



Roles of sulfur-containing amino acids in gastrointestinal physiology and pathophysiology

Uloge sumporovitih aminokiselina u gastrointestinalnoj fiziologiji i patofiziologiji

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Introduction

Sulfur-containing amino acids (SAA) are methionine (Met), cysteine (Cys), homocysteine (Hcy), and taurine (Tau). Only Met and Cys are included in protein synthesis. Amino acids (AA), apart from being incorporated in proteins, are now recognized to have other significant roles in metabolism, such as being precursors of essential molecules, acting as mediators or signal molecules, and affecting numerous functions.

Essential AA must be provided by feed and are limiting for growth as they are the building blocks for protein synthesis. For a better understanding of the physiological consequences of an insufficient intake of these AA, their nonproteinogenic functions must be also considered. Methylation processes of SAA can affect metabolism and cell functions by their participation in the control of oxidative stress¹.

There is a lot of evidence indicating that SAA metabolism in gastrointestinal tissue is linked to human health and gut diseases. Met and Cys play a metabolically and functionally important role in the gastrointestinal system². They maintain many gut functions, including the digestion, absorption, and metabolism of nutrients, the immunity of intestinal mucosal epithelial cells.

Historically, it is assumed that dietary AA are absorbed from the lumen into the portal blood without degradation. Recent results support the view that absorbed AA are captured, transformed, and degraded in tissues of the intestine before they enter portal circulation; 30% of dietary Met is metabolized by the intestine in the first pass³. Studies in rats⁴ and piglets⁵ demonstrated that the gastrointestinal tissues possess the significant activities of enzymes necessary to transform Met to Cys, and further utilization of Met by the intestine^{2,6}. Met is necessary for normal growth and development⁷. In every cell, Met is used for protein synthesis and the methylation cycle, where it is converted to S-adenosylmethionine (SAM), the principal methyl donor.

In the methylation process of DNA or proteins, SAM is transformed to S-adenosylhomocysteine (SAH), which is then hydrolyzed to Hcy⁸. Low Met intake or folate deficiency will reduce SAM concentrations, which can further induce deregulation in DNA methylation in various cancers, including colorectal cancer⁹.

Hcy is a sulfur-containing nonproteinogenic AA derived in Met metabolism by transmethylation. Hyperhomocysteinemia (HHcy), increased plasma Hcy level, is recognized as a risk factor for cardiovascular and cerebrovascular diseases¹⁰ and gastrointestinal diseases¹¹, including constipation, Crohn’s disease, inflammatory bowel disease (IBD),

and colorectal cancer^{12, 13}. The connection between inflammatory remodeling of the digestive tract and HHcy has been shown, resulting in higher production of reactive oxygen species (ROS). HHcy was also recognized as one of the risk factors for colorectal cancer, mesenteric venous thrombosis, and subsequent bowel infarction¹⁴.

Cys is an AA incorporated in the tripeptide glutathione (GSH) (Glu-Cys-Gly) and plays a key role in its cellular antioxidant function, and its availability is dependent upon Met intake¹⁵. GSH has an important role in intestinal gut redox status¹⁶. The concentration of Cys, which is the limiting AA in GSH synthesis, is very important for the maintenance of epithelial cell GSH concentration and regulation of intestinal cell redox status¹⁷. Cys plays a key role in cellular redox function and susceptibility to oxidant stress in the intestine^{18, 19}.

Tau is involved in numerous physiological functions. It regulates bile conjugation, osmolarity regulation, calcium modulation, and cytoprotective effects such as antioxidative properties, membrane stabilization, and immunomodulation²⁰⁻²². Tau is found in high concentrations in mammalian cells, and it has endogenous antioxidant and a membrane-stabilizing function²³. Tau is a protective agent against oxidative stress-induced disorders such as gastrointestinal damage²⁴ and can inhibit oxidative stress-induced apoptosis in epithelial cells²⁵.

