The Effects of Sulfur Amino Acid Intake on Immune Function in Humans

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ABSTRACT

No direct data exist on the influence of supranormal intakes of sulfur amino acids on immune function in humans. However 3 major products of sulfur amino acids, glutathione (GSH), homocysteine (Hcy), and taurine (Tau), influence, mainly, inflammatory aspects of the immune response in vitro and in vivo. Methionine intakes above ~1 g/d transiently raise plasma Tau, Hcy, and GSH. Tau and GSH ameliorate inflammation. Hcy has the opposite effect. A biphasic relation, between cellular GSH and CD4+ and CD8+ numbers occurs in healthy men. How changes in sulfur amino acid intake influence this phenomenon is unknown. In animals, high Tau intakes are antiinflammatory. How immune function in humans is affected is unknown. A positive relation between plasma neopterin (a marker of a Th-1–type immune response) and Hcy indicates that Hcy may play a part in inflammatory aspects of Parkinson's disease and aging. In vitro, Hcy, at concentrations seen following consumption of ~6 g L-methionine/d in adults, increases the interactions among T lymphocytes, monocytes, and endothelium. Whether a similar phenomenon occurs in vivo is unknown. Polyomaviruses in the methylenetetrahydrofolate reductase gene are associated with raised plasma Hcy in young but not old subjects. The relation of this observation to immune function is unknown. The relationships among Hcy, inflammatory aspects of disease, and in vitro alterations in immune cell behavior create a cautionary note about supplementation of diets with L-methionine to raise intake above ~1 g/d. Studies directly linking methionine intake, genetics, plasma Hcy, Tau, and GSH and immune function are needed.

KEY WORDS: • methionine • cysteine • glutathione • homocysteine • immune function

Sulfur amino acids and their chief metabolites are of major importance in health and disease. Methionine is classified as nutritionally essential. Cysteine is classified as semiessential due the variable capacity of the body for its production from methionine. The metabolic pathway between the 2 amino acids contains the intermediate homocysteine (Hcy). Hcy synthesis is influenced by B-vitamin intake (folic acid, vitamins B-6 and B-12) and functional single-nucleotide polymorphisms that influence folate metabolism (1–3). Sulfate and taurine are the major endproducts of sulfur amino acid metabolism.

The immune system, in its actions against invading organisms, involves a complex interrelated series of cellular and metabolic activities. The important question, therefore, is how variations in tissue availability of sulfur amino acids and the products of their metabolism interact with these processes.

Clearly, a sufficient metabolic supply of sulfur amino acids from diet and tissue protein breakdown is necessary for the synthesis of the myriad of proteins and peptides involved in normal functioning of the immune system.

The impact of a high sulfur amino acid intake on immune function has not been investigated in any depth in humans or experimental animals. Many studies have examined the effects of high intakes of methionine and cysteine on growth and mortality in rodents, chiefly rats (e.g., 4). A limited number of studies on the impact of alterations in dietary sulfur amino acid intake on the inflammatory process have also been conducted in rats (5).

In humans, the pioneering work of Young's group examined metabolic effects of increasing sulfur amino acid intake, to approximately double the requirement for methionine plus cysteine (6). No measures of immune function were reported in these investigations. Nonetheless a number of studies have reported the effects of metabolic products of sulfur amino acids [Hcy, taurine (Tau), glutathione (GSH)] in in vitro studies on various functions of human immune cells. Research in clinical nutrition has focused on the effects of sulfur amino acid precursors such as N-acetyl cysteine (NAC) and L-2-oxothiazolidine-4-carboxylate (OTC), on various aspects of human immune function. Because cysteine is unstable in its reduced form, is toxic in high doses, and is mostly degraded in the extracellular compartment, OTC and NAC have been used to deliver cysteine directly to cells. OTC is an analog of 5-oxoproline in which the 4-methylene moiety has been replaced with sulfur. It provides an excellent substrate for 5-oxoprolinase (an intracellular enzyme). The enzyme converts OTC to S-carboxy-L-cysteine, which is rapidly hydrolyzed to L-cysteine.
NAC rapidly enters the cell and is speedily deacetylated to yield L-cysteine, although there are species differences in the ability to perform this metabolic reaction.

