Methionine Metabolic Pathways and Turnover Mechanisms in Animals: Postprint

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Abstract

Methionine (Met) is an essential amino acid for animal organisms, serving as a substrate for protein synthesis, an important donor of methyl and sulfhydryl groups in organismal metabolism, and a participant in polyamine formation. Consequently, the supply status of Met and its metabolic pathways in the body influence the organism' s growth performance, physiological activities, and even the methylation modifications of DNA and functional proteins, thereby affecting normal vital activities of the organism. This article reviews the four metabolic pathways of Met and their corresponding turnover mechanisms, aiming to provide a reference for research on Met metabolic mechanisms and rational scientific application.

Full Text

Metabolic Pathway and Turnover Mechanism of Methionine in Animals

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Abstract: Methionine (Met) is an essential amino acid in animals that serves as a substrate for protein synthesis and provides important methyl and sulfhydryl groups for metabolism, while also participating in polyamine formation. Consequently, the supply status and metabolic pathways of Met in vivo influence growth performance, physiological activities, and even methylation modifications of DNA and functional proteins, thereby affecting normal life activities. This review summarizes the four metabolic pathways of Met and their corresponding turnover mechanisms to provide a reference for research on Met metabolic mechanisms and rational scientific application.

Keywords: methionine; metabolic pathway; turnover mechanism

Methionine (Met) is a sulfur-containing, non-polar, aliphatic amino acid that constitutes proteins. Also known as methionine, it is the only amino acid containing a thioether structure. Met has a non-polar side chain that is hydrophobic and exists as both L- and DL-isomers, though only the L-form occurs naturally. As an essential amino acid, Met serves not only as a substrate for protein synthesis but also as the primary methyl and sulfhydryl donor in the body. Research indicates that under the action of methionine adenosyltransferase, Met is activated and converted into S-adenosylmethionine (SAM), which can donate a methyl group to participate in biochemical reactions involving methyl transfer, playing an irreplaceable role in metabolic and regulatory processes [1]. For example, Met provides methyl groups for choline synthesis in vivo and participates in physiological metabolic activities through processes such as choline synthesis and DNA and protein methylation [2]. SAM undergoes transmethylation via S-adenosylmethionine-dependent methyltransferases to generate S-adenosylhomocysteine (SAH), which is further hydrolyzed to produce homocysteine (Hcy). Additionally, Hcy is sequentially converted to cysteine (Cys) by β-cystathionine synthase and γ-cystathionase, thereby participating in the synthesis of biologically active substances such as glutathione and taurine [3]. The sulfhydryl group in Met can scavenge free radicals, conferring certain antioxidant capacity [4]. Moreover, Met participates in polyamine formation, promoting cell growth and protein synthesis [5]. The various metabolic pathways of Met in animals exhibit both synergistic and competitive relationships that influence their respective biological functions, though the specific metabolic mechanisms and physiological roles remain incompletely understood. This paper provides a comprehensive analysis of research on Met' s metabolic pathways and regulatory mechanisms in animal organisms, aiming to offer insights for studying Met metabolism and its scientific application in animal production.

1. Overview of Met Metabolic Pathways

Met is an essential amino acid that cannot be synthesized by animal organisms and must be obtained externally. It is also a limiting amino acid for various livestock species under diverse dietary conditions [6], and has been extensively studied and applied in animal production. Different livestock species and physiological stages have varying Met requirements. For instance, Klemesrud et al. [7] suggested that growing cattle require 0.39 kg/d of metabolizable protein, with Met comprising 3.1% of this amount. The NRC (2001) [8] recommended that Met should constitute 2.4% of metabolizable protein for dairy cows. Regression analysis by Saki et al. [9] indicated that the Met or Met+Cys requirements for 22–36-week-old laying hens are 0.31% and 0.60%, respectively. Met is absorbed through intestinal absorption channels into various tissues including blood, liver, mammary gland, and skin for metabolism, representing a dynamic metabolic process [10]. The activity of Met transport into cells in tissues is influenced by intracellular Met pools, with differences in transport rates attributable to

intracellular Met concentrations rather than changes to the transport system itself [11]. Studies using 35S-labeled Met in rats showed that total portal vein Met turnover rates (K) ranged from 0.02031 to 0.02870 during pregnancy and postpartum periods [12].

