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The regulation of sulphurated amino acid junctions Fact or fiction in the field of inflammation?

Review Article

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Summary. The diet of industrialised countries is usually rich in amino acids, which are in part used as a source of calories. However, metabolic alterations are observed in diseased patients and a preferential retention of Sulphurated Amino Acids (SAA) occurs during the inflammatory response. Moreover, it has been demonstrated in a model of an acute sepsis phase of rats that the metabolism of Cysteine is modified. The liver converts Cysteine at a different ratio of Sulphate to Taurine (Tau) i.e. the sulphate production decreases while the Tau conversion increases. The Glutathione (GSH) concentration is greater in the liver, kidneys and other organs and the Cysteine incorporation into proteins is higher in the spleen, lungs and plasma (Acute Phase Proteins) while the Albumin level decreases. The pro-inflammatory cytokines such as Interleukin-1, Interleukin-6 and TNF-α are the main initiators that alter protein and amino acid metabolism.

Another important phenomenon is the impairment of Methionine conversion to Cysteine during stress. For example, premature infants or AIDS patients are capable of synthesizing Cysteine from Methionine at a much lower rate. Thus, the metabolic flow through the trans-sulphuration path may be inadequate to meet the Cysteine demand under critical conditions.

In this complex picture, an SAA supply may contribute to an immune system regulation.

Keywords: Acute Phase Reaction – Cysteine – Glutathione – N-Acetylcysteine – Metabolism – Taurine

Introduction

The aim of this review is to describe the fate of SAA in a general perturbation of the metabolism of amino acids during stress conditions. We would like to emphasize that rules of biochemistry are altered during inflammation, and that such findings can support the need for an additional supply of SAA under inflammation conditions.

Acute phase reaction and protein turnover

A recent review published in the New England Journal of Medicine Gabay (1999) gave the following definition "*The Acute-Phase Response, an important pathophysiologic phenomenon, replaces the normal homeostatic mechanisms with new set points that are presumably contributing to defensive or adaptive capabilities. The functions of these changes are highly variable and diverse: some participate in initiating or sustaining the inflammatory process, others modulate it, and still others have adaptive roles*".

Under these conditions, the main metabolic changes are:

- loss of muscle tone and a negative nitrogen balance,
- decreased gluconeogenesis,
- increased osteoporosis,
- increased hepatic lipogenesis and lipolysis in adipic tissue,
- decreased lipoprotein lipase activity in muscle and adipic tissue
- cachexia.

Moreover, the stimulation of transcription of acute phase protein (APP) genes in the liver is incorporated in the complex interchange of cytokines, growth factors and glucocorticoids hormones released during the systemic defence reaction, in response to a trauma (Fig. 1). Through the broad spectrum of their activities, this heterogeneous group of circulating proteins assists the injured organism in restoring homeostasis

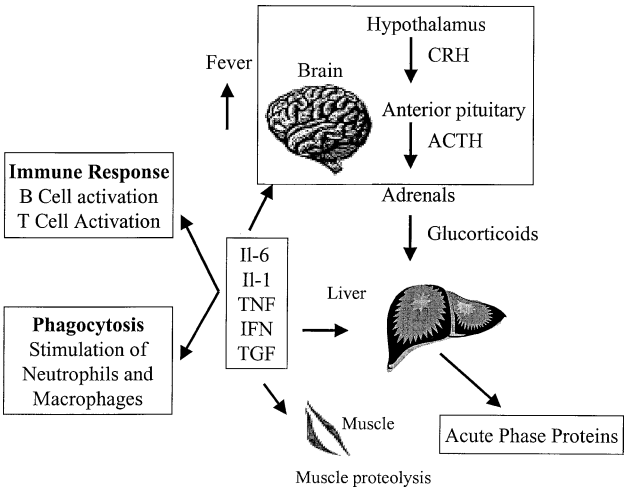

Fig. 1. Some of the organs involved in Acute Phase Response are represented. Brain is involved in fever, anorexia and synthesis of neuroendocrine hormones as Corticotropin-releasing factor (*CRH*) and Corticotropin (*ACTH*). The liver synthesises Plasma Acute Phase Proteins and releases increased amount of GSH and Tau. Proteolysis and decrease in protein synthesis have been shown in muscle. Cytokines-network orchestrates the multi-organ communication

by assuming a protective role. APPs accomplish this by inactivating vasoactive, proteolitic and cytotoxic molecules liberated from damaged tissues, and by accumulating phagocytic cells, and by participating in a feedback control mechanism that prevents the overloading of the organism's immune response.

