Adequate Range for Sulfur-Containing Amino Acids and Biomarkers for Their Excess: Lessons from Enteral and Parenteral Nutrition

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ABSTRACT The adequacy range of dietary requirements of specific amino acids in disease states is difficult to determine. In health, several techniques are available allowing rather precise quantification of requirements based on growth of the organism, rises in plasma concentration, or increases in the oxidation of marker amino acids during incremental administration of the amino acid under study. Requirements may not be similar in disease with regard to protein synthesis or with regard to specific functions such as scavenging of reactive oxygen species by compounds including glutathione. Requirements for this purpose can be assessed only when such a function can be measured and related to clinical outcome. There is apparent consensus concerning normal sulfur amino acid (SAA) requirements. WHO recommendations amount to 13 mg/kg per 24 h in healthy adults. This amount is roughly doubled in artificial nutrition regimens. In disease or after trauma, requirements may be altered for methionine, cysteine, and taurine. Although in specific cases of congenital enzyme deficiency, prematurity, or diminished liver function, hypermethionemia or hyperhomocysteinemia may occur, SAA supplementation can be considered safe in amounts exceeding 2–3 times the minimal recommended daily intake. Apart from some very specific indications (e.g., acetaminophen poisoning), the usefulness of SAA supplementation is not yet established. There is a growing body of data pointing out the potential importance of oxidative stress and resulting changes in redox state in numerous diseases including sepsis, chronic inflammation, cancer, AIDS/HIV, and aging. These observations warrant continued attention for the potential role of SAA supplementation. In particular, N-acetylcysteine remains promising for these conditions. J. Nutr. 136: 1694S–1700S, 2006.

KEY WORDS: glutathione • deficiency • N-acetylcysteine supplementation

The importance of adequate amino acid intake is unequivocal. Insufficient intake of specific amino acids can lead to functional deficiencies, but high plasma levels of some amino acids may have detrimental effects. To furnish an optimal amino acid mixture remains a challenge also because the requirements for amino acid intake are determined by many factors including age, liver function, renal function, and catabolism caused by disease or trauma. Moreover, amino acids are generally not ingested or administered as free amino acids but rather as protein or short-chain peptides after protein hydrolyzation. Adequacy of amino acid intake is not simply determined by the amount that actually enters the body.

The balance among protein, carbohydrates, trace elements, and other macronutrients in the feed, as well as the feeding frequency and modus (bolus feeding or continuous artificial feeding), determine to a large extent the efficacy of amino acid utilization to serve protein synthesis and maintenance or growth of cellular mass (1). After enteral ingestion, protein is broken down to its constituent amino acids within the gut. While still in the gut, these amino acids can be utilized for protein resynthesis, which facilitates a gradual release of amino acids in the portal vein (2). Protein thus residing in the gut is referred to as the labile protein pool. Protein with an amino acid composition that allows resynthesis of protein after digestion to amino acids while still in the gut is considered to be of high biological value because it releases its constituent amino acids to the liver and the rest of the body more gradually than protein with a low biological value (1–5). The more gradual this “autoinfusion” of amino acids from the labile protein pool, the more efficiently the amino acids can be used in functional metabolic processes, and less amino acids are “lost” to ureagenesis (2,6).

After enteral administration most amino acids are subject to first-pass extraction (7,8). The supposed influence of splanchnic extraction on sulfur amino acid requirements in enteral versus parenteral nutrition (9) remains unclarified because amino acids extracted by the gut may actually serve intestinal...
metabolism; likewise, parenterally administered amino acids may be extracted similarly after reaching the gut through the circulation.

Various methods to assess requirements of specific amino acids have been proposed (10). Obviously recommendations based on these different approaches are variable, and the external validity of these experiments may be hampered by the small sample size that is generally applied, leading to large confidence intervals (11). Most importantly, these experiments are conducted in healthy volunteers and are aimed at the general population.

However, specific amino acid requirements are altered in disease (12), and recommendations for the general population may not be valid in situations in which the adequacy of the amino acid or protein component of the diet may be crucial to sustain body composition and function. Because there is no tailor-made recipe for amino acid supplementation in various disease states, biomarkers for the adequacy of specific amino acids are needed to monitor amino acid supply. Such biomarkers should be based on physiological functions of the amino acid in question and should preferably be suitable to reflect excess as well as deficiency.

