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Which mechanisms are involved in taurine-dependent granulocytic immune response or amino- and α-keto acid homeostasis?

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Summary. We examined the effects of β-alanine (taurine analogue and taurine transport antagonist), taurine (regarding its role in neutrophil (PMN) immunonutrition) and taurine combined either with L-NAME (inhibitor of •NO-synthase), SNAP (•NO donor), DON (glutamine-analogue and inhibitor of glutamine-requiring enzymes), DFMO (inhibitor of ornithine-decarboxylase) and β-alanine on neutrophil amino- and α-keto acid profiles or important PMN immune functions in order to establish whether taurine transport-, nitric oxide-, glutamine- or ornithine-dependent mechanisms are involved in any of the taurine-induced effects. According to the present findings, the taurine-mediated effect appears to be based primarily on a modulation of important transmembraneous transport mechanisms and only secondarily on directly or indirectly induced modifications in intragranulocytic amino- and α-keto acid homoeostasis or metabolism. Although a direct relation to the parallel observed immunological modifications can only be presumed, these results show very clearly that compositional modifications in the free intragranulocytic amino- and α keto-acid pools coinciding with changes in intragranulocytic taurine levels are relevant metabolic determinants that can significantly influence the magnitude and quality of the granulocytic immune response.

Keywords: Taurine – β-alanine – DON – L-NAME – SNAP – DFMO – Neutrophils (PMN) – Amino acids – α-keto acids – Immune function

Introduction

Although Tiedemann and Gmelin in 1827 already isolated taurine from bovine bile by boiling in water, and in fact the word taurine is etymologically derived from the Latin ''Fel tauri'' meaning ''bull's bile'', this amino acid, which occurs almost ubiquitously in the animal kingdom, was initially assumed to be a metabolically neutral and inert ''cellular waste product'' without any special function (Bender, 1985; Bidri and Choay, 2003; Stapleton et al., 1997, 1998a). This view did indeed persist for decades until interest was reawoken over the last few years. This change in scientific attitude was helped by studies on leukocytes, although these findings have only been poorly researched up until now (Aruoma et al., 1988; Brosnan and Brosnan, 2006; Grimble, 2006; Gupta et al., 2005; Mühling et al., 2002a, b, 2005a; Schuller-Levis and Park, 2004; Singh et al., 2002; Stapleton et al., 1998a). Interestingly, taurine is the most abundant amino acid in leukocytes and the taurine content in neutrophils (PMN), especially, is about 60% of the total amount of free intragranulocytic amino acids (Fürst et al., 1987; Fürst, 2000; Mühling et al., 1999, 2002a, b; Learn et al., 1990). Moreover, these high taurine concentrations are also maintained against a high extra- versus intracellular gradient even with declining extracellular taurine levels, e.g. when consuming taurine-depleted diets (Banks et al., 1989; Laidlaw et al., 1987; Redmond et al., 1998; Stapleton et al., 1998a; Vinton et al., 1986; Wakayama et al., 1983; Zhang et al., 2004). This remarkable and amazing finding for immunoactive cells, was very quickly brought into association with the specific functions of these cells, also

because taurine does not appear to be involved in any of the major metabolic pathways (e.g. the citrate and urea cycles, protein biosynthesis, oxidative phosphorylation) (Bidri and Choay, 2003; Redmond et al., 1998; Schaffer et al., 2003; Schuller-Levis and Park, 2004; Stapleton et al., 1998a; Vinton et al., 1986; Wakayama et al., 1983; Zhang et al., 2004). The most recent findings allow us to presume that this amino acid is not so much a metabolic substrate for cellular energy generation or a ''building block supplier'' for essential cellular components (proteins, purines, pyrimidines), but is much more an immunoregulatory as well as an immune function maintaining agent. To this end taurine seems to possess significant membrane stabilizing, osmoregulatory and antidote-like properties (Albrecht and Schousboe, 2005; Bajnath et al., 1997; Ballatori et al., 1994; Cuisnier et al., 2002; Hoffmann and Dunham, 1995; Jesus et al., 1991; Passantes-Morales et al., 2000; Porter and Martin, 1992; Saransaari and Oja, 1998; Schaffer et al., 2000, 2003; Shimizu and Satsu, 2000; Tappaz, 2004; Yancey, 2005). Indeed, changes in the intracellular taurine pool and reductions in the intracellular taurine stocks, especially, are of great pathophysiological interest as recent studies have shown, since in almost all cases this is associated with catabolic and inflammatory events. Of special importance is the hypothesis that for different body cells (particularly ROS-secreting cells) and also the extragranulocytic matrix, taurine might represent a kind of protective factor by acting as a potent ''radical and substrate scavenger'' that protects cellular building blocks or metabolic products, secretory and degranulation products from malignant attack by reactive oxygen species produced to annihilate pathogenic agents (Atmaca, 2004; Cetiner et al., 2005; Chorazy-Massalska et al., 2004; Condron et al., 2004; Emerson et al., 2005; Farriol et al., 2002; Ito and Azuma, 2004; Kim et al., 1996; Klamt and Shacter, 2005; Marcinkiewicsz et al., 1998; McLoughlin et al., 1991; Mühling et al., 2002a, b; Neary et al., 1997; Park et al., 1998; Schuller-Levis et al., 1995; Thomas et al., 1985). Moreover, although the underlying mechanisms still remain unclear, current results suggest that nitric oxide-, polyamine- or glutamine-dependent pathways seems to be involved in the signal transmission of free radical molecule-, beneficial nutritional therapy- or maleficient pharmacological stress-induced alterations in leukocyte amino and α-keto acid homeostasis and immune response (Blaise et al., 2005; Bronte and Zanovello, 2005; Bruckdorfer, 2005; Cirino et al., 2006; Crawford and Guo, 2005; Garcia and Stein, 2006; Hauk and Hosey, 2006; Korhonen et al., 2005; Luiking et al., 2005; Mühling et al., 2006a, b; Thippeswamy et al., 2006). However, possible relationships with taurine-dependent cellular metabolical or bactericidal functions, especially, have not yet been adequately defined until now. Therefore, in our opinion further research is necessary here in order to determine the precise metabolic and metabolic-regulatory properties of taurine (and hypotaurine) as well as the metabolic functions associated with them, particularly considering their potential therapeutic application (so-called ''immunonutrition''). Concerning the intriguing question whether important PMN antibacterial host defence mechanisms can therapeutically be altered to the benefit of the individual the major goals of our studies were therefore:

1. To document the effects of *β-alanine* [β-Ala] on PMN free intracellular amino- and α-keto acid concentrations as well as on the activities of released myeloperoxidase (MPO) and the formation of superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) (as markers of PMN function and in order to show possible parallels with changes in PMN amino- and α-keto acid homeostasis).
2. To explore the effects of *taurine* (regarding its role in PMN immunonutrition) combined either with *β-alanine* [β-Ala; analogue of taurine and taurine transport antagonist], *N_ω-nitro-L-arginine-methylester-hydrochloride* [L-NAME, inhibitor of •NO-synthase], *S-nitroso-N-acetyl-penicillamine* [SNAP, •NO donor], *6-diazo-5-oxo-L-norleucine* [DON, analogue of glutamine and inhibitor of glutamine-requiring enzymes] and *α-difluoro-methyl-ornithine* [DFMO, inhibitor of ornithine-decarboxylase] on PMN amino- and α-keto acid concentrations or important PMN immune functions [MPO, O_2^- and H_2O_2] in order to establish whether taurine transport-, nitric oxide-, glutamine- or ornithine-dependent mechanisms are involved in any of the taurine-induced effects.