In the sections below, the interaction of 3 of the major metabolites and products of sulfur amino acid metabolism (GSH, Hcy, and Tau) with aspects of the immune response is considered.

Control of sulfur amino acid metabolism and metabolic changes in response to alterations in sulfur amino acid intake

The manner in which cells and tissues respond to variations in sulfur amino acid intake is constrained by the characteristics of key enzymes in the metabolic pathways. The $K_{\text{m}}$ values for the Hcy transferase enzymes (which lead to the recycling of methionine) are 2 orders of magnitude lower than those for cystathionine synthase and cystathionine $\gamma$-lyase (which process methionine toward metabolism via the transsulfuration pathway and provide substrate for GSH and Tau synthesis). Thus, at low intracellular concentrations of methionine, remethylation, via Hcy, will be favored over transsulfuration, and methionine will be conserved. Indeed, when these 2 pathways were examined in vivo, in rats fed diets containing 3, 15, and 30 g L-methionine/kg, the percentage of methionine metabolized by the 2 competing pathways changed (7,8). With increasing dietary methionine intake, substrate flux through the transmethylation pathway fell, and flux through the transsulfuration pathway increased.

Examination of the $K_{\text{m}}$ values for rate-limiting enzymes processing the major cysteine metabolites provides a further insight into how sulfur amino acid metabolism is influenced by alteration in the supply of cysteine. The $K_{\text{m}}$ for L-cysteinyl-tRNA synthetase (essential for incorporation of cysteine into protein) is less than one-tenth of that for $\gamma$-glutamyl cysteine synthetase (the rate-limiting enzyme for GSH synthesis) or cysteine dioxygenase (forming cysteine sulfinate, the precursor for sulfate and Tau). Thus, under conditions of low cysteine availability, protein synthesis will be maintained, and synthesis of sulfate, Tau, and GSH curtailed. Changes in availability of these last 2 endproducts may potentially influence immune function.

Thus, when the diet is low in sulfur amino acids, cellular methionine is highly conserved. Flux down the transsulfuration pathway, which ultimately leads to methionine catabolism (and GSH and Tau synthesis), increases only as dietary methionine intake increases. At low flux rates of substrate downstream the transsulfuration pathway, conversion of cysteine into its main metabolites will be affected so that protein synthesis will be relatively maintained while sulfate and GSH synthesis rates will fall. Synthesis of GSH, Tau, and sulfate will increase in concert as increasing levels of substrate flow through the pathway.

High dietary intakes of methionine raise plasma Hcy concentrations. When supplements of between 1.5 and >6 g/d are given, plasma Hcy increased despite an adequate intake of B vitamins (9). In a dietary controlled crossover trial, Verhoef et al. (10) compared fasting and postprandial plasma Hcy concentrations after healthy men had consumed a low-protein diet containing 1.7 g of methionine followed by a high-protein diet (breakfast, lunch, and dinner) containing 4.5 g of methionine. On the high-protein diet postprandial Hcy increased steadily between meals, from $\approx$6 to 11 $\mu$mol/L, for several hours after dinner. Ward et al. (11), in a study on 6 healthy young men fed diets supplemented with increasing amounts of methionine (25, 50, and 75 mg/kg, respectively), compared fasting Hcy concentrations at the highest level of supplementation (equivalent to 6.14 g/d). At the highest dose, fasting Hcy concentrations of 13.4 mg/dl were observed. Raised cellular Hcy concentrations may increase the adhesion of monocytes to endothelial cells, and increased plasma Hcy concentrations have been associated with activation of the immune system (12,13). Thus, nutritional and metabolic factors that raise tissue concentrations of this product of sulfur amino acid metabolism may alter immune function. In vivo studies also provide information about the magnitude of the effect of raised methionine intakes on GSH and Tau concentrations. When doses of L-methionine were fed (0.1 g/kg) ($\approx$6.8 g/supplement) to subjects with cirrhosis of the liver and healthy controls, the controls showed an approximately 2.5-fold increase in plasma cysteine, a doubling of plasma Tau, and a 2.5-fold increase in plasma GSH. Plasma concentrations of the 3 metabolites were unaffected by the L-methionine supplement in the cirrhotic patients. In the control subjects, although GSH returned to baseline values within 9 h of the dose, Tau and cysteine remained elevated until 24 h after the supplement (14). The magnitude of these changes in the 3 key products of methionine metabolism can be used to judge whether the effects of these substances reported in in vitro studies of immune function are likely to have physiological or pharmacological effects in vivo.