These changes are induced by a complex intercellular signalling system whose main constituents are inflammation-associated cytokines. Several cytokines, particularly Interleukin-6, stimulate the production of APP in response to varied stimuli.

The biochemical changes occurring during inflammation also exert a large metabolic demand on amino acid metabolism. The pro-inflammatory cytokines, Interleukin-1, Interleukin-6 and Tumor Necrosis Factor-alpha (TNF-α) are the main initiators that alter protein and amino acid metabolism to support the immune response. TNF-α release, is mainly involved in determining muscle-wasting (Martin, 1991). In this respect, the administration of Pentoxifylline (PX), an inhibitor of TNF-α, has been recently studied in a sustained rat model for studying the catabolic state of sepsis (Breuillé, 1999). PX treatment reduces muscle atrophy consequent to the infection. The same group (Breuillé, 1993) reported that PX reduces the muscle protein synthesis inhibition observed in the septic acute phase, as previously demonstrated during chronic sepsis using another phosphodiesterase inhibitor as Amrinone (Jurassinski, 1995). These data are consistent with the crucial role played by TNF-α in regulation of muscle protein turnover. Other data shows that IL-6 could directly activate muscle proteolysis and especially the lysosomal and ATP-ubiquitin-dependent pathways (Goodman, 1994; Tsujinaka, 1996).

Hunter (1994) estimated that during major infections in humans, the amount of amino acids required to produce, and maintain an increased circulation of white blood cells and APP is approximately 45 g/d. However, the supply from the peripheral tissue may not always be able to match demands due the previous dietary intake.

Thus, inflammation modifies the contribution of different organs to a protein synthesis in the whole body. The protein shortage may therefore impair the acute phase protein response in human and experimental animals.

Some considerations on Cysteine biochemistry

A normal protein-rich diet provides the physiological requirement of Cysteine for the turnover and synthesis of the proteins needed by the organism. The absorption of Cysteine/Cystine (Daniels, 1982) by the intestines, originated by a normal or a supplemented diet, is practically total, and the excess of Cysteine is known to be quickly catabolized.

Pyruvate and Taurine synthesis each account for a significant fraction of Cysteine catabolism in mice and rats; the relative contribution of Tau synthesis in mice is higher (63% of total catabolism); at a low dosage of Cystine (0.1 mol/kg expressed as Cysteine) and lower (42%) of high dosage of Cysteine (2.5 mmol/kg), suggesting a saturable catabolic path (Weinstein, 1988). Taurine synthesis also predominates (68–83% of total catabolism) in rats independently of the doses (Cho, 1984; Yamaguchi, 1973).

It has recently been reported that, after an oral administration to rats, N-acetylcysteine (NAC), a precursor of Cysteine (Holdiness, 1991) is oxidised to Tau and sulphate Waterfield (1996). The effect of a thrice-daily oral administration of 200 mg NAC for 3/6 days was investigated in two patients affected by a hereditary gluthatione deficiency. In leukocytes, the GSH concentrations were increased by 20–30%. In parallel, the plasma levels, intracellular leukocytes and urinary excretion of Tau were restored to a normal value Martensson (1989). The metabolism of a high intrave-

nous NAC dosage in patients treated prior to a liver transplantation has recently been reported (Tauft, 1999). NAC is extensively catabolised to sulphate and Tau just after the implantation of a new organ, confirming the liver's high capacity of metabolising Cysteine excess even under severe stress.

In conclusion, under stable conditions any tissue levels of free Cysteine and Cysteine equivalent are ultimately regulated and limited by the reaction of Cysteine catabolism (Weinstein, 1988).

The metabolism of Cysteine is modified during stress

The amino acid intake occurs to a large excess in a healthy condition, amino acids are therefore also used as a source of calories. This means that the excess Cysteine is metabolised to sulphate and Tau.