This review concerns the adequacy of dietary provision of the sulfur-containing amino acids (SAA)⁴ methionine and cysteine with a special focus on potential biomarkers of their deficiency or excess.

SAA metabolism

**Methionine and homocysteine.** Methionine breakdown occurs by transmethylation to homocysteine (13). The first step in this pathway is the conversion of methionine to S-adenosylmethionine, which can donate its methyl group for numerous methylation processes including DNA methylation. Separation of the methyl group yields S-adenosylhomocysteine, which can be converted to homocysteine. Homocysteine can be remethylated to methionine by the folate- and vitamin B-12-dependent enzyme methionine synthetase or enter the irreversible transsulfuration pathway.

**Transsulfuration.** Homocysteine can donate its sulfur group to serine, forming cystathionine under influence of the vitamin B-6-dependent enzyme cystathionine synthetase. Cystathionine can subsequently be broken down to cysteine and α-ketobutyrate. During this 2-step process the homocysteine sulfur group is transsulfurated to the serine carbon skeleton, forming cysteine. Transsulfuration occurs preferentially in the liver and the kidney (13). The plasma cysteine pool is quite distinct from the intracellular cysteine pool. More than 95% of protein-free cysteine in plasma is found in cysteine-cysteine dipeptides (cystine) at a total cysteine concentration ([cysteine] + 2 [cystine]) of ~180 μmol/L (14). Reduced cysteine in plasma is primarily found in albumin that contains 1 free cysteine residue with a free thiol group per molecule and accounts for 80% of the free thiols in plasma (15). Cysteine (or cystine) is transported into the cell by several sodium-dependent transporters with a Km that exceeds the normal plasma level of cysteine ~2.5-fold (16). Intracellular cysteine pools and fluxes can therefore readily be modulated by supplemental cysteine (17,18). Intracellularly most cyst(e)ine is found in its reduced form. Intracellular total cyst(e)ine ([cysteine] + 2[cystine]) concentrations range from 20 to 300 μmol/kg wet weight (19), dependent on the affinity of the various transporters on different cells (20). Cells with active cyst(e)ine metabolism such as intestinal, hepatic, and renal tubular cells generally express high-affinity transporters and have higher cyst(e)ine levels. Uptake of cyst(e)ine is also dependent on the extracellular redox state.

**GSH synthesis and metabolism.** Most cysteine within the cell is found in the tripeptide glutathione (GSH), which is synthesized from glutamate, glycine, and cysteine and is found in millimolar ranges. Its concentrations are highest in the gastrointestinal tract and the liver (14). GSH can reduce reactive oxygen species on oxidation to its disulfide GSSG and form S-conjugates with electrophilic foreign compounds by the GSH-S-transferase enzymes (21). In fact, all intracellular thiols can form disulfide bridges, forming numerous redox couples, but GSH-GSSG is by its abundance the most representative and therefore most widely studied intracellular redox couple (22). Increased oxidative stress induces a right shift in the GSH:GSSG ratio. GSSG can be reduced by the NADPH/NADP⁺-dependent enzyme glutathione reductase to GSH to restore the redox potential, but this activity can be inhibited by decreased NADPH/NADP⁺ redox level, whereafter GSSG is exported from the cell, to restore GSH redox state (23). This leads to reduction of the cellular GSH pool, and hence the cellular reductive potential becomes dependent on glutathione de novo synthesis (24). Other GSH-S conjugates are also exported from the cell.

**Taurine.** Taurine is formed from cysteine via several enzymatic steps, of which the action of cysteine sulfonic acid decarboxylase is believed to be rate limiting (25). Taurine is involved in conjugation of bile acids and is as such subject to enterohepatic cycling (26). Intracellular taurine levels are maintained 50- to 100-fold higher than extracellular concentrations by active membrane transport through the taurine transporter (25). This osmotic gradient contributes to the maintenance of cellular hydration state.

**Normal daily sulfur amino acid requirements.**

Methionine is the only essential SAA and can provide sulfur for cysteine and taurine synthesis. Animal protein is generally considered to be a better source of SAA than vegetable protein. This is primarily because the biological value of animal protein is higher than that of vegetable protein (2,6). Soy, which is the only vegetable protein used for artificial enteral nutrition, is also low in absolute SAA content (6,27).