Glutathione and the immune system

Glutathione has a pivotal role in antioxidant defense, protecting the body from oxidative damage during the immune response, and in supporting T-cell proliferation. The synthesis of GSH from its 3 constituent amino acids is mainly limited to the liver. Two consecutive steps are required to synthesize GSH. The rate-limiting enzyme in the pathway is $\gamma$-glutamyl cysteine synthetase. Under normal physiological conditions there is feedback on the activity of this enzyme by GSH. Thus, conversion of cysteine to GSH is strongly influenced by the rate of utilization and transport of GSH within and between the cells of the body. In other words, synthesis is a "demand-led" process, provided that cysteine is available. GSH is transferred to the blood and transported around the body in both plasma and cells, mainly in its reduced form (GSH). GSH is influenced by dietary sulfur amino acid intake. In an isotopic study in rats, when diets with various sulfur amino acid contents were fed, 7 molecules of cysteine were incorporated into GSH for every 10 incorporated into protein in liver at adequate sulfur amino acid intake (5). At inadequate intakes the ratio fell to <3:10. This response to a low intake of sulfur amino acids is not advantageous because antioxidant defenses will become compromised. The immune response makes large demands on these defenses and on sulfur amino acid metabolism in particular. Although there is debate about whether the cysteine moiety of NAC is available for GSH synthesis, administration of NAC increased intracellular GSH concentrations and influenced T-cell numbers (15).

Sulfur amino acid and glutathione metabolism following infection and injury.

Many of the metabolic effects of inflammation are orchestrated by the proinflammatory cytokines. The proinflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)α have widespread metabolic effects such as fever, loss of appetite, weight loss, negative nitrogen, sulfur, and mineral balance, and lethargy. The biochemistry of an infected individual is fundamentally changed in a way that will ensure that the immune system receives nutrients from within the body. Muscle protein is catabolized to provide amino acids for synthesizing new cells, GSH, and proteins for the immune response. Furthermore, amino acids are converted to glucose (a preferred fuel, together with glutamine, for the immune system). An increase in urinary nitrogen and sulfur excretion occurs as a result of this catabolic process (16). In malaria, tuberculosis, sepsis, cancer, HIV infection, and rheumatoid arthritis, inflammatory cytokines bring about a loss of lean tissue, which is associated with depleted tissue GSH content and an increased output of nitrogenous and sulfur-containing excretion products in the urine. The extent of this process is highlighted by the significant increase in urinary nitrogen excretion from 9 g/d in mild infection to 20–30 g/d following major burn or severe traumatic injury (17). The loss of nitrogen from the body of an adult during a bacterial infection may be equivalent to 60 g of tissue protein and, in malaria, equivalent to over 500 g of protein. However, during the response to infection and injury the urinary excretion of sulfur increases to a lesser extent than that of nitrogen (18), suggesting that sulfur amino acids are preferentially retained. It has been proposed that the increased retention results from raised requirements for sulfur amino acids during the inflammatory response (18).

Infection with human immunodeficiency virus (HIV) causes substantial urinary excretion of sulfate during the asymptomatic phase of the disease (19). The losses reported were equivalent to 10 g of cysteine per day, in contrast to losses of <3 g/d for healthy individuals on a "Westernized" diet. Because cysteine is the precursor for sulfates, Tau and GSH, this finding of increased loss of "sulfur" from the body in the form of sulfate, may be linked with the decline in tissue GSH pools in HIV infection (20).