Methionine

Met is an essential AA that takes part in many metabolic processes such as protein synthesis, methylation of DNA, and polyamine synthesis. Met absorption from the gastrointestinal tract is highly efficient and it is rapidly removed by tissues. In particular, the liver clears great amounts of Met from blood plasma²⁶. Among the SAA, Met is the most valuable because it can serve as a sulfur donor to generate the other two SAA, Cys, and cystine, but reversed reaction is not possible. Met makes thus a precious and versatile contribution to the daily requirement for SAA. The estimated SAA intake for adult humans ranges between 13 and 16 mg/kg *per* day (17–27 mg/g protein)²⁷.

Apart from being a sulfur donor for Cys biosynthesis, Met represents the main cellular donor of methyl groups after conversion to SAM²⁸. SAM is included in many metabolic pathways like the synthesis of norepinephrine, dopamine, and serotonin. Moreover, it has been proposed as a potential treatment for depression²⁹. Furthermore, by serving as a methyl donor for DNA methylation, SAM has key control over the whole cellular transcriptome³⁰.

Met is a proteinogenic AA responsible for the initiation of protein translation and plays a structural role in the hydrophobic cores of proteins. Apart from being incorporated in polypeptide chains, Met also has important functions as a single molecule as a redox sensor and ROS scavenger. In cell membranes, Met often attacks the lipid bilayer, which is susceptible to oxidation. Met, together with tryptophan and Cys, is one of the most susceptible AA to oxidation by ROS³¹. It is oxidized to Met-sulfoxide, which can be reduced back to

Met by Met-sulfoxide reductase. Reversible Met oxidation/reduction in proteins might act as a regulatory mechanism. Sulfoxide residues of Met are more hydrophilic compared to Met, which can lead to unfolding and progressive loss of protein function.

Met requirements are 30% lower in parenterally fed than in enterally fed piglets because in the first-pass the splanchnic tissues significantly reduced the level of Met³². Recent studies recognized that gastrointestinal tissues of rats⁷ and piglets⁵ possess significant activities of enzymes necessary to utilize Met and convert it to Cys^{2, 6}. These studies have also shown that developing gut is a significant site of Met conversion to Cys and Hcy. SAA deficiency preferentially reduces mucosal growth and antioxidant function in neonatal pigs.

In SAA-free pigs compared with control plasma levels of all SSA, total erythrocyte GSH concentration and body weight were significantly decreased. Whole-body Met and Cys fluxes were reduced, although Met utilization for protein synthesis and its remethylation were preserved, in response to SAA deficiency. Met and Cys concentrations were also reduced in intestinal tissue⁵. The activity of Met metabolic enzymes: Met adenosyltransferase, Met synthase and cystathionine-synthase, and SAM concentration in the jejunum were increased by SAA deficiency. Dietary SAA deficiency-induced small intestinal villous atrophy, small intestine weight, and protein and DNA mass were lower, lower goblet cell numbers, and Ki-67 positive proliferative crypt cells in association with lower tissue GSH, especially in the jejunum. SAA deficiency suppresses epithelial growth and upregulates intestinal Met cycle activity⁵. Met requirements in the neonatal pigs are higher than in the infant pigs, not only for protein synthesis, but also for the synthesis of SAM, the methyl donor in cells and a precursor for polyamine synthesis³³.

Transsulfuration and synthesis of Cys is another important function of Met³⁴. Cys is the only precursor for Tau synthesis and the limiting AA in the GSH synthesis³⁵. Cys also plays an important role as an extracellular reducing agent¹. SAA-free pigs had lower blood concentrations of GSH and Tau than control pigs, thus the lower transsulfuration rate and Cys flux.

Dietary restriction of Met also renders benefits. One-month dietary restriction of Met had an impact on the tight junction (TJ) barrier in rat gastrointestinal tissue. Increased transepithelial electrical resistance with lower paracellular diffusion of ¹⁴C-D-mannitol was registered in the rat colonic mucosa of experimental rats (Met restriction diet) compared to control, suggesting improved barrier function. Improved barrier function was accomplished by the modification of TJ structure proteins that could have resulted from the DNA methylation in colon epithelial cells. Therefore, Met restriction could be useful in various IBD, such as Crohn's disease³⁶.