Increasing cysteine intake can reduce methionine requirements (28). From the classical experiments of Rose (29) in healthy men, it was calculated that the minimal intake of methionine required to maintain nitrogen balance is 1.10 g/d, which comes down to ~13 mg/kg. This number was reproduced

### TABLE 1

**Daily sulfur amino acid requirements**

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th>Preschool children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Millward (30)</td>
<td>29</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Di Buono (11)</td>
<td>27</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Dewey (31)</td>
<td>27</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Young (32)</td>
<td>58</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>FAO/WHO/UNU (33)</td>
<td>58</td>
<td>27</td>
<td>13</td>
</tr>
</tbody>
</table>

Mean daily requirement of sulfur amino acids (methionine + cysteine) (mg/kg) according to different estimations. NB population safe requirements exceed the mean requirements by statistical definition of 2 standard deviations.

⁴ Abbreviations used: GSH, glutathione, GSSG, glutathione disulfide; SAA, sulfur-containing amino acids.
In several other attempts to define SAA requirements (11,30–33) (Table 1). In a recent study it was shown that this intake also is sufficient to maintain glutathione synthesis in healthy volunteers (34). In infancy and childhood, the dietary requirement for SAA is higher (Table 1). The SAA derivative taurine is considered (conditionally) indispensable in neonates and in growing children, although this indispensability may (partly) depend on lack of intestinal function. This issue is addressed below. At present, taurine is a standard component in infant feeding formulas.

SAA requirements in elderly subjects are unknown, but it has been suggested that the altered redox state reported in the elderly (35–38) requires increased ingestion of SAA. In contrast, the safe upper limit of chronic SAA supplementation may be reached earlier in the elderly because of accumulation of homocysteine, which is considered a risk factor for the development of atherosclerosis (36). Hyperhomocysteinemia may, however, be prevented by adequate vitamin B and folate supplementation.

**Biomarkers for adequate supply**

A prerequisite for the definition of biomarkers for SAA deficiency or toxicity is the definition of SAA deficiency and toxicity themselves. This requires clinical trials that prove the presence of SAA deficiency by counteracting the clinical consequences of SAA deficiency by SAA supplementation. Only in this way can potential biomarkers be linked to adequacy of SAA supplementation.

Unfortunately, most potentially interesting areas for SAA supplementation have not been investigated in larger clinical trials. Consequently, no proven valid biomarkers for potential sulfur-containing amino acid deficiency are at hand. Nevertheless, the plasma concentration and redox state of GSH are presently important surrogate endpoints of clinical studies. However, the intracellular localization of GSH metabolism, and the discrepancy between intra- and extracellular GSH concentration and redox state, together with the dynamic and rapid interconversion of thiols, makes the redox status of the GSH:GSSG and other redox couples very difficult to interpret (39).

Even when deficiencies are established, it is uncertain whether this will lead to clinically applicable biomarkers. This is exemplified by glutamine, a nonessential amino acid that has clearly been shown to become deficient in catabolic states (40). Glutamine is especially of interest in the present context because its tissue and plasma concentrations have been found to closely correspond with GSH concentrations (41–43), although this obviously does not necessarily mean that there is an actual glutamine or glutathione deficiency. Low tissue glutamine concentrations are generally believed to reflect a deficiency of glutamine supply despite the fact that these concentrations can not be increased by ample exogenous glutamine supply (up to 40 g/d) (44). Therefore, the clinical benefits of glutamine supplementation do not appear to be related to increased intracellular glutamine levels. The uphill gradient of glutamine (low in plasma, high in the cell) most likely is maintained by active ATP-driven Na\(^+\)-linked transport, which may fail in conditions of severe inflammatory activity. Therefore, low tissue glutamine levels may reflect disease state rather than glutamine depletion. This probably explains why administration of glutamine increases glutamine plasma flux and plasma concentrations of glutamine but does not increase tissue concentrations. The regulation of tissue GSH levels may be subject to similar mechanisms. The close connection with tissue glutamine concentrations, the steep uphill gradient between plasma and tissue concentrations, and the variable success of trying to raise levels by supplementing precursors suggests that low tissue levels reflect inflammatory activity rather than depletion.