Materials and methods

Subjects

The study was approved by the local ethics committee of the University Hospital Giessen and Marburg. Ten men (28 ± 5 years) with an average height of 178.0 cm (±8 cm) and weight of 74.3 kg (±8 kg) were selected: males with metabolic (diabetes, etc.), cardiopulmonary, neurological or allergic diseases or men taking drugs were excluded.

Sample preparation

Whole blood samples (lithium-heparinate plastic tubes) were withdrawn between 08:00 and 09:00 (after 10 h of fasting) taking circadian variation into account.

The following concentrations were tested in addition to a control for each substance:

1. *β-alanine* (10 mM) [a taurine-analogue and taurine transport antagonist; Sigma, Deisenhofen, Germany]
2. *Taurine (tau) combined with L-NAME, SNAP, DON, β-Ala or DFMO*
   2.1 *Tau* (1 mM; tau)
   2.2 *Tau* (1 mM) + *L-NAME* (1 mM)
   2.3 *Tau* (1 mM) + *SNAP* (100 μM)
   2.4 *Tau* (1 mM) + *DON* (100 μM)
   2.5 *Tau* (1 mM) + *β-Ala* (10 mM)
   2.6 *Tau* (1 mM) + *DFMO* (1 mM)

[*Taurine* (tau): Sigma, Deisenhofen, Germany; *L-NAME*: N_ω-nitro-L-arginine-methylester-hydrochloride; inhibitor of nitric oxide (•NO) synthase; Calbiochem, Bad Schwalbach, Germany; *SNAP*: S-nitroso-N-acetyl-penicillamine; exogenous nitric oxide donor (•NO-release: 5.6 μM/min); Sigma, Deisenhofen, Germany; *β-Ala*: β-alanine; analogue of taurine and taurine transport antagonist; Sigma, Deisenhofen, Germany; *DFMO*: α-difluoro-methyl-ornithine; irreversible inhibitor of ornithine decarboxylase; Sigma, Deisenhofen, Germany]

PMN were incubated with β-alanine for 10, 60 or 120 min to test if there was a critical duration of exposure necessary to produce any significant effects or for 120 min with taurine or taurine combined with L-NAME, SNAP, DON, β-Ala or DFMO (see Mühling et al., 2006a, b for single effects of L-NAME, SNAP, DON, DFMO on neutrophil amino- and α-keto acid profiles or important PMN immune functions). The final concentrations selected corresponded, consistently with previous work, to those used in our own preliminary studies (not published). Solutions were prepared and diluted in Hank's balanced salt solution (HBSS; Sigma, Deisenhofen, Germany), and the pH in the test solution was confirmed as 7.4. One millilitre of whole blood was incubated with 25 μl of test solution (final ornithine concentrations were as described above) at 37 °C using a shaking water bath. Corresponding volumes of HBSS were added to the control tubes. Before further processing, all fractions were immediately cooled in an ice water bath at 4 °C and 100 μg/ml phenyl methyl sulphonyl fluoride (PMSF), 10 μg/ml leupeptin, 10 μg/ml pepstatin, as well as 10 μg/ml antipain (all acquired from Sigma, USA) were added to each plastic heparin tube before the blood samples; these additions served to inhibit proteases (Mühling et al., 1999, 2003).

Highly selective separation of PMN from whole blood

Precise details of our PMN-separation technique have been described previously (Mühling et al., 1999, 2003). This method is a further development of the methods described by Krumholz et al. (1993, 1995a, b) that allows a very rapid and selective enrichment of neutrophils while preserving high cellular viability and integrity from very small quantities of whole blood.

Chromatographic amino and α-keto acid analysis

Amino acids and α-keto acids in PMN were quantified using previously described methods which fulfilled the strict criteria required for ultrasensitive, comprehensive amino acid and α-keto acid analysis, specially developed and precisely validated in our institute for this purpose. Moreover, the coefficients of variations for both the method reproducibility and reproducibilities of the retention times were also within normal ranges (for details see Mühling et al., 1999, 2003). PMN amino acid concentrations are given in 10^{-16} moles per neutrophil-cell, PMN α-keto acid concentrations are given in 10^{-17} moles per neutrophil-cell.

Determination of O_2^-, H_2O_2, and MPO

Superoxide anion (O_2^-), hydrogen peroxide production (H_2O_2) and the activity of released myeloperoxidase (MPO) were determined photometrically using modifications of known methods validated in our institute for this purpose (for further details see Krumholz et al., 1993, 1995a, b; Mühling et al., 2002a, b; Rick, 1977).

Statistical analysis

Statistical analysis and interpretation of the results were performed in close co-operation with colleagues from the Department of Medical Statistics, Justus Liebig University Giessen. All tests were performed in duplicate. Thus our PMN amino acid results represent the mean of two estimations. After the results were demonstrated to be normally distributed (Pearson-Stephens test), statistical methods were performed including Bartlett's test to check homogeneity of variance ($p \leq 0.1$). If the requirements were met, ANOVA analysis was conducted. If the requirements were not fulfilled, the Friedmann test was performed. Probability levels of $p \leq 0.05$ versus control were considered as significant. The data are given as arithmetic means ± standard deviations (mean ± SD).

Results

The free intracellular amino- and α-keto acid concentrations, superoxide anion and hydrogen peroxide generation rates and the activities of released myeloperoxidase obtained in the control cells were within normal physiological ranges (see Mühling et al., 1999, 2002a, b, 2003, 2005a, b; Krumholz et al., 1993, 1995a, b).

Effects of β-alanine on PMN amino and α-keto acid pools or immune functions

The taurine analogue β-alanine induced significant incubation time-dependent (≥60 min) changes in the levels of granulocytic taurine and hypotaurine (see Table 1). In parallel there was also a clear increase in free amino-acid pools of neutral amino acids. β-alanine also induced a significant increase in intragranulocytic pyruvate as well as α-ketobutyrate that is metabolically related to threonine. β-alanine also induced an increase in reactive oxygen metabolites and a significant reduction in myeloperoxidase activity.

Effects of taurine on PMN amino and α-keto acid pools or immune functions

Taurine led to significant alterations of the following amino acids in PMN: taurine, hypotaurine, serine, glycine, threonine, alanine and α-aminobutyrate. Together with the intracellular increase in taurine a parallel reduction in hypotaurine and neutral amino acids could also be observed (see Tables 2, 3; Fig. 1). The reduction in molar content of these amino acids induced by taurine incubation compensated, however, for the intragranulocytic taurine increase only by approximately a third. Taurine led to significant dose and incubation time-dependent reductions in intragranulocytic pyruvate and α-ketobutyrate levels and induced significant reductions in superoxide anion

Table 1. Effects of *β-alanine* [β-Ala; 10 mM] incubated with whole blood on free intracellular *taurine* [tau], *hypotaurine* [h-tau], *neutral amino acid* (10, 60 and 120 min; 10^{-16} moles per PMN-cell; mean ± SD; $n = 10$), *pyruvate* [PYR] and *α-ketobutyrate* [KB] (10 and 120 min; 10^{-17} moles per PMN-cell; mean ± SD; $n = 10$) concentrations in PMN and on PMN superoxide anion generation [fMol O_2^-/(PMN × min)], hydrogen peroxide production [fMol H_2O_2/(PMN × min)] and on PMN myeloperoxidase activity ([Units/l supernatant]; 10, 60 and 120 min; mean ± SD; $n = 10$)