High consumption of red meat is considered a risk factor for developing colorectal cancer. Met, a component of animal proteins, and folic acid are included in the one carbon cycle and play an important role in DNA methylation and cancer development. That is the reason why dietary modifi-

cations involving lower levels of Met and folic acid might inhibit colon cancer development. Carcinogenesis is associated with inflammation by inhibiting apoptosis, inducing gene mutations, and stimulating angiogenesis³⁷. Met has been recognized as a contributing factor in inflammation-induced colon cancer and in the inhibition of several pathways important in colon carcinogenesis³⁸. Therefore, it is notable that dietary Met intake might have a protective effect on colorectal cancer risk. The connection between the risk of colorectal cancer and dietary Met intake has been shown, however, the findings are conflicting, which has been proven by several epidemiological studies³⁹.

A new strategy in cancer growth control, especially for cancers dependent on Met for survival and proliferation, could be the restriction of Met. The reason for Met dependence in these cancers may be deletions, polymorphisms, or alterations in the expression of genes included in Met salvage pathways. Defects in the metabolism of folate may also lead to the Met dependence in cancer. Met-dependent cancer cells have been killed using culture media deficient in Met⁴⁰. Several studies on animals that were on Met restricted diet have reported inhibition of cancer growth and extension of a healthy life-span. Diets low in Met, such as vegan diets, could be a useful nutritional method to control cancer growth in humans⁴⁰.

Homocysteine

There are more and more research results suggesting that Hcy is an important factor for human health status. Hcy is metabolized through two major pathways: methylation and transsulfuration. In most tissues, in physiological conditions, approximately 50% of Hcy is remethylated via enzyme Met synthase (5-methyltetrahydrofolate-homocysteine methyltransferase) forming Met. In the liver, this conversion from Hcy to Met is mostly done via betaine-Hcy S-methyltransferase⁴¹. In the transsulfuration pathway, Hcy is metabolized to form cystathionine, which is the immediate precursor to Cys.

In HHcy plasma, levels of Hcy are higher than 15 $\mu\text{mol/L}$. HHcy induces oxidative stress in vascular endothelial cells, which increases cardiovascular risk⁴². The incidence of HHcy is 5–7% in the general population and 25% among people that already have some vascular diseases^{43,44}. Although there is a clear association between plasma homocysteine concentration and cardiovascular diseases, folic acid therapy was not useful in the prevention of myocardial infarction and stroke in the majority of trials^{45–47}. HHcy is also associated with kidney disorders in general and diabetic populations, apart from its important role in cardiovascular and cerebrovascular diseases^{48,49}.

There are data from the literature showing that sulfur AA can impact bowel motility. DL-Hcy thiolactone (Hct) has shown to be a potential prokinetic agent by increasing the contractile activity of isolated duodenum in rats⁵⁰. Inhibition of nitric oxide synthesis caused by N-nitro-L-arginine methyl ester (L-NAME) caused a significant increase in tone, amplitude, and frequency of the contractions in the

presence of Hct. Hct has also decreased the nonadrenergic-noncholinergic relaxation of bowel smooth muscle caused by stimulation with low-frequency electrical field⁵¹.

HHcy was reported as a risk factor for many gastrointestinal diseases such as constipation, Crohn's disease, IBD, and colorectal cancer^{12,13}. HHcy occurs in inflammatory remodeling of the gastrointestinal tract which could lead to increased oxidative stress. The reason for this state could be the disease itself because sulfur AA are metabolized and transported in the gastrointestinal tract. Moreover, HHcy has been correlated to mesenteric venous thrombosis, bowel infarction, and colorectal cancer¹⁴. HHcy can cause upregulation of inducible nitric oxide (NO) synthase, resulting in inflammatory changes during hemorrhagic shock and leading to functional and morphological injury of intestine⁵². Hcy has an important role in the pathophysiology of many inflammatory disorders of the intestine by affecting the activity of matrix metalloproteinases (MMPs). MMP-2 was reported as an enzyme that has a protective function during intestinal inflammation. However, MMP-9 can cause mucosal damages during inflammatory processes⁵³. These findings suggest that inhibition of MMPs could have a therapeutic potential in intestinal inflammatory diseases.

Hcy was suggested to be a prooxidant agent. Hcy significantly increased thiobarbituric acid-reactive substances – a marker of lipid peroxidation – in rat duodenum, ileum, colon, and liver. Likewise, the activity of catalase, an antioxidative enzyme, was significantly decreased in these tissues by acute administration of Hct⁵⁴. Acute administration of Hcy decreased activities of superoxide dismutase and glutathione peroxidase⁵⁵.