On the other hand, some degree of nutritional deficit is observed even in the case of a brief infection (Beisel, 1988). Acute Phase Response, with the increased nutritional requirements of many organs like the liver, is thought to induce of such a deficit (Breuillé, 1994; Hasselgren, 1988).

Metabolic changes are observed in diseased patients and a preferential retention of SAA occurs during an inflammatory response. After fractures or burns, urinary nitrogen excretion is enhanced to a greater extent than sulphur excretion (Grimble, 1994).

The metabolism of Cysteine is modified during the acute phase of sepsis, in rats infected with live Escherichia coli (Malmezat, 1998). Sulphate production is significantly lower, while a higher production of Tau may come to play a protective role against oxidative stress. GSH concentration is significantly greater in the liver, kidneys and other organs. Finally, Cysteine incorporation into protein is higher in the spleen, lungs and in particular in whole plasma proteins while albumin level decreases. This last effect is interpreted as inducing a synthesis of APP. Finally, it has been demonstrated that also the general Cysteine catabolism is decreased in several tissues following infection (Breuillé, 1996; Malmezat, 1998).

These data suggest an increased requirement for Cysteine during infection (Breuillé, 1994; Malmezat, 2000b).

During an infection and generally under stress, amino acids are released from peripheral tissues i.e. muscles so as to act as nutrients for cells of the immune system and for the synthesis of Tau, APP and GSH. Within the liver APP, both GSH and Tau consequently compete for the cellular sulphurated amino acid supply.

The question arises whether incorporation and metabolism of Cysteine into both of these end-products during an inflammatory response, is equally influenced by any changes in the dietary availability of sulphurated amino acid (Grimble, 1998). It should also be considered that the food intake is generally decreased due to the anorexia induced by acute inflammation.

Another aspect affecting the availability of SAA is the impairment of Methionine conversion to Cysteine in a stressed condition. Premature infants synthesise GSH from Methionine (a process dependent on the Cystathionase path) at a much lower rate than fully developed infants (Vina, 1995).

The rate of Cysteine synthesis from Methionine was found to be significantly higher in isolated hepatocytes used in controls than in hepatocytes from rats suffering from surgical stress (Vina, 1992). This was likewise observed during a sepsis in rats (Malmezat, 2000a). Most recently, the same impairment has also been reported in the case of AIDS patients (Sastre, 2001). Not much is known about other conditions, but it is likely that the conversion of Methionine to Cysteine is generally impaired in a state of inflammation. The metabolic flow through the trans-sulphuration path may be inadequate to meet the Glutathione and Cysteine requirement.

The use of SAA supplementation in animal models of inflammation has been reported. In rats, an infiltration of inflammatory cells into the lungs, in response to cytokines, was noted to occur in the absence of Cysteine and Methionine in a low protein diet, and was prevented by their addition to the diet (Grimble, 1992; Hunter, 1994). Dietary SAA adequacy influences glutathione synthesis and glutathione-dependent enzymes during the inflammatory response to endotoxin and TNF-α (Hunter, 1997). In addition, in rats a non-lethal dose of TNF-α becomes lethal if the ability of the animal to increase and maintain GSH synthesis is prevented by administration of diethylmaleate (Zimmerman, 1989).

All these findings evidence the existence of a modified path of SAA biochemistry during inflammation and justify why Cysteine, which is a simple unessential amino acid and present in a large excess in a diet, may be viewed to a be a conditionally essential agent.

Taurine is not the end-product of catabolism of sulphurated amino acids but Tau is endowed with a protective effect

While the role of GSH is crucial in regulating cell functions, such an important topic is not extensively discussed here. In short, GSH performs many physiological functions including antioxidant defence, detoxification of xenobiotics, modulation of redox regulated signal transduction, storage and transport of Cysteine, regulation of cell proliferation, synthesis of deoxyribonucleotide, regulation of immune response, and regulation of leukotriene and prostaglandin metabolism (Griffith, 1979; Kirsher, 1994; Droge, 1991; Geggel, 1985).

The main metabolite of Cysteine i.e. Tau is not an ineffective end-metabolite of sulphurated amino acid (Surinder, 1986) but provides a pharmacological effect (Stapleton, 1998). This action mechanism is not fully understood, but has been shown to act as a detoxifier, antioxidant and membrane stabiliser.

