

Review Article

Oxidation Resistance of the Sulfur Amino Acids: Methionine and Cysteine

Peng Bin,^{1,2} Ruilin Huang,¹ and Xihong Zhou¹

¹Key Laboratory of Agro-Ecological Processes in Subtropical Region, Institute of Subtropical Agriculture, Chinese Academy of Sciences, National Engineering Laboratory for Pollution Control and Waste Utilization in Livestock and Poultry Production, Changsha, Hunan 410125, China

²University of Chinese Academy of Sciences, Beijing 10049, China

Correspondence should be addressed to Xihong Zhou; xhzhou@isa.ac.cn

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Sulfur amino acids are a kind of amino acids which contain sulfhydryl, and they play a crucial role in protein structure, metabolism, immunity, and oxidation. Our review demonstrates the oxidation resistance effect of methionine and cysteine, two of the most representative sulfur amino acids, and their metabolites. Methionine and cysteine are extremely sensitive to almost all forms of reactive oxygen species, which makes them antioxidative. Moreover, methionine and cysteine are precursors of S-adenosylmethionine, hydrogen sulfide, taurine, and glutathione. These products are reported to alleviate oxidant stress induced by various oxidants and protect the tissue from the damage. However, the deficiency and excess of methionine and cysteine in diet affect the normal growth of animals; thereby a new study about defining adequate levels of methionine and cysteine intake is important.

1. Introduction

Sulfur amino acids (SAAs) are a kind of amino acids which contain sulfhydryl. Among the SAAs, methionine and cysteine are deemed as the primary SAAs. Methionine is an indispensable amino acid in mammals as it cannot be synthesized in amounts sufficient to maintain the normal growth of mammals. Nevertheless, cysteine is a semiessential amino acid in mammals, because cysteine can be produced through the transsulfuration pathway from L-methionine degradation. Thus, the content of methionine and cysteine is considered to represent the requirement of SAAs in the diet of mammals. Increasing evidence reveals that SAAs play a crucial role in protein structure, metabolism, immunity, and oxidation [1–4]. They exert momentous functions through their metabolites, such as S-adenosylmethionine (SAM), polyamines, taurine, and glutathione (GSH) (Figure 1).

Redox homeostasis is the premise of maintaining homeostatic equilibrium of organism, and it highly depends on the

balance of prooxidative and antioxidative system [5, 6]. Reactive oxygen species (ROS) is a major factor in the formation of oxidative damage, because ROS can oxidize biomolecules (including lipid, protein, and DNA) easily and thereby impairs antioxidative system and causes oxidative stress [7, 8]. Therefore, the antioxidation of SAAs attracts people's interest gradually and researchers have done many researches on it [9, 10]. A great number of researches report that SAAs have an alleviating action on various oxidant stress model, such as diabetes [11, 12], HIV infection [13], and aging [14]. Thus, our review reorganizes and highlights the antioxidation effect of two main SAAs (methionine and cysteine).

2. Methionine

In the protein structure, all amino acid residues are prone to be oxidized by diversified forms of ROS, especially methionine residues, as they are sensitive to almost all forms of ROS and the oxidation of methionine residues is reversible [15].

Moreover, Yermolaieva and his colleagues [21] found that the overexpression of MsrA significantly reduced the hypoxia-induced increase of ROS and maintained the normal growth of PC12 cells. MsrB has been discovered for only a short time [22], and its main function was now known to reduce oxidized MetO together with MsrA. The other functions of MsrB are remaining to the further exploration.

2.2. SAM. SAM is the direct product of methionine in the catalysis by methionine adenosyltransferase (MAT), and it is well known as the methyl donor for the majority of methyltransferases that modify DNA, RNA, and other proteins. SAM exerts the antioxidant capacity by this pathway: SAM increases the activity of cystathionine γ -synthase (CBS) which is the primary enzyme in transsulfuration and contributes to the synthesis of cysteine, thereby increasing the GSH level. Many studies show that SAM administration alleviates oxidant stress and restores the tissues. For example, Li et al. [23] found that SAM administration protects cells and inhibits oxidative stress induced by amyloid- β , and it activates endogenous antioxidant system by restoring the normal GSH/GSSG ratio and increasing the activities of glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST), and superoxide dismutase (SOD).