	Control	*β-alanine*		*Control*	*β-alanine*
10 min					
tau	41.0 ± 7.8	37.4 ± 7.2	*ser*	2.29 ± 0.45	2.51 ± 0.50
h-tau	1.54 ± 0.34	1.48 ± 0.32	*gly*	2.39 ± 0.50	2.64 ± 0.55
ala	1.80 ± 0.36	1.96 ± 0.48	*thr*	0.73 ± 0.12	0.80 ± 0.13
aba	0.28 ± 0.05	0.28 ± 0.05			
PYR	5.96 ± 1.19	6.43 ± 1.62	α-KB	4.20 ± 0.89	4.73 ± 1.17
O_2^-	3.536 ± 0.551	3.856 ± 0.662			
H_2O_2	1.324 ± 0.225	1.441 ± 0.257	MPO	0.685 ± 0.175	0.636 ± 0.172
60 min					
tau	40.3 ± 7.4	29.0 ± 5.7*,#	*ser*	2.19 ± 0.43	3.76 ± 0.73*,#
h-tau	1.30 ± 0.32	0.99 ± 0.24*,#	*gly*	2.30 ± 0.49	3.83 ± 0.79*,#
ala	1.79 ± 0.32	2.47 ± 0.60*	*thr*	0.69 ± 0.11	1.01 ± 0.22*
aba	0.26 ± 0.04	0.34 ± 0.06*			
O_2^-	3.461 ± 0.538	4.323 ± 0.767*			
H_2O_2	1.239 ± 0.219	1.586 ± 0.303*	MPO	0.646 ± 0.161	0.495 ± 0.149
120 min					
tau	39.8 ± 7.2	24.7 ± 5.1*,#	*ser*	2.08 ± 0.41	3.94 ± 0.83*,#
h-tau	1.39 ± 0.21	0.79 ± 0.20*,#	*gly*	2.32 ± 0.47	4.69 ± 1.11*,#
ala	1.98 ± 0.32	2.69 ± 0.57*,#	*thr*	0.66 ± 0.10	1.30 ± 0.30*,#
aba	0.26 ± 0.05	0.41 ± 0.07*,#			
PYR	5.76 ± 1.03	7.08 ± 1.35*	α-KB	4.39 ± 0.86	5.67 ± 1.20*
O_2^-	3.317 ± 0.528	4.891 ± 0.998*,#			
H_2O_2	1.154 ± 0.195	1.869 ± 0.358*,#	MPO	0.605 ± 0.153	0.437 ± 0.124*,#

*$p \leq 0.05$ versus control values; #$p \leq 0.05$ versus 10 min

Table 2. Effects of *taurine* (tau; 5 mM) incubated with whole blood for 120 min combined either with *N_ω-nitro-L-arginine-methylester-hydrochloride* [L-NAME (1 mM)], *S-nitroso-N-acetyl-penicillamine* [SNAP (100 μM)], *6-Diazo-5-oxo-L-norleucine* [DON (100 μM)], *β-alanine* [β-Ala (10 mM)] or *α-difluoro-methyl-ornithine* [DFMO (1 mM)] on free intracellular *amino acid* concentrations (10^{-16} moles per PMN-cell; mean ± SD; $n = 10$)

	Control	*tau*	*tau + L-NAME*	*tau + SNAP*	*tau + DON*	*tau + β-Ala*	*tau + DFMO*
PMN amino acids							
asn	0.41 ± 0.08	0.38 ± 0.06	0.43 ± 0.07	0.30 ± 0.06*,#	0.24 ± 0.04*,#	0.39 ± 0.07	0.35 ± 0.06*
gln	3.14 ± 0.63	3.05 ± 0.62	3.20 ± 0.68	2.32 ± 0.49*,#	1.73 ± 0.36*,#	3.02 ± 0.61	2.40 ± 0.51*,#
asp	3.01 ± 0.52	3.09 ± 0.55	3.19 ± 0.55	2.11 ± 0.38*,#	1.46 ± 0.32*,#	2.98 ± 0.50	2.38 ± 0.43*,#
glu	6.29 ± 0.96	6.49 ± 1.03	6.55 ± 1.09	4.33 ± 0.69*,#	3.37 ± 0.58*,#	6.32 ± 1.01	5.05 ± 0.80*,#
orn	0.49 ± 0.08	0.48 ± 0.10	0.46 ± 0.09	0.39 ± 0.08*,#	0.28 ± 0.06*,#	0.50 ± 0.11	0.74 ± 0.14*,#
lys	0.65 ± 0.12	0.67 ± 0.12	0.62 ± 0.11	0.58 ± 0.11	0.72 ± 0.14	0.59 ± 0.10	0.70 ± 0.15
arg	0.33 ± 0.05	0.30 ± 0.06	0.34 ± 0.08	0.25 ± 0.05*,#	0.17 ± 0.04*,#	0.35 ± 0.07	0.41 ± 0.08*,#
cit	0.12 ± 0.02	0.12 ± 0.02	0.13 ± 0.03	0.10 ± 0.02*,#	0.08 ± 0.02*,#	0.11 ± 0.02	0.16 ± 0.04*,#
ile	0.56 ± 0.08	0.49 ± 0.07	0.48 ± 0.07	0.75 ± 0.14*,#	1.03 ± 0.22*,#	0.52 ± 0.08	0.66 ± 0.10*,#
leu	0.90 ± 0.15	0.81 ± 0.14	0.76 ± 0.13	1.24 ± 0.23*,#	1.77 ± 0.41*,#	0.84 ± 0.14	1.10 ± 0.16*,#
val	0.51 ± 0.09	0.44 ± 0.08	0.42 ± 0.08	0.74 ± 0.15*,#	0.96 ± 0.18*,#	0.46 ± 0.08	0.65 ± 0.14*,#
met	0.23 ± 0.04	0.24 ± 0.04	0.19 ± 0.04	0.27 ± 0.05	0.26 ± 0.05	0.23 ± 0.04	0.24 ± 0.05
tau	41.0 ± 7.1	50.9 ± 7.8*	52.6 ± 9.9*	43.1 ± 7.3#	39.3 ± 8.3#	34.0 ± 6.7*,#	46.8 ± 8.7
h-tau	1.86 ± 0.32	1.08 ± 0.17*	1.19 ± 0.23*	0.94 ± 0.25*,#	0.47 ± 0.13*,#	0.69 ± 0.17*,#	1.43 ± 0.32*,#
ser	2.01 ± 0.51	1.10 ± 0.19*	1.04 ± 0.20*	0.86 ± 0.20*,#	0.65 ± 0.16*,#	3.03 ± 0.47*,#	0.99 ± 0.23*
gly	2.34 ± 0.39	1.37 ± 0.23*	1.30 ± 0.29*	1.05 ± 0.24*,#	0.80 ± 0.17*,#	3.29 ± 0.54*,#	1.18 ± 0.33*
thr	0.76 ± 0.11	0.48 ± 0.09*	0.44 ± 0.08*	0.37 ± 0.08*,#	0.28 ± 0.05*,#	1.01 ± 0.25*,#	0.45 ± 0.08*
ala	1.96 ± 0.36	1.19 ± 0.26*	1.20 ± 0.33*	0.98 ± 0.23*	0.79 ± 0.22*,#	2.46 ± 0.40*,#	1.41 ± 0.26*
aba	0.27 ± 0.05	0.14 ± 0.02*	0.16 ± 0.04*	0.14 ± 0.03*	0.12 ± 0.02*,#	0.33 ± 0.06*,#	0.20 ± 0.05*,#

