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REVIEW ARTICLE

The role of methionine on metabolism, oxidative stress, and diseases

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Abstract Methionine is an aliphatic, sulfur-containing, essential amino acid, and a precursor of succinyl-CoA, homocysteine, cysteine, creatine, and carnitine. Recent research has demonstrated that methionine can regulate metabolic processes, the innate immune system, and digestive functioning in mammals. It also intervenes in lipid metabolism, activation of endogenous antioxidant enzymes such as methionine sulfoxide reductase A, and the biosynthesis of glutathione to counteract oxidative stress. In addition, methionine restriction prevents altered methionine/transmethylation metabolism, thereby decreasing DNA damage and carcinogenic processes and possibly preventing arterial, neuropsychiatric, and neurodegenerative diseases. This review focuses on the role of methionine in metabolism, oxidative stress, and related diseases.

Keywords Methionine · Mammalian · Endogenous antioxidant enzyme · ROS · Cancer · Disease

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Introduction

Mammals rely on nutrients such as amino acids, fatty acids, vitamins, and minerals from ingested food to maintain an adequate nutritional status for the regulation of metabolic, physiological, and neuronal homeostasis, as well as for the prevention of diseases (Trumbo 2008; Stover et al. 2017). Amino acids are natural compounds involved in various important biological processes, such as metabolism, growth, and immunity (He et al. 2011). They are the building blocks of proteins and precursors to functional molecules (Kim et al. 2007; Li et al. 2007; Wu et al. 2007). Some amino acids are conditionally indispensable/essential for certain developmental and physiological situations. Amino acids are crucial for normal physiology and must be supplied in sufficient amounts by the diet (Blachier et al. 2013).

In the field of animal production, it is common for synthetic amino acids to be added to feed to achieve rapid correction of any nutrient deficiencies. These "ideal compounds" also help to reduce the emission of nitrogen into the environment. In addition, some essential amino acids are currently used as nutraceutical supplements to control enteric processes, reduce pathogenic microorganisms and harmful lipids, and improve growth performance (Vieira et al. 2004).

Many factors can influence the concentrations of amino acids required in the diet, such as the chemical composition of the feed, the ambient temperature of the feeding environment, the sex and age of the animal, and the grain size of the feed. All these parameters can alter the consumption of amino acids and their subsequent metabolic processing. Sulfur amino acids are important in mammalian nutrition, because they are limiting nutrients, especially when crystalline amino acids, such as lysine, tryptophan, and threonine, are supplemented (Dauer and Przedborski 2003). Methionine sulfoxide reductase A (MsrA) is a key endogenous antioxidant enzyme that can promote longevity in animals. Many papers have reported that methionine plays a key role in antioxidant processes (Soares et al. 2017).

Oxidative stress is the result of an imbalance of prooxidant and antioxidant homeostasis, causing irreversible damage to macromolecules and cells and resulting in serious damage to the organism as a whole (Gonsette 2008). Mammalian tissue has an innate antioxidant capacity that is made up of non-enzymatic systems and endogenous enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Gonsette 2008; Lowe 2014; Del et al. 2015).

Mitochondria are cellular organelles that are implicated in several physiological processes that are essential for cell survival, such as the synthesis of adenosine triphosphate (ATP), the control of intracellular Ca^{2+} homeostasis, the regulation of cell cycles, and neurotransmission and synaptic activity in the brain (Serviddio et al. 2011; Kasahara and Scorrano 2014; Romano et al. 2017). The brain is highly susceptible to mitochondrial impairment because of its high energy requirements and vulnerability to oxidative stress (Uttara et al. 2009). Thus, oxidative stress and mitochondrial dysfunction can trigger many neuropsychiatric disorders and neurodegenerative diseases, such as schizophrenia (Ben-Shachar and Laifenfeld 2004) and Alzheimer's disease (Dauer and Przedborski 2003; Clay et al. 2011; Serviddio et al. 2011; Yao and Keshavan 2011; Cassano et al. 2012; Manji et al. 2012; Scola et al. 2013).

