; Nurcombe et al., 1991), and impaired capability to generate Tau-Cl in vitro (Kontny et al., 2002) is characteristic. These functional defects of neutrophils suggest diminished production of Tau-Cl in rheumatoid joints that is probably to low to inhibit inflammatory response. However, this suggestion needs further studies because the actual concentrations of Tau-Cl in affected rheumatoid tissues are so far unknown.

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