Metabolic studies in rats, using isotopically labeled cysteine and methionine, show that activation of the immune system by bacteria leads to an enhancement of the transsulfuration pathway (21) and increased hepatic Tau production with an increase in GSH concentrations in liver, spleen, kidney, and muscle (22). Despite enhanced flux of substrate through the transsulfuration pathway, supplies of cysteine may not meet the requirements for maintaining GSH concentrations under conditions of raised oxidant stress. Observations in experimental animals and patients indicate that antioxidant defenses become depleted during infection and after injury. For example, in mice infected with influenza virus, there were 27, 42, and 45% decreases in the vitamin C, vitamin E, and...
GSH contents of blood, respectively (23). In asymptomatic HIV infection, substantial decreases in GSH concentrations in blood and lung epithelial lining fluid have been noted (24). In patients undergoing elective abdominal operations, the GSH content of blood and skeletal muscle fell by over 10% and 42%, respectively, within 24 h of the operation (25). Furthermore, reduced tissue GSH concentrations have been noted in hepatitis C, ulcerative colitis, cancer, and cirrhosis (26). When GSH status was reduced in rats by injection of diethyl maleate, which binds irreversibly to GSH, rendering it inactive, a sublethal dose of TNF became lethal (27), thus illustrating the importance of GSH in protection from the adverse effects of proinflammatory cytokines. The onset of sepsis in patients leads to a transient decrease in the total antioxidant capacity of blood plasma (a functional measure of the total antioxidant content) (28). The capacity normalized over the following 5 days in patients who survived but not in those who died.

A reduction in the strength of antioxidant defenses may increase the risk of damage to the host via transcription factor activation leading to up-regulation of proinflammatory cytokine production (see below). Thus, from the foregoing description of events in patients, it may be beneficial to increase methionine intake above the levels encountered in a normal dietary intake. However, special attention should be paid to folic acid and vitamins B-6 and B-12 under these circumstances.

Mechanism of the effects of oxidants and glutathione on immune function. Antioxidants not only suppress inflammatory components of the response to infection and trauma but enhance components related to cell-mediated immunity. The reverse situation applies when antioxidant defenses become depleted. The oxidant molecules produced by the immune system may activate at least 2 important families of proteins that are sensitive to changes in cellular redox state. The families are nuclear transcription factor NF-κB (NF-κB and activator protein 1 (AP1)). NF-κB is present in the cytosol in an inactive form by virtue of being bound to IκB. Phosphorylation and dissociation of IκB renders the remaining NF-κB dimer active. Activation of NF-κB can be brought about by a wide range of stimuli including proinflammatory cytokines, hydrogen peroxide, mitogens, bacteria, and viruses and their related products, and UV and ionizing radiations. The dissociated IκB is degraded, and the active NF-κB translocates to the nucleus, where it binds to response elements in the enhancer and promoter regions of genes. A similar translocation of AP1, a transcription factor composed of the protooncogenes c-fos and c-jun, from cytosol to nucleus, also occurs in the presence of oxidant stress. Binding of the transcription factors is implicated in activation of a wide range of genes associated with inflammation and the immune response, including those encoding cytokines, cytokine receptors, cell adhesion molecules, acute-phase proteins, and growth factors (29).

Unfortunately, NF-κB activates transcription of HIV genes and accounts for the ability of minor infections to speed the progression of individuals who are infected with HIV toward AIDS. If antioxidant defenses are poor, each encounter with general infections results in cytokine and oxidant production, NF-κB activation, and an increase in viral replication. It is thus unfortunate that reduced cellular concentrations of GSH are a common feature of asymptomatic HIV infection (24).

Oxidant damage to cells will indirectly create a proinflammatory effect by the production of lipid peroxides. This situation may lead to up-regulation of NF-κB activity because the transcription factor has been shown to be activated in endothelial cells cultured with linoleic acid, the main dietary n-6 polyunsaturated fatty acid, an effect inhibited by vitamin E and NAC (30). In cirrhosis, lipid peroxide production is increased. In a study on such patients, an inverse relationship between GSH concentration and the ability of monocytes to produce IL-1β, IL-8, and TNF-α was observed (31). Furthermore, treatment of the patients with OTC increased monocyte GSH content and reduced IL-1β, IL-8, and TNF-α production. Thus, antioxidants might act to prevent NF-κB activation by quenching oxidants. However, not all transcription factors respond to changes in cell redox state in the same way. When rats were subjected to depletion of effective tissue GSH pools by administration of diethyl maleate, there was a significant reduction in lymphocyte proliferation in spleen and mesenteric lymph nodes (32). In an in vitro study using HeLa cells and cells from human embryonic kidney, both TNF and hydrogen peroxide resulted in activation of NF-κB and AP1 (33). Addition of the antioxidant sorbitol to the medium suppressed NF-κB activation (as expected) but (unexpectedly) activated AP1. Thus, the antioxidant environment of the cell might exert opposite effects on transcription factors closely associated with inflammation (e.g., NF-κB) and cellular proliferation (e.g., AP1). Evidence for this biphasic effect was seen when GSH was incubated with immune cells from young adults (34). A rise in cellular glutathione content was accompanied by an increase in IL-2 production and lymphocyte proliferation and a decrease in production of the inflammatory mediators PGE_2 and LTB_4. Modification of the GSH content of liver, lung, spleen, and thymus in young rats, by feeding diets containing a range of casein (a protein with a low sulfur amino acid content) concentrations, changed immune cell numbers in lung (35).