*$p \leq 0.05$ versus control values; #$p \leq 0.05$ versus 10 min

Table 3. Effects of *taurine* (tau; 5 mM) incubated with whole blood for 120 min combined either with *N_ω-nitro-L-arginine-methylester-hydrochloride* [L-NAME (1 mM)], *S-nitroso-N-acetyl-penicillamine* [SNAP (100 μM)], *6-Diazo-5-oxo-L-norleucine* [DON; 100 μM], *β-alanine* [β-Ala; 10 mM] or *α-difluoro-methyl-ornithine* [DFMO; 1 mM] on free intracellular *α-keto acid* concentrations [α-ketoglutarate (KG), pyruvate (PYR), α-ketobutyrate (KB), α-ketoisovalerianate (KIV), α-ketoisocapronate (KIC), p-hydroxy-phenylpyruvate (PPY) and α-keto-β-methylvalerianate (KMV); 10^{-17} moles per PMN-cell; mean ± SD; $n = 10$] in PMN

	Control	*tau*	*tau + L-NAME*	*tau + SNAP*	*tau + DON*	*tau + β-Ala*	*tau + DFMO*
PMN α-keto acids							
KG	1.14 ± 0.18	1.28 ± 0.32	1.09 ± 0.21	0.67 ± 0.18$^{*,\#}$	0.48 ± 0.13$^{*,\#}$	1.20 ± 0.29	0.88 ± 0.19$^{*,\#}$
PYR	5.73 ± 1.01	3.93 ± 0.76*	3.64 ± 0.84*	3.09 ± 0.72$^{*,\#}$	2.23 ± 0.63$^{*,\#}$	7.86 ± 2.09$^{*,\#}$	3.38 ± 0.89*
KB	3.91 ± 0.55	2.78 ± 0.51*	2.49 ± 0.62*	2.30 ± 0.45$^{*,\#}$	1.32 ± 0.38$^{*,\#}$	5.34 ± 1.37$^{*,\#}$	2.59 ± 0.46*
KIV	2.02 ± 0.37	1.95 ± 0.40	1.85 ± 0.50	1.24 ± 0.22$^{*,\#}$	0.90 ± 0.23$^{*,\#}$	2.50 ± 0.71	1.54 ± 0.31$^{*,\#}$
KIC	0.35 ± 0.05	0.34 ± 0.06	0.32 ± 0.07	0.23 ± 0.05$^{*,\#}$	0.16 ± 0.04$^{*,\#}$	0.36 ± 0.07	0.28 ± 0.05$^{*,\#}$
PPY	0.30 ± 0.06	0.29 ± 0.06	0.29 ± 0.06	0.22 ± 0.05$^{*,\#}$	0.15 ± 0.04$^{*,\#}$	0.35 ± 0.08	0.28 ± 0.05
KMV	0.74 ± 0.11	0.78 ± 0.14	0.70 ± 0.17	0.51 ± 0.12$^{*,\#}$	0.35 ± 0.09$^{*,\#}$	0.97 ± 0.28	0.64 ± 0.12$^{*,\#}$

$^{*}p \leq 0.05$ versus control values; $^{\#}p \leq 0.05$ versus 10 min

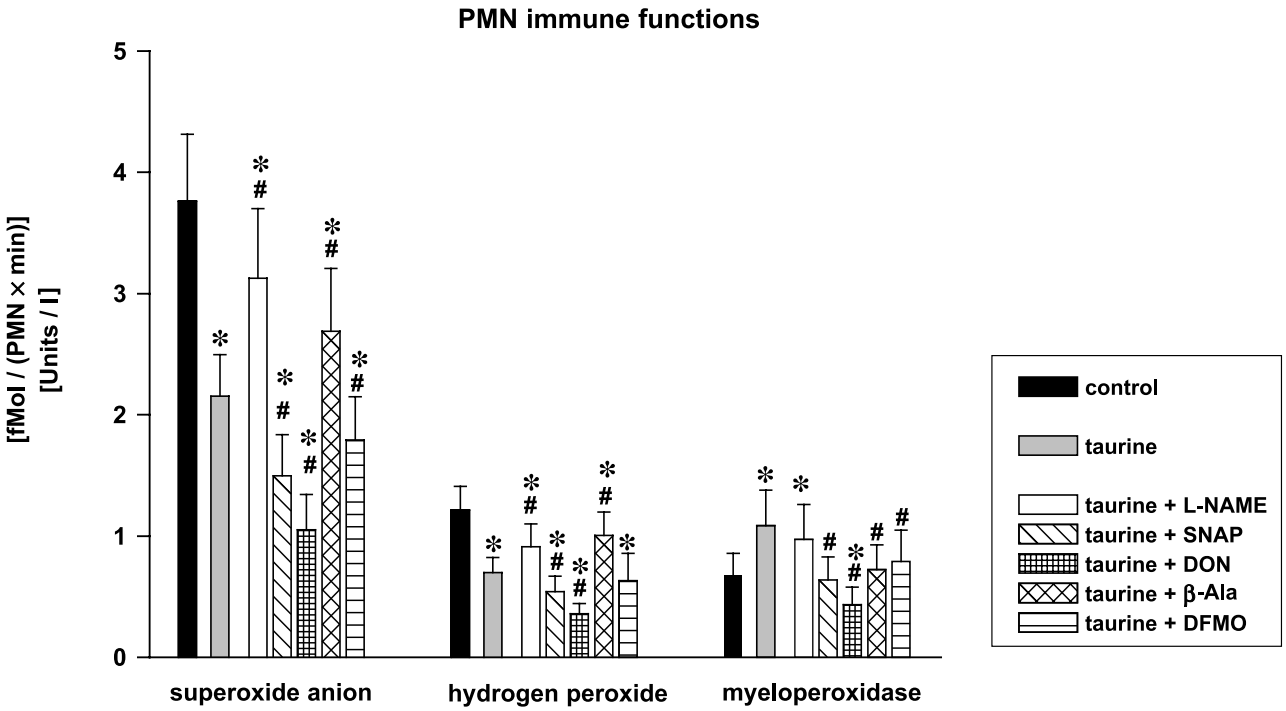

Fig. 1. Effects of *taurine* (tau; 5 mM) incubated with whole blood for 120 min combined either with *N_ω-nitro-L-arginine-methylester-hydrochloride* [L-NAME (1 mM)], *S-nitroso-N-acetyl-penicillamine* [SNAP (100 μM)], *6-Diazo-5-oxo-L-norleucine* [DON; 100 μM], *β-alanine* [β-Ala; 10 mM] or *α-difluoro-methyl-ornithine* [DFMO; 1 mM] on PMN superoxide anion generation [fMol O_2^-/(PMN × min)], hydrogen peroxide production [fMol H_2O_2/(PMN × min)] and on PMN myeloperoxidase activity (Units/l supernatant). $^{*}p \leq 0.05$ versus control values; $^{\#}p \leq 0.05$ versus 10 min [mean ± SD; $n = 10$]

and hydrogen peroxide production. In parallel, it also brought about an increase in myeloperoxidase activity.