Tau is a constitutive element of the organism and found in higher concentration in the lungs, heart and inflammatory cells as neutrophil, which represents the most abundant source of intracellular amino acids (Timbrell, 1995; Wright, 1986; Fukuda, 1982).

Tau is released from inflamed tissues and pro-inflammatory cells and, in particular, from the lungs during inflammatory processes.

Inside the neutrophil and eosinophil, Tau reacts with hypochlorous acid to produce the less aggressive compound known as Taurine Chloramine (TauCl) (Kim, 1996; Park, 1993). This is a physiological mechanism meant to protect against the reactivity of hypochlorous acid, without impairing the phagic activity.

The TauCl function has been extensively reported (Park, 1995, 1997; Marcinkiewicz, 1997, 1998). TauCl exerts a dosage-related inhibitory action at a micromolar concentration (0.1–1 mM) against the release of a macrophage inflammatory mediator (Superoxide Anion, Nitric Oxide, TNF, IL-6, and PGE2). It is likely that TauCl inhibits the production of nitric oxide and TNF by mechanisms involving transcriptional and translational events, e.g. iNOS mRNA.

Park and Colleagues commented the role of TauCl with the following words (Park, 1993): *Considering the temporal and spatial domains of the leukocyte microenvironment during an inflammatory response, the concentrations of Tau-Cl are indeed physiologic. We show active transport of Tau-Cl into RAW 264.7 cells, inhibition of NO and TNF production by Tau-Cl, and irreversible inhibition of NOS by Tau-Cl. These data suggest that Tau-Cl (0.2–1.0 mM) may modulate the localised inflammatory response at Tau-Cl concentration that is physiologically relevant.*

Our main interest is in the respiratory area. In this contest, a great body of evidence is available; Tau is known to protect against lung damage in animal models, such as during acute exposure to inhalation of Nitrogen Dioxide, Bleomycin, Ozone, etc. (with an emphasis on *in vivo* results, a selection of the published results is given in a dedicated chapter in the references).

Human airway secretion of bronchiectasis, chronic bronchitis and cystic fibrosis patients were found to have a high Tau concentration. In contrast, Tau is undetectable in normal individuals. Tau may play a role in protecting lung epithelial cells against myeloperoxidase-derived oxidants (Cantin, 1994). The action mechanism, underlying the protective effect of Tau, could be related to the control exerted on the chemical toxicity of HOCI synthesised by neutrophils and eosinophils and to the anti-inflammatory effects elicited by TauCl (to a minor extent by Tau itself), versus the macrophage release of pro-inflammatory species, e.g. NO, PGE_2, TNF, cytokines, etc.

Other papers describe higher levels of Tau in the lungs under pathological conditions (Witko-Sarsat, 1995; Hofford, 1997). Such evidence provides a strong further support for the pulmonary protective role played by Tau.

Recently, we have examined the effect of NAC on Bleomycin-induced lung fibrosis in rats (Cortijo, 2001). NAC (3 mmol kg^{-1}; oral) is given daily from one week prior to a single intratracheal instillation of Bleomycin (2.5 U kg^{-1}) or saline instillation until 14 days after instillation. In this study, we confirmed that oral NAC is useful for partially preventing the lung damage produced by Bleomycin, but since NAC is a Cysteine pro-drug, the metabolic fate of Cysteine has been explored by examining whether oral treatment with NAC increases the Tau levels in bronco-alveolar lavage fluid (BALF), plasma and granulocytes. BALF Tau levels are increased in groups treated with NAC (Fig. 2A) but not exposed to Bleomycin, on the other hand, Bleomycin alone also increases Tau levels in BALF and NAC treatment produces a further increase of BALF Tau levels. The same is found in plasma. While Tau levels in plasma are not signifi-