It was found that in unstrained animals the number of lung neutrophils decreased as dietary protein intake and tissue glutathione content fell. However, in animals given an inflammatory challenge (endotoxin), liver and lung GSH concentrations increased directly in relation to dietary protein intake. Lung neutrophils, however, became related inversely with tissue GSH content. Addition of methionine to the protein-deficient diets normalized tissue GSH content and restored lung neutrophil numbers to those seen in unstrained animals fed a diet of adequate protein content (35).

Thus, it can be hypothesized that antioxidants exert an immunoenhancing effect by activating transcription factors that are strongly associated with cell proliferation (e.g., AP1) and an ant-inflammatory effect by preventing activation of NF-κB by oxidants produced during the inflammatory response. An increased intake of methionine may facilitate this situation.

**Direct effects of glutathione on immune function.** One of the first indications that GSH influences aspects of immune function that are related to T lymphocytes came from a study in which the concentrations of lymphocytes was measured in a group of healthy volunteers (15). The numbers of helper (CD4^+^) and cytotoxic (CD8^+^) T cells increased in parallel with intracellular GSH concentrations up to 30 nmol/mg proteins. However, the relation between cellular GSH concentrations and cell numbers was complex, with numbers of both subsets declining at intracellular GSH concentrations between 30 and 50 nmol/mg protein. The study also revealed that cell numbers were responsive to long-term changes in GSH content. When the subjects engaged in intensive exercise daily for 4 weeks, a fall in GSH concentrations occurred. Individuals with GSH concentrations in the optimal range before exercise, who experienced a fall in concentration after exercise, showed a 30% fall in CD4^+^ T-cell numbers. The decline in T-cell number was prevented by administration of NAC. Thus, immune cell function may be sensitive to a range of intracellular sulfhydryl compounds including GSH and cysteine. In HIV^+^ individuals and patients with AIDS, a reduction in cellular and plasma GSH has been noted (24). It is unclear, at present, whether the depletion in lymphocyte population that occurs in these subjects is related to this phenomenon. However, in a large randomized, double-blind, placebo-controlled trial, administration of 600 mgd of NAC for 7 mo resulted in both antiinflammatory and immunoenhancing effects (19). A decrease in plasma IL-6 concentration occurred, together with an increase in lymphocyte count and in the stimulation index of T lymphocytes in response to tetanus toxoid. The precise mechanism underlying the complex effects of changes in cellular GSH content are not clear, and whether they related to GSH function as an antioxidant or to some other property is not apparent. However, a recent study suggests that GSH promotes IL-12 production by antigen-presenting cells, so driving T helper cells along the Th1 pathway of differentiation (36).

**Influence of dietary sulfur amino acid intake on tissue glutathione content and immune function.** Cellular concentrations of GSH have been linked to T-cell numbers in healthy subjects (15). How alterations in sulfur amino acid intake influence this relation is unclear. Tissue GSH content responds to sulfur amino acid intake as detailed earlier. The other 2 amino acid precursors glutamine and glycine have an impact of tissue GSH concentrations (37–40). Three potential ways of enhancing cellular GSH content are administration of the 3 amino acids (cysteine, glutamic acid, and glycine) that comprise the tripeptide, either singly or in various combinations; administration of cofactors for the metabolic pathways leading to GSH production (i.e., vitamin B-6, riboflavin, and folic acid); and administration of NAC or OTC, which become converted to precursors of GSH.

