Nutritional and Functional Importance of Intestinal Sulfur Amino Acid Metabolism

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ABSTRACT The metabolism of sulfur amino acids, methionine and cysteine, has been linked to several key aspects of human health and cellular function. In addition, the metabolism of dietary amino acids by the gastrointestinal tract is nutritionally important for normal function. In the case of sulfur amino acids (SAAs), in vivo, stable isotope studies in adults suggest that the splanchic tissues utilize as much as 30–44% of the dietary methionine and cysteine. Similarly, the dietary methionine requirement is 30% lower in total parenteral nutrition (TPN)-fed piglets, a condition in which dietary nutrients largely bypass intestinal metabolism. These data suggest that intestinal metabolism of methionine is substantial, yet the intestinal metabolic fate of dietary methionine is largely unknown. Dietary cysteine likely plays a key role in intestinal epithelial antioxidant function as a precursor for glutathione. Moreover, cysteine and glutathione may also regulate cellular redox status by virtue of its thiol (–SH) moiety, but also as a precursor of glutathione, a major cellular antioxidant. The liver is generally considered to be the primary site of dietary methionine and cysteine metabolism in the body. However, in this review, we will discuss the evidence suggesting that intestinal sulfur acid metabolism may be nutritionally relevant and why it is important for gut function.

SAA metabolism. Methionine is a dietary indispensable amino acid because it cannot be synthesized in amounts sufficient to sustain normal growth in mammals. However, many tissues of the body are capable of converting methionine to cysteine via the enzymatic processes of transmethylation and transsulfuration (5). Because a portion of dietary methionine is normally converted to cysteine, numerous studies have shown that providing dietary cysteine can “spare,” reduce, or replace a portion of the requirement for methionine by as much as 50–80% in mammals and birds. Three important metabolic functions of methionine are: 1) transmethylation to form a primary methyl donor, S-adenosylmethionine (SAM), which methylates compounds to form products such as creatine and phosphatidylcholine, resulting in the product of methylation homocysteine being produced (Fig. 1); SAM can also be decarboxylated to form decarboxylated SAM, which then donates an aminopropyl group for polyamine synthesis after which methionine will be reproduced; 2) transsulfuration to form cysteine, which in turn is catabolized to taurine or glutathione; and 3) protein synthesis. Methionine can also enter the body pool by remethylation of homocysteine or protein breakdown. Key enzymes in the transsulfuration of methionine are: 1) cystathionine β-synthase, which condenses serine and homocysteine to form cystathionine, and 2) γ-cystathionase, which then cleaves cystathionine into cysteine and α-ketobutyrate.

Studies using isotopic tracers in adult humans indicate that both transmethylation and transsulfuration are twice as high during feeding than during fasting (6). Similarly, adult humans fed methionine alone [24 mg/(kg · d)] had higher rates of transmethylation and transsulfuration and lower rates of remethylation than adults fed 13 mg methionine/(kg · d) and 11 mg cysteine/(kg · d) (7). Moreover, the methionine-sparing effect of dietary cysteine appears to occur largely via reduction in transsulfuration (8). Stengink and Den Besten (9) were the first to show that the splanchic organs are an important site of transmethylation and transsulfuration of dietary methionine for the synthesis of cysteine. They found that the circulating cystine concentration was higher in adults given a cystine-free nutrient solution via the nasogastric compared with the i.v.

There is increasing evidence that sulfur amino acids (SAAs), methionine and cysteine, play an important metabolic and functional role in human health and disease. A greater understanding of whole-body metabolism of the SAAs is needed. Clinical studies indicate that elevated plasma levels of homocysteine, a key product of methionine metabolism, are strongly associated with increased risk of cardiovascular disease and more recently, Alzheimer’s disease (1,2) in adults, and with ischemic and hemorrhagic stroke in infants and children (3,4). Evidence suggests that the prooxidant properties of homocysteine contribute to oxidative stress and vascular injury, although the causal link between homocysteine and these diseases has not yet been established. Cysteine also plays a key role in cellular redox status by virtue of its thiol (–SH) moiety, but also as a precursor of glutathione, a major cellular antioxidant. The liver is generally considered to be the primary site of dietary methionine and cysteine metabolism in the body. However, in this review, we will discuss the evidence suggesting that intestinal sulfur acid metabolism may be nutritionally relevant and why it is important for gut function.