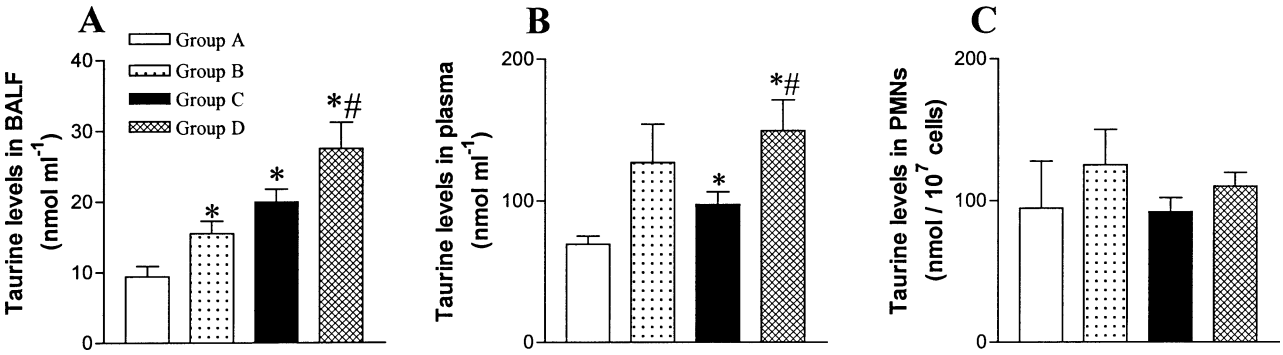

Fig. 2. Taurine levels in bronchoalveolar lavage fluid (panel **A**), plasma (panel **B**), and polymorphonuclear leukocytes (panel **C**) in different experimental groups as indicated. Data are mean ± sem of 5 (group A), 6 (group B), and 11 (groups C and D) animals; *P < 0.05 from group A; #P < 0.05 from group C. *Group A*, vehicle; *Group B*, NAC + vehicle; *Group C*; vehicle + bleomycin; *Group D*, NAC + bleomycin

cantly increased by treating it with NAC, in rats unexposed to Bleomycin, a clear trend is observed (Fig. 2B). Finally, the Tau levels measured in granulocytes does not evidence significant changes in rats, regardless of their exposure to Bleomycin or treatment with NAC (Fig. 2C).

The study confirmed the increased Tau levels in BALF and plasma of Bleomycin-treated rats. The administration of NAC, a precursor of Cysteine, further enhances the Tau levels in BALF and plasma of rats receiving Bleomycin. Tau may therefore be contributing to the beneficial effect of NAC.

Conclusions

- The production of cytokines, APP, Tau and GSH are strongly modified during inflammation.
- The evolution of inflammation is influenced by the adequacy of amino acid availability in certain SAA.
- Because Cysteine participates in a very important physiological balance, the potential cause of a Cysteine deficit has been identified.
- The higher demand of Cysteine need may be crucial in maintaining a constant level of GSH and Tau.
- Tau elicits a protective action under inflammatory conditions, in particular in the lungs.
- The metabolism of SAA is deeply modified during inflammation and Cysteine is a product-limiting step in many biochemical approaches leading to an effective response.

References

General

Beisel WR (1988) Use of animals for the study of relations between nutrition and infection diseases. In: Beynen AC, West CE (eds) Use of animal models for research in human nutrition. Comparative animal nutrition, vol. 6. Karger, Basel, pp 33–55

Breuillé D, Frages MC, Rosé F, Arnal M, Attaix D, Obied C (1993) Pentoxifylline decreases the body weight loss and muscle protein wasting characteristics of sepsis. Am J Physiol 265: E660–E666

Breuillé D, Rosé F, Arnal M, Melin C, Obied C (1994) Sepsis modifies the contribution of different organs to whole-body protein synthesis. Clin Sci 86: 663–669

Breuillé D, Arnal M, Rambourdin F, Rosé F, Obied C (1996) Increased cysteine requirements Induced by sepsis. Clin Nutr 15: 21 (Abs.)

Breuillé D, Voisin L, Contrepos M, Arnal M, Rosé F, Obied C (1999) A sustained rat model for studying the long-lasting catabolic state of sepsis. Infection Immunity 67: 1079–1085

Cantin A (1994) Taurine modulation of hypochlorous acid-induced lung epithelial cell injury in vitro. J Clin Invest 93: 606–614

Cho E, Johnson N, Snider B (1984) Tissue glutathione as a cyst(e)ine reservoir during cystine depletion in growing rats. J Nutr 114: 1853–1862

Cortijo J, Cerdá-Nicolás M, Serrano A, Bioque G, Estrela JM, Santangelo F, Esteras A, Llombart-Bosch A, Morcillo EJ (2001) Preventive effect of oral N-acetylcysteine on bleomycin-induced lung injury in rats. Eur Respir J 17: 1–8