2.3. Administration of Methionine. It is reported that the supplementation of methionine mitigated the ROS-induced damage by increasing the activity of GSH [24]. Interestingly, methionine restriction, which restricts the methionine supplementation in animal diet, is also reported to alleviate oxidant stress. For example, methionine restriction significantly reduces mitochondrial ROS generation [25, 26]. In addition, methionine deficiency in a dietary model causes a series damage to body, like hepatic pathology [27], suppression of intestinal epithelial growth [28], impairment of growth performance [29], and so on, while excessive methionine supplementation may lead to methionine poisoning and even shorten the lifespan of animals [30]. What is more, the requirement of methionine in different stages of animals is discrepant. Thus, the administration of methionine for animal production is a valuable research topic.

3. Cysteine

Similar to the methionine residues, cysteine residues also easily suffered from oxidation. Cysteine residues are with the properties of regulating redox since its special chemical characteristics made it easily react with H_2O_2 [31, 32]. In addition, serving as a precursor for GSH, cysteine is the limiting amino acid of glutathione synthesis in transsulfuration pathway. Moreover, the antioxidant property of cysteine is mainly reflected by the product of GSH, hydrogen sulfide (H_2S), and taurine.

3.1. GSH. In mammals, GSH is mainly synthesized by two enzymatic ATP-dependent reactions from cysteine, glutamate, and glycine: (1) Cysteine and glutamate consume ATP to form γ -glutamylcysteine (γ -Glucys) by the catalysis of γ -glutamylcysteine synthetase (GCS). (2) GSH synthetase

catalyzes γ -Glucys and glycine to form GSH, and this reaction also consumes ATP (Figure 1). In the synthesis of GSH in cell, cysteine is the rate-limiting reaction substrate [33] and supplementation with L-cysteine in humans improves synthetic rate and concentration of GSH [34]. What is more, Yin et al. [35] quantified the main source of GSH precursors by supplementation with different concentrations of L-cysteine, L-glutamate, and glycine in mice diet, and their result revealed that dietary with L-cysteine and L-glutamate increased the concentration of GSH in liver, while they also found that the excessive supplementation of L-cysteine inhibited GSH synthesis.

GSH is a cysteine-containing tripeptide and plays a vital role in cellular antioxidation in animal [36]. GSH is easily oxidized by the free radicals and other ROS (e.g., lipid peroxyl radical, H_2O_2 , and hydroxyl radical) to form glutathione disulfide (GSSG) by the catalysis of GSH-Px. And then by the catalysis of glutathione reductase, GSSG is reduced to GSH. Therefore, cycle of GSH/GSSG contributes to the scavenging of free radicals and other reactive species and to the prevention of oxidation of biomolecules. In addition, as the substrate of GSH-Px, GSH also plays an assistant role in the antilipid peroxidation of GSH-Px. It is generally believed that the low level of GSH may lead to lipid peroxidation. For example, Agar et al. [37] employed ethanol to consume the GSH in cerebellum of mice and then found that lipid peroxidation was increased significantly. Thus, the concentration of GSH and the activities of GSH-related enzyme acted as the sign of antioxidant status in the body.

3.2. H_2S . H_2S has long been considered as a toxic gas produced in substantial amounts by mammalian tissues, while recent research reveals that it is an anti-inflammatory, antioxidant, and neuroprotective agent and plays very important roles in many physiological functions [38]. L-Cysteine is a major substrate to produce about 70% endogenous H_2S by either enzyme (cystathionine β -synthase and cystathionine γ -lyase) [39]. And, in recent years, it is observed that D-cysteine produces H_2S by a novel pathway and it may be more effective than L-cysteine in protecting primary cultures of cerebellar neurons from oxidative stress induced by hydrogen peroxide [40]. H_2S is a potent antioxidant, except for directly scavenging the reactive oxygen and nitrogen species to protect tissues [41]; it also increases the activity of γ -glutamylcysteine synthetase and upregulates cystine transport, thereby enhancing the production of GSH to resist oxidant stress [42]. Furthermore, it is reported that H_2S may protect gastric mucosal epithelial cells against oxidative stress through stimulation of MAP kinase pathways [43]. These pathways provide the mechanisms for H_2S to protect the tissues from oxidative stress.