Met participates in metabolic activities across various animal tissues and cell types through a complex biochemical reaction system involving multiple enzymes. As a substrate, Met is involved in protein biosynthesis, and in prokaryotes, formylated Met serves as the initiating amino acid for protein synthesis. Met can also be activated by ATP to form S-adenosylmethionine, which acts as a methyl donor in creatine and choline synthesis, and additionally functions in transsulfuration [13]. Overall, Met metabolism primarily comprises four metabolic pathways centered around the Met-Hcy cycle. The first pathway involves reversible exchange between the Met pool and proteins, with protein synthesis representing the major fate of Met in growing animals. The second pathway involves transmethylation to generate SAM, an important active methyl donor that can be regenerated to Met through remethylation via choline or tetrahydrofolate, forming the Met cycle to prevent excessive Met loss through transmethylation. The third pathway involves SAM participation in polyamine formation. The fourth pathway is the transsulfuration reaction that generates cystathionine and subsequently Cys, which is irreversible. The following sections discuss the metabolic mechanisms and physiological functions of these four pathways.

2. Mechanism and Physiological Role of Met in Protein Synthesis

As a substrate for protein biosynthesis, Met directly participates in protein synthesis. Under the catalysis of methionyl-tRNA synthetase and using ATP for energy, Met is activated at its carboxyl group to form aminoacyl-adenosine monophosphate (AMP), which then binds with methionyl-tRNA synthetase to form a ternary complex. This complex subsequently binds with tRNA that transports Met. The aminoacyl group is transferred to the amino acid arm of tRNA (the 3' terminal CCA-OH), and under mRNA guidance, the anticodon recognizes the codon and brings it to the corresponding position on mRNA to elongate the peptide chain and ultimately synthesize protein. Aminoacyl-tRNA synthetases exhibit extremely high specificity and perform proofreading; upon detecting incorrect connections, they promptly hydrolyze them to ensure translation accuracy [14].

As an essential amino acid for protein synthesis, Met is the first limiting amino acid for growth and production in most animals under various dietary conditions, particularly in wool-producing animals [15]. Met deficiency in broilers results in lower plasma triiodothyronine (T3) levels [16]. Met affects animal physiology, growth, and production; for example, young rats lacking Met cannot develop normally, while growing chickens exhibit feed intake without weight gain and reduced levels of growth-related factors such as insulin-like growth fac-

tor (IGF)-1 and IGF-2 [17]. The biological value of animal and plant proteins depends partly on their Met content. Studies show that increasing dietary Met levels from 0.28% to 0.48% in piglets significantly reduces feed-to-gain ratio, increases average daily gain, and tends to increase feed intake [3]. Wen et al. [3] supplemented broiler diets with 0.60% and 0.53% Met during days 1–21 and 22–42, respectively, resulting in improved daily weight gain and breast muscle percentage, reduced feed-to-gain ratio, and decreased hepatic protein degradation capacity with increasing dietary Met levels.

Research on Met as a nutritional substrate for protein synthesis indicates that protein synthesis in guinea pig megakaryocytes using 35S-labeled Met is completed within 24 hours of uptake [18]. Isotopic labeling studies using 13C-Met and 3H-Met in piglets revealed that approximately 80% of Met is utilized for protein synthesis [19]. Correspondingly, Met supplementation can improve animal growth and production performance [20-21]; for instance, dietary Met supplementation enhances wool production in sheep, while Met and its analogs significantly increase rat weight gain [22], and rumen-protected Met supplementation increases milk yield in dairy cows from peak to mid-lactation [23] and improves essential amino acid utilization efficiency [24]. Currently, synthetic Met additives are widely used in animal production to compensate for insufficient Met in natural feed ingredients and enhance protein digestion and utilization.

3. Met Methylation Cycle and Turnover Mechanism

Methylation is an important modification of proteins and nucleic acids. DNA methylation can silence certain gene activities, while demethylation reactivates and induces gene expression [25]. Histone methylation functions primarily in heterochromatin formation, genomic imprinting, X-chromosome inactivation, and transcriptional regulation [26]. As the primary methyl donor in the body, Met supply influences methylation reactions. Studies using 14C-labeled Met showed that rat liver nuclear proteins contain 0.6% labeled Met, while histones contain 1.5% [27].