Daniels K, Tipanuk M (1982) The effect of dietary cysteine level on cysteine metabolism in rats. J Nutr 112: 2130–2141

Droge W (1991) Modulation of lymphocyte functions and immune response by cysteine and cysteine derivatives. Am J Med 91: 140s–143s

Fukuda K, Hirai Y, Yoshida H, Nakaijma T, Usui T (1982) Free amino acid content of lymphocytes and granulocytes compared. Clin Chem 28: 1758–1761

Gabay C, Kushner I (1999) Acute-proteins and other systemic responses to inflammation. N Engl J Med 340: 448–454

Geggel H (1985) Nutritional requirement for taurine in patients receiving long-term parenteral nutrition. N Engl J Med 312: 142–146

Goodman MN (1994) Interleukin-6 induces skeletal muscle protein break-down in rats. Proc Soc Exp Biol Med 205: 182–185

Griffith OW (1979) Glutathione: interorgan translocation, turnover and metabolism. Proc Natl Acad Sci USA 76: 5606–5610

Grimble R (1994) Nutritional antioxidants and the modulation of inflammation: theory and practice. New Horizons 2: 175–185

Grimble R, Grimble G (1998) Immunonutrition: role of sulfur amino acids, related amino acids and poliamines. Nutrition 14: 605–610

Grimble R, Jackson A, Persaud C, Wride M, Delers F, Engler R (1992) Cysteine and glycine supplementation modulate the metabolic response to tumor necrosis factor alpha in rats fed a low protein diet. J Nutr 122: 2066–2073

Haselgren P, Pederson P, Sax C, Waener BP, Fisher JE (1988) Current concept of protein turnover and amino acid transport in liver and skeletal muscle during sepsis. Arch Surg 123: 992–999

Holdiness M (1991) Clinical pharmacokinetic of N-acetylcysteine. Clin Pharmacokin 20: 123–134

Hunter E, Grimble R (1994) Cysteine and methionine supplementation modulate the effects of TNF-alpha on protein synthesis, glutathione and zinc content of liver and lung in rats fed a low protein diet. J Nutr 124: 2319

Hofford J, Milakofsky L, Pell S, Fish J, Peters S, Pollice M, Vogel W (1997) Levels of amino acids and related compounds in bronchoalveolar lavage fluids of asthmatic patients. Am J Respir Crit Care Med 155: 432–435

Hunter E, Grimble R (1994) Cysteine and methionine supplementation modulate the effects of TNF-α on protein synthesis, glutathione and zinc content of liver and lung in rats fed a low protein diet. J Nutrition 124: 2319–2328

Hunter E, Grimble R (1997) Dietary SAA adequacy influences glutathione synthesis and glutathione-dependent enzymes during the inflammatory response to endotoxin and TNF-α. Clin Science 92: 297–305

Huxtable R (1992) Physiological actions of taurine. Physiol Rev 72: 101–163

Huxtable R (1996) Taurine: past, present and future advances. Experimental Medicine and Biology 43: 641–650

Kim C, Park E, Quinn M, Schuller-Levis G (1996) The production of superoxide anion and nitric oxide by cultured murine leukocytes and the accumulation of TNF-α in conditioned media is inhibited by taurine chloramine. Immunopharmacology 34: 89–95

Jurassinki C, Kilpatrick L, Vary T (1995) Amrinone prevents muscle protein wasting during cronic sepsis. Am J Physiol 268: E491–E500

Kirscherf ET (1994) Effect of GSH depletion and oral N-acetylcysteine treatment on Cd4+ and Cd8+ Cells. FASEB J 8: 448

Malmezat T, Breuillé, Pouyet C, Patureau M, Obled C (1998) Metabolism of cysteine is modified during the acute phase of sepsis in rats 128: 97–105

Malmezat T, Breuillé D, Pouyet C, Buffière C, Denis P, Mirand P, Obled C (2000a) Methionine transsulfuration is increased during sepsis in rats. Am J Physiol Endocrinol Metab 279: E1391–E1397

Malmezat T, Breuillé D, Capitain P, Mirand P, Obled C (2000b) Glutathione turnover is increased during the acute phase of sepsis in rats. J Nutr 130: 1239–1246