A high growth rate is one of the most characteristic features of malignant cells, thus they require more Met because the synthesis of proteins is increased, while normal cells can cover their Met consumption from Hcy remethylation. However, malignant cells in the colon cannot convert Hcy to Met, they accumulate Hcy and are Met dependent. A higher level of Hcy is related to the concentration of folate. Folate cofactors play an important role as intermediators in Hcy remethylation to Met, in the synthesis of SAM, and also in the production of nucleotides for DNA/RNA synthesis. SAM/SAH ratio is significantly lower in Met-dependent cells comparing to normal cells. Reduction of intracellular SAM levels can cause repression of tumor suppressor genes and activation of protooncogenes by altering cytosine methylation in CpG islands of DNA which induces malignant transformation⁵⁶. A high level of SAH increases Hcy level as long as Hcy is not converted to Cys by transsulfuration pathways. Higher Hcy level and normal plasma level of Cys were detected in patients with cancer⁵⁷.

HHcy is found in about 5% of the general population and it is considered an important risk factor for arterial and venous thrombosis^{35,58}. The presence of Hcy in the IBD, patients' mucosa has been demonstrated, which can be, at least partially, brought into a relationship with the inflammation of the IBD endothelium⁵⁹ and recent meta-analysis by Oussalah et al.⁶⁰ suggested that HHcy was four times more frequent in IBD patients. Vascular complications in patients

with IBD are very common and appear earlier than in the general population. Although reports have been mainly focused on venous thromboembolism, there are also series that have documented arterial thromboembolism in IBD patients.

HHcy takes place in atherosclerosis pathophysiology. It increases oxidative stress and decreases NO production, which results in impaired endothelial function, and finally, in aberrant remodeling and atherosclerotic plaques⁶¹. Few reasons are explaining this phenomenon. Nutritional deficiencies of vitamins B6, B12, and folate are related to poor intake and/or malabsorption. The use of drugs that reduce folate absorption (sulfasalazine) or inhibit its metabolism (methotrexate) reduces intracellular folate stores⁶². Third, folate activity can be compromised by genetic factors such as a mutation in the methylenetetrahydrofolate reductase gene^{60, 63}. The choline status of patients with IBD has been minimally explored, except for two studies in patients with active ulcerative colitis (UC). The results of those studies demonstrated the reduction of choline and betaine concentrations in colonic mucosa and serum^{64, 65}.

Cysteine

L-Cys is a semi-essential AA that can be absorbed from diets or got from the transsulfuration pathway from Met degradation and catabolism of endogenous proteins. L-cystine is the main form of Cys because it is more stable when oxidized in physiological conditions. Cys is included in many metabolic reactions like protein synthesis, the generation of GSH, Tau, pyruvate, and inorganic sulfur⁶⁶. The metabolic pathways of Cys catabolism to H₂S, Tau, and especially GSH show important therapeutic and nutritional implications in the improvement of human and animal health. A recent study recognized that a three-week-long i.p. application of Cys and Met can lead to significantly lower concentrations of cholesterol, urea, and creatinine in rats compared to control⁶⁷. Biochemical evaluation of liver and pancreatic function in the condition of high Met intake showed lower concentrations of aspartate aminotransferase and alkaline phosphatase and higher serum amylase levels compared to control⁶⁷. The ratio between Cys and L-cystine (its oxidized form) is very important in controlling oxidative stress and inflammatory response⁶⁸⁻⁷⁰. Dietary intake of SAA affects cell signaling via modulation of postprandial Cys and L-cystine concentrations and Cys/L-cystine redox ratio^{71, 72}. There is a growing interest in the use of Cys for improving health in animals and humans. Maintaining normal redox status is particularly important in intestinal epithelial cells, which are exposed to high levels of oxidative stress because of intensive metabolism and exposure to luminal toxins and oxidants derived from diets^{73, 74}. These findings may be important for the treatment of diseases related to oxidant injury in the digestive organs.