In the case of glutathione, this view is substantiated by the fact that, in renal tubular cells, mitochondrial glutathione concentration almost exclusively relies on transport because GSH is synthesized in the cytoplasm and not in the mitochondria. This transport is carrier linked, which may be influenced by different disease states (45). It is therefore not yet established which of the intermediates and products, or which of the kinetic characteristics of GSH metabolism, may serve as a biomarker or as a marker of depletion or sufficiency. Identification of a biomarker is further complicated by the fact that free thiols exist as cysteinylglycine, as cysteine, as GSH and as protein bound cysteine or GSH. All these thiols can readily interconvert to form disulfide bridges with other thiols and most likely do so at different speeds, hampering simple establishment of a status parameter or biomarker.

Ideally, a biomarker should reflect adequacy of a biological function in a precise manner. In the case of GSH, most attention is paid to its potential to scavenge reactive oxygen species. Subsequently, this function should closely correspond with other surrogate markers such as malondialdehyde, peroxynitrite, superoxide dismutase, and, most importantly, clinical outcome. One of the few evidence-based indications for N-acetylcysteine (N-acCys) supplementation is acetaminophen intoxication. This acute situation, however, may not be optimal to study intermediate metabolism of GSH and to monitor potential biomarkers. More promising (because predictable) fields to study biomarkers for cysteine adequacy in relation with GSH metabolism may be found in standardized human situations of increased GSH oxidation. Promising examples in this context are the administration of radioactive iodine in radiology (46) or the application of hepatic inflow occlusion in liver surgery, which induces ischemia of a large part of the healthy liver for a fixed period of time, giving rise to oxidative stress (Fig. 1). Another, more general approach to monitor amino acid adequacy has been proposed by Bérard et al. and involves the assessment of changes in amino acid levels during artificial nutrition. If changes in amino acid levels reflect their over- or undersupply, a tailor-made mixture could be offered based on these changes. This approach improved nitrogen balance in a small population of surgical patients (47).

![FIGURE 1](https://academic.oup.com/jn/article-abstract/136/6/1694S/4664460/fig1)
Potential SAA deficiencies and rationale for supplementation

**Methionine.** As for any essential amino acid, inadequate methionine intake impairs protein synthesis (29,48). Chronic dietary folate insufficiency causing methionine deficiency, and DNA hypomethylation has been implicated in carcinogenesis (49,50) This theory is circumstantially supported by large longitudinal epidemiologic studies showing that low intake of methionine, and more frequently of folate is related to the development of colorectal cancer (49,50) and breast cancer (51). An accumulation of methionine is likely to occur in patients with disturbances in the transmethylation and transsulfuration pathways as a result of genetic polymorphisms or or hepatic dysfunction (52). Burn patients may have an increased demand for methionine to maintain nitrogen balance (53).

**Cysteine.** Cysteine deficiency may occur as a result of insufficient intake, transsulfuration defects, and in cases of increased demand (increased need for GSH synthesis). Cysteine deficiency has been suggested to occur and to lead to changes in GSH metabolism (17,18,35,38,39,54–58) (Table 2). Also, glycine and glutamate depletion have been implicated in diminished glutathione synthesis (42,57), but based on its pool size, cysteine is most frequently named as the rate-limiting constituent (59). In a previous part of this article we already indicated that free cysteine has a very small pool size, but cysteine thiol is abundantly available in di-, tri-, and polypeptides and in protein, both as thiols and as disulfides.

Because GSH metabolism is an almost exclusively intracellular process that does not equilibrate with the plasma compartment, disturbances in GSH and cysteine metabolism are difficult to assess in vivo. GSH synthesis can be assessed in vivo by measuring the rate of incorporation of precursors during stable isotope infusion. Human data on glutathione synthesis exclusively concern erythrocyte metabolism. Decreased synthesis rates in erythrocytes have been found in healthy volunteers receiving an SAA-free diet (59), in weight-losing obese patients (60), in septic children (18,56), and in HIV-positive patients (17).

It has been shown in several studies that short-term supplementation of N-acCys leads to an increase in GSH synthesis (17,18) as well as to an improved redox state (38). Interestingly, erythrocyte glutathione synthesis decreased transiently when protein intake was reduced from habitual intake to the recommended amount (34). This may reflect substrate-induced down-regulation of GSH-synthesizing enzymes and cast some doubt on the long-term effects of cysteine supplementation.