S-adenosylmethionine synthetase, also known as methionine adenosyltransferase (MAT), catalyzes the formation of SAM from Met and ATP. The methyl group attached to SAM is highly activated and readily transferred to receptor substrates under the catalysis of various methyltransferases (MTs) in transmethylation reactions, forming numerous methylated compounds. SAM availability influences most methylation reactions in cells, from DNA methylation [28] to phospholipid methylation related to cell membrane fluidity [29]. For example, changes in key protein methylation in brain tissue play important roles in neurodegeneration, while the degree of Met deficiency in rodent diets correlates with DNA hypomethylation and affects the incidence of diseases such as liver cancer [30]; increased SAM can alleviate liver cancer progression [31]. As shown in Figure 1 [Figure 1: see original paper], SAM undergoes transmethylation to generate SAH, which can be further hydrolyzed to Hcy by adenosylhomocysteine hydrolase (AHCY). As an important metabolic interme-

diate, Hcy can be remethylated to Met via betaine-homocysteine methyltransferase (BHMT) using methyl groups from betaine (a choline metabolite), or via methyltetrahydrofolate-homocysteine methyltransferase (MS) using methyl groups from folate, forming the transmethylation-remethylation Met cycle.

The physiological significance of this cycle lies in indirectly regenerating Met to prevent substantial Met consumption through the transmethylation pathway. Studies using 14C- and 3H-labeled Met perfusion in piglets showed that approximately 26% of labeled Met participated in transmethylation reactions, while about 8% was involved in remethylation [19]. Feeding 35-day-old broilers diets containing 0.55% and 0.25% Met for 19 days resulted in abdominal fat percentages of 1.62% and 1.73%, respectively, and feed conversion efficiencies of 3.1 and 3.4 [32]. Elshorbagy et al. [33] demonstrated that Cys supplementation reversed obesity induced by Met restriction in rats by regulating stearoyl-CoA desaturase-1 (SCD-1) activity. Although studies show that dietary betaine and choline (each 500 mg/kg) can mitigate the decline in broiler breast muscle yield when Met content is reduced by 0.10%–0.20% as an essential amino acid, they cannot replace its essential function [34]. However, the quantitative relationships among various methyl donors in providing methyl groups for cellular methylation reactions remain unclear [35].

4. Polyamine Formation Mechanism and Physiological Effects

Polyamines include putrescine, spermidine, and spermine, which promote growth by regulating cell signal transduction, DNA replication and transcription, and protein translation. Polyamine depletion arrests cell differentiation [36]. Studies confirm that polyamines affect cell differentiation by regulating translation initiation and elongation mechanisms [37-38]. Cell differentiation rate also correlates with intracellular polyamine levels. Generally, cells maintain relatively stable free polyamine levels at millimolar concentrations within a narrow range. Excessively low polyamine levels reduce cell differentiation and growth rates, while excessively high levels are cytotoxic. Precise polyamine level regulation depends on synthesis, interconversion, transport rates, and periodic oxidative catabolism [39].

The Met metabolic intermediate SAM forms decarboxylated S-adenosylmethionine (dcAdoMet) under the catalysis of S-adenosylmethionine decarboxylase (AdoMetDC) to participate in polyamine formation [1]. As shown in Figure 2 [Figure 2: see original paper], dcAdoMet and putrescine generate spermidine under the catalysis of spermidine synthase (SPDS), producing methylthioadenosine (MTA) as a byproduct. Spermidine then combines with dcAdoMet under the action of spermine synthase (SPMS) to form spermine and MTA [5]. The byproduct MTA can be metabolized to 5-methylthioribose-1-phosphate by MTA phosphorylase (MTAP), which can be further metabolized to Met and adenine to replenish consumed Met [5].

In theory, as a precursor for polyamine synthesis, Met levels influence SAM synthesis and consequently polyamine levels. However, under normal conditions, effective cellular mechanisms regulate polyamine fluctuations within a small range to maintain normal levels. This regulatory mechanism relates to MAT isozyme types that metabolize Met in different tissues. MAT enzymes have two genotypes: MAT1A and MAT2A. Studies show that the MATII isozyme expressed from the MAT2A gene produces higher polyamine levels and exhibits greater cell growth rates [40]. Meanwhile, SAM concentration exerts strong negative feedback inhibition on MATII isozyme, maintaining tissue polyamine levels and methylation reactions when SAM increases [41]. When SAM concentration decreases, SAH decarboxylase and ODC activities increase to promote polyamine synthesis [42], maintaining metabolism and growth in various tissues. Overall, tissues preferentially regulate transsulfuration and decarboxylation reactions to maintain methylation status and polyamine levels, preserving physiological stability and life activities.