Effects of taurine combined either with L-NAME, SNAP, DON, β-Ala or DFMO on the free amino acid pools in PMN

The combined administration of taurine with L-NAME (for single effects of L-NAME, SNAP, DON, DFMO on neutrophil amino acid profiles please see Mühling et al., 2006a, b), compared with taurine administration alone, did not produce any additional changes. However, the application of taurine and SNAP and in particular the combination of taurine with DON induced very clear changes in amino acids (see Table 2). Here there were significant antagonizing or additive findings only with regard to the intracellular taurine, hypotaurine as well as the neutral amino acid levels. Concerning the acidic

amino acids, their acidic amides, the basic and branched-chain amino acids, SNAP and DON induced effects that usually corresponded to those of single application of SNAP or DON regarding their magnitude. β-alanine combined with taurine, however, significantly influenced intragranulocytic amino acid levels: there were additive effects with regard to hypotaurine concentrations and antagonizing effects regarding the taurine and neutral amino acid levels. Taurine combined with DFMO led with the acidic amino acids as well as their acidic amides to purely DFMO-dependent effects. Taurine itself exerted no influence on the cellular content of these amino acids. These results were also found with the basic and branched-chain amino acids. An effect corresponding to an inhibition of taurine's effects was only observed with the free hypotaurine and α-aminobutyrate pools.

Effects of taurine combined either with L-NAME, SNAP, DON, β-Ala or DFMO on the free α-keto acid pools in PMN

Taurine combined with L-NAME, SNAP, DON, β-alanine or DFMO (for single effects of L-NAME, SNAP, DON, DFMO on neutrophil α-keto acid profiles please see Mühling et al., 2006a, b) led to the following important effects: L-NAME led to no effects exceeding those of single taurine administration. Combined with SNAP and DON, further significant reductions in pyruvate and α-ketobutyrate were shown. Furthermore SNAP and DON, consistently with SNAP and DON single incubation, led to clear alterations in all the α-keto-acids studied here. Although a combination of taurine with DFMO led to no additional modifications in pyruvate and α-ketobutyrate, it did lead to changes in intracellular α-ketoglutarate, α-ketoisovalerianate, α-ketoisocapronate as well as α-keto-β-methylvalerianate levels in the same way as single DFMO application. On the other hand combination of β-alanine and taurine led to a complete cancellation of the taurine effects with increases in the pyruvate and α-ketobutyrate pools above control levels (see Table 3).

Effects of taurine combined either with L-NAME, SNAP, DON, β-Ala or DFMO on PMN oxidative response and myeloperoxidase activity

Single effects using L-NAME, SNAP, DON, DFMO on important neutrophil immune functions have previously been described (for details please see Mühling et al., 2006a, b). With regard to the observed superoxide anion and hydrogen peroxide production, the combination of L-NAME with taurine led to an augmented amino acid-induced reduction in these parameters below control levels. With myeloperoxidase activity there were no differences from single taurine application. SNAP and especially also DON in combination with taurine induced further significant decreases in superoxide anion and hydrogen peroxide production. Regarding the myeloperoxidase activity, SNAP and DON led to a decrease in the taurine-induced increase. β-alanine in association with taurine led to a significant increase in granulocytic superoxide anion production and hydrogen peroxide formation, compared to isolated taurine administration. The results remained, however, below control levels. Regarding the myeloperoxidase activity, the combination of β-alanine and taurine led to a cancellation of the taurine-induced increase in activity. Superoxide anion production was significantly reduced by combining DFMO and taurine while hydrogen peroxide formation during combined taurine-DFMO administration showed no alterations exceeding the effect of isolated taurine application (see Fig. 1). The nutritionally-conditioned increase in myeloperoxidase activity was also reversed by DFMO.

Discussion

As described in the introduction, taurine exists at very high concentrations within neutrophils. According to results presented here, intracellular taurine levels in neutrophils (PMN) amount to 40×10^{-16} moles per neutrophil cell (≈10.250 µmol/l PMN cell volume [NCV]; plasma: 114 ± 27 µmol/l) and with that are about 6 and 13 times higher than the free glutamate- (6.3×10^{-16} moles per PMN cell, ≈1615 µmol/l NCV; plasma: 30 ± 16 µmol/l) and glutamine levels (3.1×10^{-16} moles per PMN cell, ≈795 µmol/l NCV; plasma: 521 ± 78 µmol/l). Compared with taurine, hypotaurine is substantially less abundant (1.5×10^{-16} moles per PMN cell; ≈385 µM PMN cell volume [NCV]; plasma: 1.7 ± 0.4 µmol/l). The intragranulocytic taurine-hypotaurine concentration ratio is about 23.5. It is interesting, however, that both hypotaurine and taurine are very strongly accumulated within granulocytes compared to the free plasma levels. The intra- versus extracellular concentration gradient according to our results almost amounts to 90:1 for taurine and approximately 225:1 for hypotaurine. As current studies have reported, the causes underlying this nevertheless extremely high intragranulocytic taurine and hypotaurine accumulation (compared to other cells) depend of direct intracellular synthesis as well as both the active and passive uptake of these amino acids from the extracellular

medium (Banks et al., 1989; Bidri and Choay, 2003; Grimble, 2006; Gupta et al., 2005; Jacobson et al., 1986; Kopple et al., 1990; Laidlaw et al., 1987; Mühling et al., 2002a, b; Porter et al., 1991; Shimizu and Satsu, 2000; Stapleton et al., 1997, 1998a; Wakayama et al., 1983). The de novo intragranulocytic synthesis of taurine and hypotaurine can occur for example from methionine and cysteine via a decarboxylation reaction involving the elimination of carbon dioxide through cysteinsulphonic acid or cysteinic acid, or after oxidation of hypotaurine itself (with release of O_2) (Brosnan and Brosnan, 2006). The acidic groups of both amino acids, unlike all other physiological amino acids, do not therefore originate from a COOH group, but much rather from SO_3H- (taurine) or SO_2H groups (hypotaurine). But former findings described that the active taurine sequestration from the extracellular compartment, especially with neutrophils, exceeds the intracellular de novo synthesis many times (approximately by 9:1) (Banks et al., 1989; Grimble, 2006; Gupta et al., 2005; Jacobson et al., 1986; O'Flaherty et al., 1997; Porter et al., 1991; Porter and Martin, 1992; Shimizu and Satsu, 2000; Wakayama et al., 1983). Here, taurine and hypotaurine both compete for the active, temperature and sodium-dependent and saturable alpha-amino acid transport system, where about 10% of the uptake can be accounted for directly by transmembraneous diffusion (Brosnan and Brosnan, 2006). Qualitatively, the active taurine transport does not differ from other taurine- and hypotaurine uptake mechanisms studied in other body cells. If these transport mechanisms or other essential metabolic functions, such as for example the oxidative phosphorylation which is essential for cellular energy generation, are pharmacologically influenced or competitively inhibited, an intracellular taurine and hypotaurine depletion occurs as our results and earlier findings have shown (Grimble, 2006; Gupta et al., 2005; Redmond et al., 1998; Stapleton et al., 1997, 1998a).

