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Review article

Methionine: A metabolically unique amino acid

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Abstract

Methionine is a dietary essential amino acid that plays unique roles, both in protein structure and in metabolism. Methionine serves as the initiating amino acid in eukaryotic protein synthesis. In globular proteins, most methionine residues are buried inside the hydrophobic core. Some methionine residues, located on the surfaces of proteins are susceptible to oxidation to methionine sulfoxide. These may be reduced back to methionine by methionine sulfoxide reductase. Methionine's principal metabolic function lies in its conversion to *S*-adenosylmethionine which is the principal biological methylating agent. Methionine metabolism may be divided into transmethylation, remethylation and transsulfuration. *S*-adenosylmethionine, via allosteric mechanisms, exerts control over these processes. Creatine synthesis is a major user of *S*-adenosylmethionine-derived methyl groups. Piglets acquire considerable quantities of creatine during growth. About one third of this is provided in the milk; two thirds is synthesized within the piglet. This requires very high rates of creatine synthesis and has the potential to be a significant drain on dietary methionine.
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Keywords: Cysteine; *S*-adenosylmethionine; Transmethylation; Remethylation; Transsulfuration; B vitamins

Contents

1. Introduction

A key amino acid for protein structure and for metabolism, methionine, is one of four common sulfur-containing amino acids. Of the other three, only cysteine is incorporated into proteins; homocysteine arises as a metabolic intermediate in methionine metabolism and

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taurine arises during cysteine catabolism. The structures of these four amino acids are shown in Fig. 1. Methionine's structure also accounts for its name, as it contains a methyl group covalently bonded to a sulfur atom. Both the methyl group and the sulfur are crucial for its structural and metabolic functions.

2. Methionine in proteins

The emphasis of this review paper is on the metabolic functions of methionine. Nonetheless, it must be acknowledged that the twenty amino acids commonly found in proteins were primarily selected for their role in proteins; metabolic utility was secondarily exploited. We must, therefore, explore methionine's role in protein structure and function. There are three aspects of this: hydrophobicity, oxidation of the sulfur and initiation of protein synthesis. The terminal methyl group gives the methionine side-chain a highly hydrophobic character; indeed, it is one of the most hydrophobic amino acids. This, in turn, results in more than two thirds of the methionine residues of globular proteins being buried in the hydrophobic interior of these proteins (Brosnan and Brosnan, 2006). However, as many as one third of them may be found on the protein surface. Thus, they are susceptible to attack by reactive oxygen species such that the sulfur atom can be oxidized to a sulfoxide (Levine et al., 1996).

Fig. 2 shows the oxidation of a protein-bound methionine by hydrogen peroxide. Such oxidation may be regarded as one of the routine hazards of life with reactive oxygen species. Levine et al. (1996) studied methionine oxidation in *E. coli* glutamine synthetase. They point out that the superficial methionine residues are not scattered randomly on the protein surface; rather, they are clustered around the active site. They view these methionine residues as playing the role of molecular lightning rods, in that they may guard access to this site by reactive oxygen species. They report that oxidation of these residues has little effect on the catalytic activity of the enzyme. These oxidized methionine residues may be

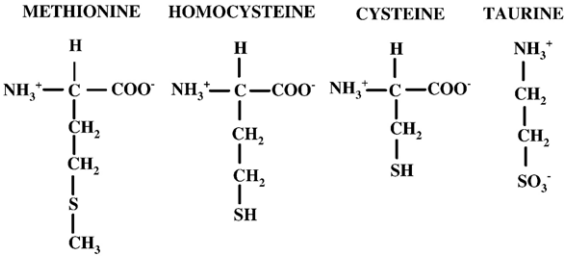

Fig. 1. The common sulfur-containing amino acids.

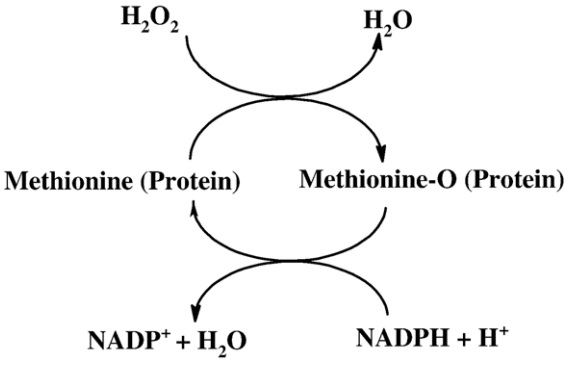

Fig. 2. Oxidation of methionine residues in proteins to methionine sulfoxide and the protein repair action of methionine sulfoxide reductase.

reduced to methionine by the enzyme methionine sulfoxide reductase (Moskovitz, 2005). Thus an oxidation–reduction cycle occurs in which surface-exposed methionine residues are oxidized by reactive oxygen species and reduced by NADPH (Fig. 2). Methionine sulfoxide reductase is a critical enzyme; impaired activity of this enzyme is associated with the accumulation of methionine sulfoxide residues and age-related diseases (e.g. neurodegeneration) and reduced life-span (Moskovitz, 2005). In addition, it has also been suggested that oxidation of methionine residues on protein surfaces may serve as part of a signaling pathway (Stadtman et al., 2003).

Finally, we must point out the unique role of methionine in the initiation of protein synthesis. Methionine is the initiating amino acid in the synthesis of eukaryotic proteins; *N*-formylmethionine serves the same function in prokaryotic organisms. Most of these methionine residues are subsequently removed, indicating that their essential role is in the initiation of translation rather than in protein

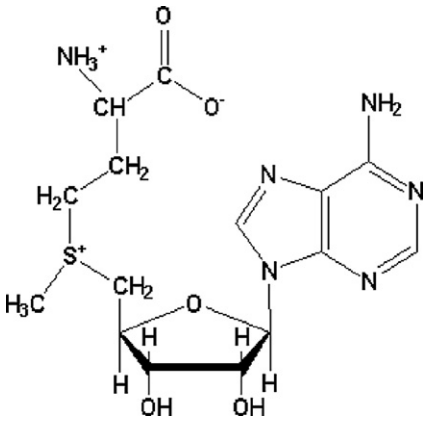

Fig. 3. *S*-adenosylmethionine.

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