5. Cys Generation Mechanism and Physiological Role

Met is the most fundamental sulfur-containing compound in animals. As shown in Figure 3 [Figure 3: see original paper], the transsulfuration pathway of methionine involves the intermediate Hcy condensing with serine to form cystathionine under the catalysis of cystathionine-β-synthase (CBS). Cystathionine is then hydrolyzed by cystathionine-γ-lyase (CSE) to generate Cys, α-ketobutyrate, and ammonia [41,28]. The resulting Cys is a precursor for glutathione (GSH), an important antioxidant and free radical scavenger, while α-ketobutyrate is converted to succinyl-CoA for metabolism through the tricarboxylic acid cycle. Additionally, CBS and CSE enzymes generate endogenous hydrogen sulfide (H2S) molecules during catalysis, and Cys further metabolized to pyruvate by aspartate aminotransferase (AST) and mercaptopyruvate sulfurtransferase (MST) also produces endogenous H2S. H2S is recognized as the third endogenous gaseous signaling molecule discovered after nitric oxide and carbon monoxide, regulating many important cellular functions through intracellular signaling pathways [43-44]. Studies show that the cardiovascular protective effects of garlic also function through H2S generated from allicin-derived polysulfides metabolized in red blood cells [45].

Met can be converted to important Cys via the transsulfuration reaction. Studies using 14C- and 3H-labeled Met indicate that approximately 20% of labeled Met is utilized for transsulfuration in piglets [46]. The transsulfuration pathway serves important physiological functions, such as providing sulfhydryl groups for enzyme proteins and membrane proteins to maintain normal physiological and biochemical reactions [47]. The electron-rich sulfhydryl groups can also adapt to various oxidation states [48]. Cys is a precursor for the tripeptide GSH, which contains sulfhydryl groups and exhibits antioxidant effects by scavenging free radicals and peroxides, as well as detoxification effects by removing heavy metals and aflatoxins. Maaike et al. [19] found that reduced Met levels decrease Cys

synthesis through transsulfuration, ultimately reducing GSH levels and affecting antioxidant function. Castellano et al. [49] reported that feeding Met-restricted diets to weaned piglets decreased hepatic GSH levels and increased oxidative status and antioxidant enzyme activity in subcutaneous adipose tissue. Notably, Cys generated through transsulfuration cannot be converted back to Met, and dietary Cys can only partially replace Met used in the transsulfuration pathway. Finkelstein et al. [41] demonstrated that supplemental Cys in rat diets reduced hepatic CBS activity and SAM and serine levels, thereby decreasing Met transsulfuration metabolism and preserving more Met. However, supplementing Cys on top of Met-restricted diets did not increase hepatic Met content (26.8 vs. 30.6 nmol/g) [50]. Studies also found that intestinal tissue exhibits high net Hcy production from Met transmethylation and transsulfuration [51]. While certain research results on tissue-specific transsulfuration exist, further studies across different species and tissues are needed to elucidate the patterns of Met transsulfuration reactions.

In summary, Met is an essential amino acid for nutritional metabolism that is irreplaceable for protein synthesis in animals. Simultaneously, Met serves as an important methyl donor, sulfhydryl donor, and metabolic source of the endogenous gaseous signaling molecule H2S, while also regulating polyamine formation. Therefore, adequate Met supply and normal metabolic function are fundamental for maintaining physiology, growth, and normal life activities. Conversely, insufficient supply may lead to metabolic disorders and pathological changes such as cancer resulting from inadequate methylation of nucleic acids or functional proteins. Although current research indicates that organisms possess systematic regulation of Met metabolic pathways, the quantitative proportions of each pathway, changes in metabolic flux during deficiency, and metabolic allocation relationships among related substitutes remain unknown and require further investigation.

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Note: Figure translations are in progress. See original paper for figures.