As the results in this study also showed, both the saturation of the taurine-hypotaurine-amino acid transport system by administration of high β-alanine doses, as well as the pharmacological influencing of essential intracellular metabolic processes (i.e. following changes in intracellular glutamine or polyamine metabolism as well as an increase or decrease of extra- and intracellular nitric oxide concentrations), lead to significant decreases in intragranulocytic taurine and hypotaurine content (please see Mühling et al., 2006a, b for detailed description and conscientious discussion of single L-NAME-, SNAP-, DON- or DFMO-effects on neutrophil amino- and α-keto acid homeostasis or immune response). Conversely, a taurine supplementation leads, also consistently with earlier studies on other different cell types, to a further increase in intragranulocytic taurine concentrations, despite the high intra- versus extracellular gradients and in a manner associated with decreases in hypotaurine concentrations (Jacobson et al., 1986; Laidlaw et al., 1987; Redmond et al., 1998; Stapleton et al., 1997, 1998a; Tappaz, 2004). The required taurine concentrations, however, are high (>0.5 mM) and lie very clearly above the physiological plasma concentrations. Concerning the current results of this investigation, such taurine-dependent nutritional effects interestingly can also pharmacologically be influenced by modulating cellular glutamine metabolism and by incubation with •NO donors, or can be completely reversed by using β-alanine to blockade the amino acid transport system, thus confirming initial signs from earlier studies (Mühling et al., 2006a, b). Therefore, we believe from our results that, irrespective of which pharmacological, metabolism-inhibiting or receptor-mediated mechanisms were involved, nitric oxide as well as polyamine-dependent pathways seems to be involved in the signal transmission of free radical molecule, beneficial nutritional therapy or maleficient pharmacological stress-induced alterations in PMN taurine homeostasis. Moreover, an impairment of granulocytic glutamine uptake, modulation of intracellular glutamine metabolisation and/or de novo synthesis as well as a blockade of important glutamine-dependent metabolic processes may also lead to significant modifications of intragranulocyte taurine concentrations as well as taurine-dependent physiological and immunological functions of the affected cells. But with regard to our own former findings and the results presented here [in consistence with the immunofunctional results from other research groups (i.e. Blaise et al., 2005; Bronte and Zanovello, 2005; Bruckdorfer, 2005; Cirino et al., 2006; Crawford and Guo, 2005; Garcia and Stein, 2006; Hauk and Hosey, 2006; Korhonen et al., 2005; Luiking et al., 2005; Mühling et al., 2005, 2006a, b; Thippeswamy et al., 2006) we believe that the observed effects on taurine homeostasis appears to be based primarily on a modulation of important transmembraneous taurine transport mechanisms and only secondarily on directly or indirectly induced modifications in intragranulocytic amino- and α-keto acid-dependent metabolism [i.e. alterations in energy supply metabolisation of glutamine by the TCA cycle, changes in glutamine-dependent supply of intracellular carbon, nitrogen precursors and NADPH for various metabolic pathways (i.e. NADPH-oxidase) or •NO concentration-dependent inhibition of ribonucleotide reductase (DNA synthesis), ADP-ribosyltransferase and

glyceraldehyde-3-phosphate-dehydrogenase (i.e. glycolysis and gluconeogenesis) as well as an •NO-mediated influencing of enzymes of the respiratory chain (i.e. ubiquinone reductase, cytochrome C oxidase) or the citric acid cycle (i.e. cis-aconitase)]. Indeed, regarding the pathophysiological processes associated with high intracellular taurine and hypotaurine concentrations (i.e. membrane stabilization, cellular calcium homoeostasis, stimulation of glycolysis and glycogenolysis, modulation of cell growth, modulation of vision, etc.), the maintenance of cellular osmoregulation seems to be particularly important for PMN cells along with certain metabolic functions involved in granulocytic immune reactions, as shall be discussed later (Yancey, 2005). Indirect signs for the validity of earlier hypotheses claiming a possible participation of taurine and hypotaurine in granulocytic osmoregulation as well as cellular volume homoeostasis were found in this paper when neutral amino acids and their metabolically associated α-keto acids were taken into consideration. According to the findings of earlier studies there are important indications that both taurine as well as hypotaurine assume important functions related to cellular volume regulation in various body cells, and particularly immune cells (Bajnath et al., 1997; Ballatori et al., 1994; Cuisinier et al., 2002; Hoffman and Dunham, 1995; Jesus et al., 1991; Kingston et al., 2004; Pasantes-Morales et al., 2000; Redmond et al., 1998; Schaffer et al., 2003; Stapleton et al., 1997, 1998a). Pharmacologically-induced alterations in intracellular cell volume, combined particularly with changes in intracellular osmolarity, lead in addition to concentration changes in osmoregulatorily active metabolites (due to the increased transmembraneous taurine influx and efflux), to important and osmotically effective changes in intracellular taurine levels. Conversely, however, any significant pharmacological metabolic-modulatory and nutritionally-induced modification in intracellular taurine concentrations can lead to a direct modification of cellular volume homoeostasis. The involvement of taurine in these volume regulatory mechanisms is, according to former findings (Bajnath et al., 1997; Ballatori et al., 1994; Cuisinier et al., 2002; Hoffman and Dunham, 1995; Jesus et al., 1991; Pasantes-Morales et al., 2000; Redmond et al., 1998; Schaffer et al., 2000, 2003; Stapleton et al., 1994, 1997, 1998a), almost 30%. In order to balance the automatic disruption in cell volume homoeostasis associated with a raised taurine influx or efflux, the cell must adjust its cell volume (''swelling'' and ''shrinking'') and resort to the transmembraneous flux of other important osmoregulatory amino acids (i.e. the neutral amino acids glycine, serine, threonine, α-aminobutyrate and alanine). The transmembraneous transport of these amino acids occurs ubiquitously via an active energy and sodium-dependent transport system, the so-called ''system A''. Modifications in intra- and extracellular tonicity already lead early on to an activation of ''system A'' with a stimulus-dependent, intracellular accumulation of neutral amino acids, as well as a secretion of these amino acids into the extracellular space (Bidri and Choay, 2003; Schaffer et al., 2000, 2003; Soeters et al., 2004). The proportion of neutral amino acids in the entire complement of transmembraneously transported free amino acids in this case is up to 80% depending on cell type. In the same way the content of individual neutral amino acids upon intracellular accumulation can increase from between two to even ten-fold (Bidri and Choay, 2003; Engel et al., 2005; Redmond et al., 1998; Schaffer et al., 2000, 2003; Soeters et al., 2004; Stapleton et al., 1997, 1998a). As our findings have shown, exogenously-induced alterations in intragranulocytic taurine concentrations can lead to directly counteracting alterations in the content of neutral amino acids as well as to converse alterations in the α-keto acids that are metabolically associated with the neutral amino acids. Alanine, consistently with earlier studies, also participates in these regulatory processes. Thus taurine supplementation, and also competitive blockade of the taurine transport system by β-alanine, leads to parallel and counteracting changes in the levels of serine, glycine, threonine, α-aminobutyrate, pyruvate and α-ketobutyrate. Neutral amino acids, however, cannot completely compensate for the intragranulocytic changes in taurine within PMN. As the present results show, their maximum participation in these homoeostatic processes lies only at approx. 30–40% (Bender, 1985; Bajnath et al., 1997; Mühling et al., 2002b; Schaffer et al., 2003; Yancey, 2005). This close association was also shown with regard to pharmaceutically-induced taurine changes (Mühling et al., 2002a, 2005b). Regarding cellular alanine levels, but also considering the α-keto-acids derived from the neutral amino acids, a ''decoupling'' of this connection occurs that is presumably due to an only secondary and osmoregulatorily-based influencing of other important cellular metabolic processes. Additional findings of our study presented here, have now also confirmed a high level of dependence of these effects on a pathophysiologically unimpaired metabolic state and a balanced ratio of inter- and intracellular signal molecules and messengers. Through a specific influencing of granulocytic glutamine-, •NO- and ornithine-mediated cellular metabolic processes, a significant influencing of intragranulocytic taurine levels,

as well as an almost complete annulment of the close association between taurine/hypotaurine and the neutral amino acids and their associated α-keto-acids can be induced.