Studies using animal models of inflammation have shown that a low-protein diet will suppress GSH synthesis, a situation that is reversed by provision of cysteine or methionine (35,41). Beneficial effects on immune function, morbidity, and mortality were observed in burned children when additional protein in the form of whey protein (the milk protein richest in sulfur amino acids) was fed (42).
Recent animal studies and clinical trials with NAC and OTC have demonstrated the ability of these compounds to enhance GSH status (20, 43, 44). In patients with sepsis, NAC infusion was shown to increase blood GSH, decrease plasma concentrations of IL-8 and soluble TNF receptors (an index of TNF production), improve respiratory function, and shorten the number of days needed in intensive care (44, 45). Although not affecting mortality rates, administration of NAC shortened hospital length of stay by >60%. OTC administration increased whole-blood GSH in peritoneal dialysis patients, normalized tissue GSH in rats fed a sulfur amino acid-deficient diet, and decreased the extent of inflammation in a rat peritonitis model (44). In a randomized double-blind controlled study on asymptomatic HIV-infected patients, oral OTC treatment increased GSH concentrations in whole blood (19). Other randomized studies on asymptomatic HIV-positive patients in the presence and absence of antiretroviral therapy have shown that NAC can raise blood GSH, increase natural killer cell activity, and enhance stimulation indices of T cells incubated with mitogen or tetanus toxin (19, 46). Furthermore, survival time was improved in HIV+ patients who maintained high concentrations of GSH in CD4+ T lymphocytes (47). It could therefore be surmised that improved T-cell function and reduced inflammation are modulated by improvement of antioxidant status in these patients.

Homocysteine and immune function

In vitro studies, using Hcy concentrations within a similar range to that shown in the in vivo study of Ditscheid et al. (9), show activation of monocytes and increased adhesion to endothelial cells, a proatherogenic effect. It is unclear whether a similar phenomenon would necessarily occur in vivo as cells in culture are free from the physiological control system they encounter in vivo (13). Nonetheless, a study on patients with Parkinson's disease showed a positive relation between serum Hcy and neopterin concentrations (an index of a Th1 type immune response), indicating that raised inflammatory stress and Hcy accumulation are interlinked (14).

Raised plasma Hcy has been linked with an increased risk of atherosclerosis. Recent studies have shown that the inflammatory arm of the immune system is intimately linked to the pathogenesis of atherosclerosis. Potentially, therefore, metabolic and nutrition conditions that raise concentrations of this metabolite might be expected to modulate immune function. An increased intake of methionine, inadequacy of folic acid (and possibly Vitamins B-6 and B-12), and a genotype that results in reduced recycling of Hcy to methionine are all conditions that enhance plasma Hcy concentration. Recent studies in young women show that, even with an adequate intake of folic acid, individuals with the TT variant of the methylenetetrahydrofolate reductase (MTHFR) 677 C→T polymorphism have an increased synthesis rate of Hcy and raised plasma concentrations (3). Although no direct measures of immune function have been performed in any study examining the effects of dietary or genomic factors on Hcy concentrations, in vitro studies using Hcy concentrations within a similar range show activation of monocytes and increased adhesion to endothelial cells, a proatherogenic effect. It is unclear whether a similar phenomenon would occur in vivo (13). Aging is associated with a decrease in immunocompetence associated with an increase in inflammatory stress; it is thus interesting to note that in a study where plasma neopterin and Hcy were examined in men and women ranging from 33 to 95 y of age that there was a steady increase in both substances (48, 49). The association between Hcy and neopterin suggests that either monocyte activation enhances Hcy synthesis or that Hcy acts as a stimulator of monocyte activity. The latter seems most likely. In a study in which the interaction between monocytes and cultured endothelial cells was examined, Hcy was shown to activate both cell types and bring about adhesion (13). This important observation indicates a cellular change that is associated with an early step in atherosclerosis. Widner et al. (14) noted a positive relation between the 2 molecules in a study on patients with Parkinson's disease. It is interesting to note that the raised plasma Hcy concentrations that occurred in the study of Ditscheid et al. (9), in which daily supplements of 1.5 g L-methionine were given, correspond to the lower end of the relation reported by Widner et al. (14). This may suggest an increase in monocyte activation following high dietary doses of L-methionine. However, caution should be applied to this conclusion because the methionine supplementation study was conducted on healthy subjects, whereas the Widner study was carried out on patients with Parkinson's disease (14).