3.3. Taurine. Taurine is the most abundant free amino acid in mammals, and it plays an important role in many physiological functions, like visual development, neural development, detoxification, antioxidation, anti-inflammatory, and so on. Two main sources contribute to taurine synthesis in the mammals: absorption from diets and the metabolism of cysteine. Taurine is synthesized by three steps: first, cysteine is

catalyzed to form cysteine sulfinic acid by the catalysis of cysteine dioxygenase; second, cysteine sulfinic acid removes carboxyl to form hypotaurine by cysteine sulfinic acid decarboxylase; third, hypotaurine is oxidized to taurine. Many researches confirm that increasing the dosage of cysteine in diet contributes to the activation of cysteine dioxygenase [44], and dietary supplementation of cysteine increased plasma taurine level in HIV-infection people [13].

In particular, taurine shows its protection for tissue in many models which are induced by various oxidants [45, 46]. The antioxidant capacity of taurine is associated with ROS scavenging. Chang et al. [46] proved that taurine supplements in rat diet lowered the hyperhomocysteinemia-induced ROS production, and Palmi et al. [47] reported that taurine inhibited the production of ROS by stimulating mitochondrial Ca^{2+} absorption. In addition, taurine also increases the activities of many antioxidant enzymes in oxidant-induced models. It is confirmed that taurine restores the activities of Mn-SOD and GSH-Px in mice mitochondrion after tamoxifen infection [48]. Furthermore, Choi and Jung [49] in their studies pointed out that taurine supplementation increased hepatic SOD activity on the calcium deficiency condition, but the activities of GSH-Px and catalase (CAT) were not significantly different between normal mice and calcium deficient mice.

4. Conclusion

In conclusion, as the powerful antioxidants, SAAs play a crucial role in maintaining the equilibrium and stability of free radicals in the body. Hence, SAAs are widely used as food additive and applied to medical care and animal breeding. Although SAAs have the excellent antioxidant capacity, of particular note is the administration of SAAs in the process of animal production, because different dosage of SAAs may have different effects on animals. Thus, further study about the appropriate dosage of SAAs will be explored in animal feeding.

Abbreviations

SAA:	Sulfur amino acids
SAM:	S-Adenosylmethionine
GSH:	Glutathione
ROS:	Reactive oxygen species
MetO:	Methionine sulfoxide
Th(SH) ₂ :	Thioredoxin
MsrA:	Methionine sulfoxide reductase A
MsrB:	Methionine sulfoxide reductase B
MAT:	Methionine adenosyltransferase
CBS:	Cystathionine γ -synthase
GSH-Px:	Glutathione peroxidase
GST:	Glutathione-S-transferase
SOD:	Superoxide dismutase
H ₂ S:	Hydrogen sulfide
γ -Glucys:	γ -Glutamylcysteine
GCS:	γ -Glutamylcysteine synthetase
GSSG:	Glutathione disulfide.

Disclosure

This review article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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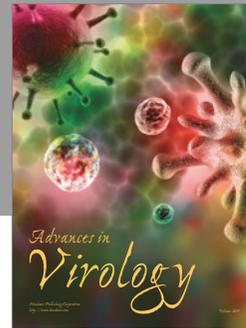
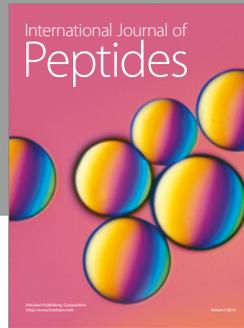
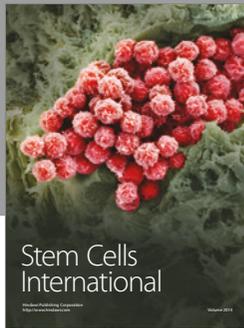
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