The idea that taurine and hypotaurine may have important metabolic modulatory functions for the granulocytic immune response has grown over the last 10 years, although it is neither utilized in cellular protein synthesis nor does it act as an important metabolic substrate for important amino acid metabolic cycles (Ito and Azuma, 2004; Grimble, 2006; Schuller-Levis and Park, 2003, 2004; Stapleton et al., 1997, 1998a, b). Indeed, high intracellular taurine concentrations are found primarily in tissues and cells that either produce bactericidal, fungicidal or virucidal metabolites themselves, or tissues and cells that lie in close contact with pathophysiological inflammatory events (Aruoma et al., 1988; Atmaca, 2004; Cetiner et al., 2005; Chorazy-Massalska et al., 2004; Condron et al., 2004; Emerson et al., 2005; Ergun et al., 2006; Farriol et al., 2002; Grimble, 2006; McLoughlin et al., 1991; Mühling et al., 1999; Panasenko et al., 2005; Schuller-Levis and Park, 2003, 2004; Thomas et al., 1985). In addition to a possible, but as yet inadequately confirmed participation of taurine in so-called ''cell, granula, vacuole and phagolysosome membrane stabilizing'' processes in immune cells, the results of intense research today seem to be pointing towards a pathophysiologically very interesting explanatory model: i.e. taurine may act as a radical and substrate scavenger for reactive oxygen species (ROS)-secreting cells as well as for the extragranulocytic inflammatory matrix and the tissue and organ cells contained there (Kendler, 2006; Kim et al., 1996; Klamt and Shacter, 2005; Maher et al., 2005; Marcinkiewicsz et al., 1998; Mühling et al., 2002a, b, 2005a; Neary et al., 1997; Raschke et al., 1995; Redmond et al., 1998; Schaffer et al., 2003; Schemmer et al., 2005; Stapleton et al., 1998a; Suleiman et al., 1997; Weiss et al., 1982; Zhang et al., 2004). In this way it protects cellular and membrane elements as well as cellular metabolic products from the parallel activated deleterious attack by reactive oxygen metabolites or other secretory and degranulation products that are produced to destroy pathogenic agents. According to this hypothesis, changes in the intra- and extracellular taurine content would have direct effects on the inflammatory event itself or on intra- as well as extracellularly-secreted immunofunctional parameters (i.e. Aruoma et al., 1988; Atmaca, 2004; Bidri and Choay, 2003; Brosnan and Brosnan, 2006; Cetiner et al., 2005; Chorazy-Massalska et al., 2004; Condron et al., 2004; Farriol et al., 2002; Grimble, 2006; Kim et al., 1996; McLoughlin et al., 1991; Naskalski, 1977; Park et al., 1998; Redmond et al., 1998; Schaffer et al., 2003; Schuller-Levis and Park, 2004; Stapleton et al., 1998a, b). These ideas are supported by the results of our own research activity (i.e. Engel et al., 2005; Mühling et al., 2002a, b, 2005a, b). As the present findings confirm clearly, there is a high dependence of the studied immunofunctional parameters secreted into the extracellular matrix on intragranulocytic taurine levels altered for example by taurine substitution or depletion. As the results show, the increase in taurine levels associated with a taurine supplementation leads to dose- and incubation time-dependent decreases in superoxide anions and hydrogen peroxide secreted by the granulocytes. In parallel, there is also an increase in the activity of myeloperoxidase secreted extracellularly by the PMN. A reduction in intracellular taurine levels, induced by competitive inhibition of transmembraneous taurine transport (i.e. induced by β-alanine), leads to the opposite findings. The dependency of extragranulocytically secreted immune functions on intracellular changes in taurine levels basically occurs within the confines of the parallel pharmaceutically, metabolically or nutritionally conditioned modification in intragranulocytic taurine content, as the results presented here show. Although a range of different *in vivo* and *in vitro* studies confirm these immunological findings (i.e. Atmaca, 2004; Bidri and Choay, 2003; Brosnan and Brosnan, 2006; Fürst, 2000; Grimble, 2006; Gupta et al., 2005; Redmond et al., 1998; Schaffer et al., 2003; Schuller-Levis and Park, 2003, 2004; Singh et al., 2002; Stapleton et al., 1997, 1998a), intensive parallel studies on intracellular taurine and hypotaurine changes as potential causes or symptoms of a modified neutrophil immune response have not yet been published in the literature. Exemplary studies include those by Raschke et al. (1995), Bednar et al. (1996) and McLoughlin et al. (1991), who all showed that a taurine supplementation to PMN *in vitro* leads to a significant reduction in zymosan-activated chemiluminescence as well as an increase in myeloperoxidase activity in the culture medium. Moreover, Dallegri et al. (1987) and Wagner et al. (1986) showed that a zymosan-activated, granulocyte-mediated erythrocyte lysis and killing of *Candida albicans pseudohyphae* in the ''microtitre plate killing assay'' could be almost completely reversed by taurine administration. Schuller-Levis and Park (2003, 2004), Schuller-Levis and Sturman (1990, 1992), and Schuller-Levis et al. (1990, 1995) also found that diet-induced modifications in the body and cellular taurine content, induced for example in cats and rats fed with taurine enriched or