Marcinkiewicz J (1997) Neutrophil chloramine: missing links between innate and acquired immunity. Immunology Today 18: 577–580

Marcinkiewicz J, Grabowa A, Bereta J, Bryniarski K, Nowak B (1998) Taurine chloramine down-regulates the generation of murine neutrophil inflammatory mediators. Immunopharmacology 40: 27–38

Martensson J, Gustafsson J, Larsson A (1989) A therapeutic trial with N-acetylcysteine in subjects with hereditary gluthatione synthetase deficiency. J Inherit Met Disp 12: 120–130

Martin LF, Vary C, Davis PK, Munger BL, Lynch JL, Spangler S (1991) Intravascular plastic catheters-how they potentiate tumor necrosis factor release and exacerbate complications associated with sepsis. Arch Surg 126: 1087–1093

Park E, Quinn M, Wright C, Schuller-Levis G (1993) Taurine chloramine inhibits the synthesis of nitric oxide and the release of tumor necrosis factor in Activated Raw 264.7 Cells. J Leukocyte Biology 54: 119–124

Park E, Schuller-Levis G, Quinn M (1995) Taurine chloramine inhibits production of nitric oxide and TNF-α-Alpha in activated Raw 264.7 cells by mechanism that involves transcriptional and translational events. J Immunology 154: 4778–4784

Park E, Schuller-Levis G, Jun-Hua J, Quinn M (1997) Preactivation exposure of Raw 264.7 cells to taurine chloramine attenuates subsequent production of nitric oxide and expression of INOS mRNA. Leukocyte Biology 61: 161–166

Sastre J, Asuncion JG, Pallardo, Vina J (2001) Hepatic gamma-cystathionase deficiency: a key factor to explain glutathione depletion in Aids patients. JAMA 285: 1444–1445

Stapleton P, O'Flaherty R, Redmond P, Bouchier-Hayes D (1998) Host defence – a role for the amino acid taurine? J Parent Enter Nutr 22: 42–48

Surinder R, Sanders T (1986) Taurine concentration in the diet, plasma, urine and breast milk of vegans compared with omnivores. Br J Nutr 56: 17–27

Taut FJH (1999) Sulfur-containing metabolites of N-acetylcysteine in patients undergoing orthotopic liver transplantation. Transplant Proc 31: 411

Timbrell J, Sebra V, Waterfield C (1995) The in vivo and in vitro protective properties of taurine. Gen Pharmacol 26: 453–462

Tsujnaka T, Fujita K, Ebisui C, Yano M, Kominami E, Suzuki K, Tanaka K, Katsume A, Ohsugi Y, Shiozaki H, Monden M (1996) Interleukin 6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice J Clin Investig 97: 244–249

Vina J, Gimenz A, Puertes I, Gasco E, Vina J (1992) Impairment of cysteine synthesis from methionine in rats exposed to surgical stress. Br J Nutr 68: 421–429

Vina J, Vento M, Garcia-Sala F, Purtes I, Gasco E, Sastre J, Asensi M, Pallardo V (1995) L-Cysteine and glutathione metabolism are impaired in premature infants due to cystathionase deficiency. Am J Clin Nutr 61: 1067–1069

Waterfield CJ, Timbell JA (1996) The biosynthesis of taurine from N-acetylcysteine and other precursors in vivo and in rat hepatocytes. Amino Acids 10: 173–185

Weinstein C, Haschemejer R, Griffith O (1988) In vivo studies of cysteine metabolism. J Biolog Chem 263: 16568–16579

Witko-Sarsat V, Delacourt C, Rabier D, Bardet J, Thu Nguyen A, Descamps-Latscha B (1995): Neutrophil-derived long-lived oxidant in cystic fibrosis sputum. Am J Respir Crit Care Med 152: 1910–1916

Wright C, Tallan H, Lin Y, Gaull G (1986) Taurine: biological update. Ann Rev Biochem 55: 427–453

Yamaguchi K, Sakakibaka S, Asamizu J, Ueda I (1973) Induction and activation of cysteine oxidase of rat liver II. The measurement of cysteine metabolism in vivo and the activation of in vivo activity of cysteine oxidase. Biochim Biophys Acta 29: 48–59