Human data concerning GSH concentrations and GSH:GSSG ratio indicate that tissue GSH concentrations and redox state are depressed in inflammatory bowel disease (39), following abdominal surgery (57), as well as in critical illness (42), aging, and cancer (38) (Table 2). In addition, it has been suggested that maintenance of GSH concentration and redox status coincides with maintenance of functional performance in elderly people and with a delay the process of aging.

Interesting data from the group of Dröge (38) suggest that the plasma and intracellular redox state is causally related to a decrease in body cell mass and functional capacity in cancer patients. Oral administration of N-acCys improved redox state. This change was related to an increased body cell mass and decreased inflammatory activity in some selected patient groups and improved quality of life. However, confirmation of these findings by other groups is necessary to establish their value.

A few well-designed trials concerning children with protein-energy malnutrition (61) and patients undergoing abdominal surgery (62) failed to show significant effects on clinical endpoints. In a recent meta-analysis it was shown that N-acCys may reduce contrast-induced nephrotoxicity (46), but in several subsequent large randomized clinical trials this conclusion was disregarded again (63–65).

Currently the only robust indication for N-acCys use is in the treatment of acetaminophen-induced hepatotoxicity (54).

**Taurine.** It has been shown that children receiving parenteral nutrition without supplemental taurine developed low taurine plasma levels and neuronal (especially retinal) dysfunction, which could be counteracted by addition of taurine to the feed (66). The indispensability of taurine in this condition is generally ascribed to low expression of taurine biosynthetic enzymes, which can account for only a very slow renewal of the total body pool of taurine. Consequently, adequate mechanisms should operate to conserve the body pool of taurine including enterohepatic cycling of taurine (26). Most children on long-term parenteral nutrition suffer from intestinal malabsorption inducing substantial losses of bile acids and taurine in their stools. In children with healthy intestines and normal enterohepatic cycling, taurine may not be indispensable. Similarly adult patients with intestinal malabsorption, for example cholestatic diarrhea, may suffer substantial losses of taurine. No data, however, are available on this subject.

### TABLE 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tissue</th>
<th>Methods</th>
<th>Reference</th>
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<tbody>
<tr>
<td>HIV</td>
<td>Erythrocytes</td>
<td>Stable isotopes</td>
<td>(17)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Intestinal mucosa</td>
<td>GSH concentration</td>
<td>(39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GSH:GSSG ratio</td>
<td></td>
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<tr>
<td>Elective surgery</td>
<td>Muscle</td>
<td>GSH concentration</td>
<td>(57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GSH:GSSG ratio</td>
<td></td>
</tr>
<tr>
<td>Critical illness</td>
<td>Muscle</td>
<td>GSH concentration</td>
<td>(18, 56)</td>
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<tr>
<td></td>
<td>Erythrocytes</td>
<td>GSH:GSSG ratio</td>
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<tr>
<td></td>
<td></td>
<td>Stable isotopes</td>
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<tr>
<td>Ischemia reperfusion</td>
<td>Liver</td>
<td>GSH concentration</td>
<td>(55)</td>
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<td></td>
<td></td>
<td>GSH:GSSG ratio</td>
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<tr>
<td>Aging</td>
<td>Plasma</td>
<td>GSH concentration</td>
<td>(35)</td>
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<tr>
<td></td>
<td></td>
<td>GSH:GSSG ratio</td>
<td></td>
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<tr>
<td>Cancer</td>
<td>PBMCs</td>
<td>GSH concentration</td>
<td>(38)</td>
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<td></td>
<td></td>
<td>GSH:GSSG ratio</td>
<td></td>
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<tr>
<td>Acetaminophen poisoning</td>
<td>Liver</td>
<td>N-Acetylcysteine supplementation</td>
<td>(54)</td>
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<tr>
<td>Burns</td>
<td>Leukocytes</td>
<td>GSH concentration</td>
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The particularly high abundance of taurine in lymphocytes suggests an important role in the immune system. Taurine further has been suggested to be involved in stabilization of cell membrane potential and regulation of Ca^{2+} transport through several calcium-ion channels and to control cardiomyocellular contraction, which provides a rationale for addition of taurine to commercially available energy drinks. Although taurine is not considered essential in human nutrition, it has been suggested that subjects on strictly vegetarian diets run the risk of developing taurine deficiency because taurine is primarily found in animal protein (67). Convincing data supporting this claim are lacking, however (68).