depleted food, produced modifications in ROS generated by PMN, as the phagocytosis of *Staphylococcus epidermidis* revealed. With a taurine-free diet, an increase in extracellularly detectable superoxide anion and hydrogen peroxide activity could be shown. Leading on from these findings, the above-mentioned authors concluded that taurine depletion leads to an ''activation'' of leukocyte function, while a taurine supplementation leads to a reduction in defined and immunologically important granulocyte functions (Schuller-Levis and Sturman, 1992). The ''activation'' can be explained by the reduced ROS radical scavenging function following the intra and extracellular taurine depletion (Aruoma et al., 1988; Marquez and Dunford, 1994; Redmond et al., 1998; Stapleton et al., 1996, 1997, 1998a; Thomas et al., 1985). The results found in the present study support the data published up until now as well as the hypotheses derived from such data, that both intracellularly accumulated taurine, the taurine that is also extracellularly released during PMN activation, and a dietary increase in extracellular taurine levels exert anti-oxidative effects by complexing the HOCl formed from H_2O_2 (superoxide dismutase mediated from O_2^- and Cl^-) in the form of taurine chloramine ($Cl–NH_2–CH_2–CH–SO_3H$), and that the intracellular and extracellularly secreted myeloperoxidase activity is very closely associated with the intra- and perigranulocytic taurine levels (Bozeman et al., 1992; Coble et al., 1984; Cunningham et al., 1998; Marquez and Dunford, 1994; Penttila, 1990; Redmond et al., 1998; Schuller-Levis and Park, 2003, 2004; Schuller-Levis et al., 1995; Stapleton et al., 1997, 1998a; Weiss et al., 1982). This would represent a mechanism by which taurine during an excessive PMN activation could both maintain enzyme activity and ensure protection of the extracellular matrix and the PMN cells from deleterious attack by toxic metabolites (Cunningham et al., 1998; Stapleton et al., 1994, 1996, 1998a, b; Thomas et al., 1985) but would also explain the decrease in extragranulocytically secreted myeloperoxidase activity occurring with taurine depletion, and the increase occurring with supplementation as seen in the present investigation as well as earlier studies. As Coble et al. (1984) as well as Bozeman et al. (1992) could show, HOCl leads mainly to an inhibition of myeloperoxidase activity measured in the extracellular matrix. However, the complexing of HOCl by high taurine doses neutralizes these effects and also exerts a protective effect on the function of this enzyme (Marcinkiewitz, 1997; Marcinkiewitz et al., 1995, 1998; Marquez and Dunford, 1994; Schuller-Levis et al., 1995; Stapleton et al., 1998b). The taurine-induced increase in myeloperoxidase activity, however, does not remain uncontrolled. As Naskalski (1977), Marcinkiewitz (1997), Marcinkiewitz et al. (1995, 1998) and also Stapleton et al. (1998a, b) could confirm, a progressive taurine chloramine formation leads to a partial inhibition of the measured enzyme activity. But one has to consider that the $O_2^-/H_2O_2/MPO/Cl^-$ system, because of its non-specificity in its effects towards pathogens and cells, appears in a pathophysiological sense to suit a certain ''Jekyll and Hyde'' role (Atmaca, 2004; Bidri and Choay, 2003; Brosnan and Brosnan, 2006; Fürst, 2000; Grimble, 2006; Gupta et al., 2005; Marcinkiewitz, 1997; Marcinkiewitz et al., 1995, 1998; Redmond et al., 1998; Schaffer et al., 2003; Schuller-Levis and Park, 2003, 2004; Singh et al., 2002; Stapleton et al., 1997, 1998a). In particular, the HOCl formed from the myeloperoxidase reaction via H_2O_2 has highly-potent properties and is an indispensable component of PMN-mediated immune defence especially for destroying bacteria. Its ability to oxidise almost all cellular and tissue components (carbohydrates, amino acids, proteins, nucleic acids), to act as a substrate even for the origin of other reactive metabolites, and to act as a pro-inflammatory mediator for the activation of complement or also macrophages, makes HOCl a universal and exceptional weapon in the immune arsenal. The toxicity associated with HOCl, as described above, is unfortunately not just restricted to bacterial, viral or also tumour cell membranes, but can act of course act against normal physiological components (Fürst, 2000; Gupta et al., 2005; Kim et al., 1996; Panasenko et al., 2005; Redmond et al., 1998; Schaffer et al., 2003; Schuller-Levis and Park, 2003, 2004; Singh et al., 2002; Stapleton et al., 1997, 1998a). As addressed earlier (i.e. Bednar et al., 1996; Kim et al., 1996; Kingston et al., 2004; Klamt and Shacter, 2005; Krumholz et al., 1993; Marcinkiewicz, 1997; Marcinkiewicz et al., 1995, 1998; Marquez and Dunford, 1994; Mühling et al., 1999, 2002a, b, 2003, 2005a, b; Penttila, 1990; Weiss et al., 1982) and also found in our studies (i.e. Mühling et al., 1999, 2002a, b, 2003, 2005a, b), the activation of PMN leads to an immense production of ROS stored with other immunoactive metabolites and enzymes in vesicles and granules intracellularly in phagolysosomes, but which are also secreted and degranulated into the extracellular matrix. This can lead, apart from the destruction of pathogenic agents, to a damage of the body's own tissues and cells especially where there is additional malfunction of required protective mechanisms and antioxidant functions (e.g. catalase, vitamins C, A and E, glutathione peroxidase, β-carotene). If one considers the pathophysiology in the context of immunological tau-

rine effects presented here, taurine could be of clinical significance as a potent intra- and extracellular radical scavenger, e.g. for certain diseases where a raised ROS production occurs. Interestingly enough, low intra- and extracellular taurine concentrations are found with severe, acute or also chronic inflammatory and catabolic processes (Bidri and Choay, 2003; Brosnan and Brosnan, 2006; Cetiner et al., 2005; Chrorazy-Massalska et al., 2004; Cuisinier et al., 2002; Ergun et al., 2006; Fürst, 2000; Grimble, 2006; Gupta et al., 2005; Ito and Azuma, 2004; Kendler, 2006; Kingston et al., 2004; Neary et al., 1997; Raschke et al., 1995; Redmond et al., 1998; Schaffer et al., 2003; Schemmer et al., 2005). Here it is particularly worthy of note that the observed reductions in extracellular taurine levels can be induced for example by an increased taurine sequestration of the activated immune-competent cells (Banks et al., 1989; Condron et al., 2004; Farriol et al., 2002; Grimble, 2006; Gupta et al., 2005; Jacobson et al., 1986; Laidlaw et al., 1987; McLoughlin et al., 1991; Neary et al., 1997; Porter and Martin, 1992; Porter et al., 1991; Thomas et al., 1985; Wakayama et al., 1983; Zhang et al., 2004) or, as shown in this study, following a pharmacological influencing of essential intracellular metabolic processes. A possible ''pathophysiological taurine indispensability'' of the body's own cells and tissues with regard to the inflammatory process was shown in experiments where taurine was artificially depleted. Thus, for example, after a diet-mediated reduction of intra- and extracellular taurine levels in animal experiments, the appearance of pulmonary oedemas and interstitial lung fibrosis could be induced through the application of pro-inflammatory mediators ($\bullet NO_2$, TNF-α, nitrite) (Bidri and Choay, 2003; Engel et al., 2005; Fürst, 2000; Redmond et al., 1998; Schuller-Levis and Sturman, 1990, 1992; Schuller-Levis et al., 1990; Singh et al., 2002; Stapleton et al., 1996, 1997; Vinton et al., 1986; Zhang et al., 2004). These effects are partly reversible by application of taurine, or can barely or not be induced after previous taurine administration. However, also with respect to ischemic disease, experimentally-induced myocardial reperfusion damage and epithelial cell necrosis in animal experiments, pharmaceutically (niacin, bleomycin, amiodaron) or pro-inflammatorily [interferon, lipopolysaccharide (LPS)] induced inflammation reactions with collagen deposition and lipid peroxidation syndromes, taurine appears to have protective and immune-modulating as well as metabolism-modulating functions (Aruoma et al., 1988; Banks et al., 1989; Chorazy-Massalska et al., 2004; Condron et al., 2004; Ergun et al., 2006; Farriol et al., 2002; Ito and Azuma, 2004; Jacobson et al., 1986; Kopple et al., 1990; Laidlaw et al., 1987; Maher et al., 2005; McLoughlin et al., 1991; Murina et al., 2004; Park et al., 1998; Raschke et al., 1995; Stanbro, 1998; Suleiman et al., 1997; Yancey, 2005) These initial observations have not yet been adequately confirmed, however, in any of the disease forms examined until now.

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