Taurine and immune function

Taurine and sulfate can be regarded as biochemical endproducts of cysteine metabolism. However, it is apparent that Tau also plays a role in immune function. It is the most abundant free nitrogenous compound in cells. It is a membrane stabilizer and regulates calcium flux, thereby controlling cell stability. It has been shown to possess antioxidant properties and to regulate the release of proinflammatory cytokines in hamsters, rats, and humans (50–52).

The possibility that Tau might have immunomodulatory properties was indicated in studies in obligate carnivores, such as cats, in which taurine is an essential nutrient because of an inability to synthesize the compound. Premature infants have similar metabolic difficulties. In cats deprived of taurine, substantial impairment of immune function occurs (51). A large decline in lymphocytes, an increase in mononuclear cells, and a decrease in the ability of these cells to produce a "respiratory burst" and to phagocytose bacteria occurs. There was a rise in γ-globulin concentrations in deficient animals. Spleen and lymph nodes showed regression of follicular centers and depletion of mature and immature B-lymphocyte numbers. The changes were reversed by inclusion of taurine in the diets. Studies in other species have also reported effects of supplementation on immune system and function. In mice, administration of Tau prevented the decline in T-cell number that occurs with aging and enhanced the proliferative responses of T cells in both young and old mice (26). The effect was more marked in cells from old than young animals. Tau has been shown to ameliorate inflammation in trinitrobenzene sulfonic acid–induced colitis.

Taurine interacts with hypochlorous acid, produced during the "oxidant burst" of stimulated macrophages, to produce taurine chloramine (TauCl). This compound may have important immunomodulatory properties and may be responsible for properties that have been ascribed earlier to taurine. In vitro studies have shown that an increase in taurine concentration from physiological to superphysiological concentrations has no effect on proinflammatory cytokine production by peripheral blood mononuclear cells. However, TauCl inhibits nuclear factor-κB activation and the capacity for proinflammatory cytokine production, producing an antinflammatory effect (52). TauCl inhibited NO, PGE2, TNF-α, and IL-6 production from stimulated macrophages in culture and the ability of antigen-presenting cells to process and present ovalbumin (28). Furthermore, in in vitro studies on human PBMCs, no taurine concentration in a range 0 to 500 μmol/L was shown to influence TNF-α or IL-1β production, but a concentration of TauCl above 250 μmol/L was able to decrease production of both cytokines (53). An oral dose of 0.1 mg/kg L-methionine raises plasma taurine to 120 μmol/L; thus, the effect may not be of physiological significance (12). In in vitro studies with murine dendritic cells, the compound altered the balance of Th1 to Th2 cytokines, suggesting that it might play a role in maintaining the balance between the inflammatory response and the acquired immune response.

Concluding remarks

Without doubt sulfur amino acids play an important role in maintaining immune function. Their actions also play a pivotal role in the effectiveness of antioxidant defense. This latter action indirectly influences immune function by modulating the actions of oxidant stress in transcription factor activation. Despite the clear theoretical importance of sulfur amino acids in immune function, little direct experimentation has been performed on human subjects to explore the full effects of this important group of amino acids on immune function. The findings of raised plasma Hcy concentrations following consumption of increased amounts of L-methionine and the ability of Hcy to stimulate inflammatory events in vitro sound a cautionary note as far as the impact that supplementary L-methionine might have in human diets. There is, however, no strong scientific basis for this caution until definitive studies have been performed. In these studies a number of areas of uncertainty need investigation before it can be claimed that high doses of L-methionine have no influence on immune function: 1) concomitant measurements of glutathione and immune function (T-cell activity, inflammatory stress) in individuals at different stages in the life cycle; 2) concomitant measurements of Hcy and immune function (as above) when high doses of L-methionine are added to a normal diet and diets enhanced with folic acid, vitamins B-6 and B-12; and 3) investigations on the impact of functional single-nucleotide polymorphisms that influence folate metabolism on the areas highlighted above.

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