The intestinal barrier is important as a selective barrier against endogenous and exogenous noxious antigens and pathogens⁷⁵. Disruption of the intestinal barrier promotes luminal antigens to penetrate subepithelial tissues, inducing a mucosal and systemic inflammatory response, which is the

major pathogenic mechanism for most intestinal diseases⁷⁶. Multiple factors, including inflammation and oxidative stress, can give rise to intestinal barrier damage^{76, 78}. Overproduction of pro-inflammatory cytokines and ROS can disrupt the intestinal epithelial integrity and function⁷⁷⁻⁷⁹. Therefore, inhibition of intestinal inflammation and oxidative stress may exert beneficially prevent the greater intestinal disruption. Cys could alleviate oxidative stress via GSH synthesis in IBD⁷⁷, and it has been established that Cys supplementation ameliorated local inflammation and improved intestinal barrier restoration in induced porcine colitis model⁸⁰. These data demonstrated that Cys was effective in suppressing inflammation and oxidative stress and recognize Cys as a promising nutritional agent for intestinal integrity protection.

N-acetylcysteine (NAC) is acting as a precursor for the substrate Cys in the synthesis of GSH⁸¹. NAC is an antioxidant and has gastroprotective (antiulcerative), anti-inflammatory effects in rat models⁸².

Taurine

Tau is SAA that is not incorporated into the cellular proteins nor metabolized^{83, 84}. Studies have demonstrated that a high level of extracellular Tau can protect cells against damaging stimuli such as ROS, toxic xenobiotics, cellular excitotoxicity, and osmotic derangements⁸⁵. Tau is involved in many biological and physiological functions: conjugation of bile salt, membrane stabilization, calcium modulation, osmoregulation, anti-oxidation, and immunomodulation.

Sukhotnik et al.⁸⁶ showed a protective effect of Tau on intestinal recovery following intestinal ischemia-reperfusion injury in rats. It is well known that during reperfusion of ischemic tissue ROS and reactive nitrogen species are generated in excess. Tau was found to be a protective agent against oxidative stress in developed atherosclerosis⁸⁷, complications of diabetes mellitus^{88, 89}, hepatic^{90, 91}, and gastrointestinal damage⁹¹. In addition, taurine was also reported to have anti-apoptotic properties⁹¹⁻⁹³. Tau inhibits oxidative stress-induced apoptosis in several cells, such as hepatocytes⁹¹, cardiomyocytes⁹², and epithelial cells⁹³.

Myeloperoxidase activity generates high levels of hypochlorous acid in the inflamed colon tissue and produces Tau-chloramine in the reaction with Tau. Administration of Tau reduces inflammation and activity of colonic MPO in rats with induced colitis⁹⁴. The effects of Tau treatment may be partly through Tau-chloramines⁹⁵. However, Tau can also have an anti-inflammatory effect not only through Tau-chloramines, but also directly by inhibition of IL-8 secretion induced by TNF- α ⁹⁶. Moreover, Tau in synergy with 5-aminosalicylic acid also shows an anti-inflammatory effect by decreasing the level of interleukin-1 β ⁹⁵.

Recent findings indicate that Tau can have a significant inhibiting effect on cell proliferation⁹⁷. It is also shown that Tau induced apoptosis in human colon cancer cells and that this effect is based upon regulation of p53-upregulated modulator of apoptosis.

Conclusion

Further investigations should examine the real advantages and disadvantages of high sulfur-containing AA diets and the restriction of these AA in particular digestive diseases such as inflammatory bowel disease and colorectal cancer. Advanced studies are needed to understand: the role of new preventative dietary supplements or medicaments, which will decrease plasma Hcy level, the molecular background of Hcy interaction with its target molecules in gastrointestinal tissues, and the epigenetic alteration of DNA methylation profiles in correlation with the pathogenesis of digestive diseases. Therapeutic lowering of Hcy level and supplementation of Cys and N-acetylcysteine in the preven-

tion of gastrointestinal disorders are promising tools. Future studies should test some of the medical applications of Met restriction and its ability to enhance epithelial Tjs and barrier function in various diseases whose etiology likely involves changes in Tj proteins, for example, inflammatory bowel diseases such as Crohn's disease. Diets low in Met, such as vegan diets, could be a useful nutritional method for cancer growth control in Met-dependent tumors.

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