Zimmerman R, Marafino Jr B, Chan A, Landre P, Winkelhake J (1989) The role of oxidant injury in tumour cell sensitivity to recombinant human tumor necrosis factor in vivo. Implication for mechanism of action. J Immunol 142: 1405–1409

Taurine in respiratory field models

Al-Zaid NS (1988) Effect of taurine on the lung collagen content In myopatic hamsters. Acta Physiol Hungari 72: 111–114

Blaisdell R, Schiedt M, Giri Sn (1994) Dietary supplementation with taurine and niacin prevents the increase in lung collagen cross-links in the multidose bleomycin hamster model of pulmonary fibrosis. J Biochem Toxicol 9: 79–86

Giri SN, Wang Q (1992) Taurine and niacine offer a novel therapeutic modality in prevention of chemically-induced pulmonary fibrosis in hamsters. Adv Exp Med Biol 315: 329–340

Giri SN, Blaisdell R, Rucker R, Wang Q, Hyde D (1994) Amelioration of bleomycin-induced lung fibrosis in hamster by dietary supplementation with taurine and niacin: biochemical mechanisms. Environ Health Perspect 102 [Suppl 10]: 137–148

Gordon R, Shaked A, Solano D (1986) Taurine protects hamster bronchioles from acute NO_2-induced alterations. Am J Pathol 125: 585–600

Gordon R, Heller R, Heller R (1994) Distribution of taurine in hamster lungs. J Histotechn 17: 29–32

Gordon R, Park E, Laskin D, Schuller-Levis G (1998) Taurine protects rat bronchioles from acute ozone exposure: a freeze fracture and electron microscopy study. Exper Lung Res 24: 659–674

Gurjeyalakshi G, Swartnalatha N, Iyer N, Hollinger MA, Giri SN (1996) Procollagen gene expression is down-regulated by taurine and niacin at the transcriptional level in the bleomicyn hamster model of lung fibrosis. J Pharm Exper Ther 277: 1152–1157

Gurujieyalakshmi G, Hollinger M, Giri S (1998) Regulation of transforming growth factor-β1 Mrna expression by taurine and niacin in the bleomycin hamster model of lung fibrosis. Am J Resp Cell Mol Biol 18: 334–342

Lehnert B et al (1994) Lung injury following exposure of rats to relatively high mass concentrations of nitrogen dioxide. Toxicology 89: 239–277

Mcloughlin D, Staleton P, Bloomfield F (1991) Influence of taurine and a substituted taurine on the respiratory burst pathway in the inflammatory response. Biochem Soc Transactions 19: 73–78

Schuller-Levis G et al (1994) Taurine protects against oxidant-induced lung injury: possible mechanism of action. Adv Exper Med Biol 359: 31–39

Schuller-Levis G, Gordon R, Park E, Pendino K, Laskin D (1995) Taurine protects rat bronchioles from acute ozone-induced lung inflammation and hyperplasia. Exp Lung Res 21: 877–888

Song L, Wang D, Cui X, Hu W (1998) The protective action of taurine and L-arginine in radiation pulmonary fibrosis. J Envir Pat Tox Oncol 17: 151–157

Wang Q, Giri SN, Hyde D, Nakashima J (1989) Effects of taurine on bleomycin-induced lung fibrosis in hamster. Proc Soc Exp Biol Med 190: 330–338

Wang Q, Giri SN, Hyde D, Li C (1991) Amelioration of bleomycin-induced pulmonary fibrosis in hamster by combined treatment with taurine and niacin. Biochem Pharm 42: 1115–1122

Wang Q, Hyde D, Giri SN (1992a) Abatement of bleomycin-induced increases in vascular permeability, inflammatory cell infiltration and fibrotic lesions in hamster lungs by combined treatment with taurine and niacin. Lab Invest 67: 234–242

Wang Q, Hollinger M, Giri S (1992b) Attenuation of amiodarone-induced lung fibrosis and phospholipidosis in hamster by taurine and/or niacin treatment. J Pharm Exper Ther 262: 127–132

Zhang X, Lombardini J (1998) Effects of in vivo depletion on induced-chemiluminescence production in macrophages isolated from rat lungs. Amino Acids 15: 179–186

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