**KEY WORDS:** methionine • cysteine • homocysteine • transmethylation • transsulfuration • neonate
The original studies by Finkelstein (5) demonstrated that gastrointestinal tissues possess the enzymes necessary to metabolize methionine to cysteine, albeit at lower levels of activity than the liver. However, there are few reports describing the kinetics of methionine metabolism in the gut, either in vivo or in vitro with isolated enterocytes. Recent studies based on in vivo isotopic tracers in ruminants imply that methionine transmethylation occurs in the ruminant gut (20). Methionine transmethylation in the gut, without subsequent remethylation or transsulfuration, could result in net release of homocysteine into the circulation. Indeed, recent in vitro studies demonstrated that Caco-2 cells, a model of human colonic epithelial cells, produced substantial amounts of homocysteine and cystathionine, suggesting that the intestine may export homocysteine and contribute to the plasma homocysteine load (21). In agreement with these in vitro data are in vivo data that showed plasma total homocysteine to be significantly higher in enterally fed piglets than in parenterally fed piglets fed a similar diet, without any cysteine (22).

In the case of dietary cysteine, studies in pigs indicate that the rate of appearance in the portal blood is very limited (<20% dietary intake), suggesting extensive intestinal utilization of cysteine (14,23). The first step in cysteine catabolism is conversion to cysteine sulfinate via the enzyme cysteine dioxygenase. Approximately 70–90% of cysteine sulfinate is subsequently decarboxylated via cysteine sulfinate decarboxylase to produce hypotaurine, which is then oxidized to taurine via a poorly characterized enzymatic reaction (24). Alternatively, cysteine sulfinate may undergo transamination or oxidative deamination to form the putative intermediate, β-sulfobutyrate, which spontaneously decomposes to yield pyruvate and sulfite; this pathway accounts for 10–30% of cysteine sulfinate degradation. Rodent studies with 14C-labeled cysteine demonstrated significantly higher oxidation when given via the intragastric (70%) than intraperitoneal (41%) route, suggesting that nearly half of the whole-body cysteine oxidation occurs in splanchic tissues (24). More importantly, subsequent work demonstrated that intestinal enterocytes extensively metabolize cysteine via cysteine dioxygenase to cysteinesulfinate (25). In vivo rodent studies with i.v. infusion of isotopically labeled 13C-cysteine indicated that an important metabolic fate of cysteine in the gut is incorporation into glutathione (GSH), which would not involve oxidation of cysteine (26). Thus, it appears that the intestine has the enzymatic capacity for transmethylation and transsulfuration of methionine, and for oxidation of cysteine and GSH synthesis.

**Importance of SAAs in total parenteral nutrition (TPN)-fed neonates.** The metabolism of SAAs is particularly important in the nutritional support of neonatal infants. In neonatal animals, the slow maturation of the enzyme cystathionase may limit de novo cysteine synthesis (27–29). However, cystathionase activity is present in the adrenals and kidneys of both premature and term infants, suggesting that
term infants may not require additional cysteine (30). A second key consideration is that most preterm infants are administered TPN for a period of days to weeks before full enteral feeding is attained. Studies in parenterally fed, preterm infants (29 wk gestational age) showed that cysteine synthesis is virtually absent (31). Furthermore, in human neonates and adults and in pigs, parenteral feeding caused a reduction in plasma cysteine and cystine (9–11). These findings led to the idea that cysteine is conditionally indispensable in parenterally fed neonates, yet few commercial parenteral solutions contain appreciable amounts of cysteine and others contain no cysteine at all. Furthermore, if the gut is an important site of transsulfuration, then the observation of low plasma cysteine concentrations under conditions of TPN may be a result of the bypassing of intestinal methionine metabolism.