**SSA supplementation and toxicity**

**Methionine.** As an essential amino acid, methionine is a standard component of artificial feeding formulas. According to the reported methionine amount and dose recommendation of standard tube feeds (Table 3), the daily amount of methionine administered to enterally or parenterally fed patients is ~26 mg/kg per day, which apparently is twice the minimally required amount. Disease-specific feeds for malnutrition or metabolic stress are even higher in total protein and SSA content and provide ~4 times the recommended daily dose of SSA.

Amino acid concentrations of pediatric protein and hydrolysate-based enteral formulas exceed that of breast milk, leading to a moderate increase of plasma levels of amino acids and urea nitrogen in enterally fed children (69). The consequences of this mild elevation of blood nitrogen concentration are difficult to assess in the light of the other differences between formula feeds and mother milk. However, no clinical data indicating specific amino acid toxicity in formula-fed children without errors in metabolism are known.

Methionine intake in infants at 14–28 d with various formulas may reach up to 120 mg/kg per day (70). A methionine-fortified hydrolysate providing up to 260 mg/kg per day to newborn healthy children was shown to induce only moderate elevations in methionine plasma level and no signs of methionine toxicity (71). In a retrospective case study of 10 children without enzyme deficiencies receiving the same methionine-fortified formula, however, severe hypermethionemia was found, which may have induced brain edema in 2 patients (70). References 70 and 71 are summarized in Figure 2. A conclusive explanation for the increased sensitivity to high methionine intake was not given, but these findings led the authors to suggest that precaution is especially warranted in premature children, children with a very low birth weight, and children with liver disease.

Toxicity of methionine in liver disease was established half a century ago, but in selected cases receiving the same formula that did experience severe hypermethionemia (71). The circles represent individual methionine intake in 58 children receiving a methionine-fortified protein hydrolysate without experiencing any side effects or adverse events that could be directly ascribed to methionine toxicity (70).

**FIGURE 2.** Summary of 2 studies describing the effects of high methionine intake in formula-fed children. The solid line represents a histogram of methionine intake in 58 children receiving a methionine-fortified protein hydrolysate without experiencing any side effects or hypermethioninemia (71). The circles represent individual methionine intake in selected cases receiving the same formula that did experience hypermethioninemia without (open circles) or with (closed circles) adverse effects that could be directly ascribed to methionine toxicity (70).
The metabolic value of supplemental taurine in nondepleted adult subjects is doubtful because it has been shown that 70% of supplemental taurine is excreted in the urine unchanged and another 25% is degraded by enteral bacteriae (80). Because of its supposed positive inotropic effects, taurine has been added to commercially available energy drinks in large amounts (1000 mg/L) with no untoward side effects. Although the true benefit of taurine on cardiovascular and mental performance is doubtful, it underlines the safety of high-dose taurine supplementation.

**Summary**

The adequacy range of dietary requirements of specific amino acids in disease states is difficult to determine. In health, several techniques are available that allow rather precise quantification of requirements either on the basis of growth of the organism or on the basis of rises in oxidation of a specific amino acid during its incremental administration. These requirements may not be similar in disease with regard to protein synthesis or with regard to specific functions such as scavenging of reactive oxygen species by glutathione. Requirements for such specific functions can be assessed only when such functions or sensitive surrogate markers can be measured and related to clinical outcome.

SAA supplementation can be considered safe in amounts exceeding 2–3 times the minimal recommended daily intake, and apart from methionine toxicity in liver disease, true SAA toxicity has been reported only anecdotally or in patients with inborn enzyme deficiencies. Apart from some very specific indications, the usefulness of SAA supplementation is not yet established. There is, however, an ever-growing body of data pointing out the potential importance of disturbances in redox state in numerous disease states including sepsis, chronic inflammation, cancer, AIDS/HIV, and aging. These observations warrant continued attention for the potential role of SAA supplementation. In particular, N-acetylcysteine remains a potentially promising drug for a variety of conditions in which redox state is disturbed.

**LITERATURE CITED**