**Oxidant stress and intestinal SAA metabolism.** SAAs, especially cysteine, play a key role in antioxidant status and cellular function (32,33). Glutathione is the most important cellular antioxidant in mammals and has a critical function in responding to reactive oxygen species and maintaining cellular redox status. Reduced glutathione (GSH) is a ubiquitous tripeptide (-Glu-Cys-Gly) present throughout the body at relatively high intracellular concentrations, especially in the small intestine. Cellular GSH homeostasis is maintained through de novo synthesis from precursor SAAs (methionine and cysteine), regeneration from its oxidized form glutathione disulfide (GSSG), and uptake of extracellular intact GSH. Mediating oxidant stress and maintaining normal redox status is especially important in intestinal epithelial cells, which function as an innate defense barrier against luminal toxins and oxidants derived from the diet. In this regard, glutathione is essential for normal intestinal function (34) and is related to an increased susceptibility to carcinogenesis, oxidative injury, metal intoxication, and common intestinal pathologies (35). Studies with intestinal epithelial cells indicate that increased oxidant stress and redox imbalance suppress cell proliferation and induce apoptosis and that this is closely correlated with a higher oxidized glutathione state, as measured by the ratio of GSH/GSSG (36–38). In vitro studies found that cells grown in cysteine-deficient media have suppressed GSH concentrations and cell proliferation rates, both of which are increased with cysteine supplementation (39,40). Other studies with human colonic epithelial cells (Caco-2) indicated that differentiation proceeds, cell GSH concentration and proliferation rate decrease, whereas the apoptosis rate increases (41). Collectively, these studies suggest that cysteine availability and local GSH concentration have a direct influence on epithelial cell proliferation and survival and is inversely proportional to cellular differentiation state.

**Methionine transsulfuration and intestinal cell function.** A possible mechanistic link between methionine transsulfuration and intestinal function is the role of methionine in epithelial cell turnover and antioxidant status. It is evident from the foregoing discussion that cysteine availability is important for maintenance of epithelial cell GSH level and cell survival. However, it is poorly understood whether methionine can affect cysteine availability in epithelial cells via transsulfuration, and hence cell function. Evidence in support of this idea is the finding that in HepG2 cells, oxidant stress increased transsulfuration measured by cystathionine synthesis and 13S-methionine incorporation into glutathione (42). In addition, homocysteine flux through the transsulfuration pathway is decreased when exposed to antioxidants (43). Moreover, studies in HepG2 cells also showed that cystathionine synthase activity is coordinately regulated with proliferation via a redox-sensitive mechanism (44). These results imply that cells exposed to oxidant stress may meet the increased cysteine requirement for GSH synthesis via activation of methionine transsulfuration. A broader implication of this result is that maintenance of normal intestinal epithelial cell proliferation and survival requires active methionine transsulfuration for synthesis of cysteine and GSH.

In conclusion, there is substantial evidence that first-pass splanchnic metabolism, specifically by the intestine, plays an important role in SAA metabolism. Transmethylation, remethylation, transsulfuration, and glutathione synthesis were shown to be affected by the addition or removal of nutrients, methionine and cysteine, enzymatic cofactors, and antioxidants and that this metabolism is regulated differently when intestinal metabolism is bypassed during parenteral feeding. The gut may be a quantitatively important site for conversion of dietary methionine to both homocysteine and cysteine, yet there is limited direct evidence to confirm this idea. If this were confirmed, it may have implications for nutritional strategies to manipulate homocysteine metabolism as a means to reduce the risk of cardiovascular disease and stroke. Given that first-pass splanchnic metabolism plays an important role in SAA metabolism, there are also implications for the formulation of parenteral solutions. The functional importance of dietary methionine and cysteine for intestinal growth and function, beyond its role as a precursor for protein synthesis, warrants further investigation. Furthermore, given that cysteine has a key role in cellular antioxidant function, which is a determinant of cell proliferation and survival, understanding to what extent methionine can serve as an intracellular precursor for cysteine in intestinal epithelial cells also warrants further study.

**LITERATURE CITED**