Stover et al. (2017) reported that it may be necessary to supplement the diet with essential nutrients (such as amino acids and fatty acids) to stem the development of disease, because the nutritional requirements change according to the health of the individual in question. Brain-specific nutrient deficiencies can initiate disease, its progression, and related comorbidities (Ho et al. 2010; Molero-Luis et al. 2015). The clinical management of brain nutrients can provide meaningful therapeutic benefits (Papakostas et al. 2012).

The WHO has reported that cancer is the second leading cause of death globally, responsible for around 9 million deaths annually. The leading risk factors for cancer are a high body mass index, low fruit and vegetable intake, lack of physical activity, and the consumption of tobacco and alcohol (Torre et al. 2015). Recently, there has been great interest in the use of antioxidants such as vitamins (C and E), polyphenols (flavonoids), minerals (Zn), and amino acids (Met) to decrease oxidative stress and delay the onset of cancer (Nimse and Pal 2015). Because of the regulatory role of methionine in endogenous antioxidant enzymes and other metabolic processes, this amino acid may play a leading role in reducing the prevalence of cancer. The role of methionine restriction in methionine/transmethylation metabolism—which directly influences the risk of cancer occurring and could be used as a palliative treatment—is currently being discussed (Xiao et al. 2014; Maddocks et al. 2016). This paper addresses the role of methionine in metabolism, oxidative stress, and diseases.

Methionine in metabolism

An organism has many different proteins, which are made up of 20 amino acids in different sequences and combinations. Other non-protein amino acids can also be found in living organisms. Of the 20 amino acids that are the basic components of the body's proteins, nine are considered to be essential, as they cannot be synthesized endogenously via metabolic pathways and thus must be provided by dietary sources. Amino acids can be classified as aliphatic, aromatic, or heterocyclic, with aliphatic amino acids being the most common (Blachier et al. 2013).

It is known that beneficial gut microorganisms affect the digestion of proteins and the metabolism of amino acids (Li et al. 2004; Libao-Mercado et al. 2006; Yin and Bie 2010). The efficiency of proteins and amino acids is limited by the catabolism of luminal microbes (Li et al. 2008; Deng et al. 2009; Fang et al. 2010; Yin et al. 2010). Furthermore, during some infections, the intestinal mucosa may need additional energy resources such as amino acids (Blachier et al. 2013). In these instances, branched-chain amino acids (leucine, isoleucine, and valine), histidine, lysine, methionine, phenylalanine, threonine, and tryptophan are used by the intestinal cells (Yin et al. 2004). However, it is not yet fully understood how these amino acids are transported to and processed in the intestinal tract (Chen et al. 2007; Wang et al. 2009).

Methionine, a precursor of succinyl-CoA, homocysteine, cysteine, creatine, and carnitine, is an essential sulfur-containing amino acid. It is necessary for the metabolism of polyamines, creatine, and phosphatidylcholine. Methionine is the precursor for cellular methylation and the synthesis of cysteine, and can thus decrease the dietary cysteine requirement (Finkelstein et al. 1988; Mackay et al. 2012). The cysteine produced can be used in protein translation and the synthesis of the antioxidant glutathione and the osmolyte taurine (Rezzi et al. 2007; Nicholson et al. 2008). Methionine also participates in the recycling of the sulfur

that is assimilated in energy-consuming reactions (Pirkov et al. 2008; Albers 2009). A deficiency of this amino acid suppresses epithelial growth in newborn animals by decreasing intestinal activity in the L-methionine cycle (Bauchart-Thevret et al. 2009).

Stoll et al. (1999) reported that the net portal balance of methionine in piglets represents 48% of the intake, which indicates that some of the methionine is used by the intestine. The parenteral methionine requirement is thus approximately 69% of the enteral requirement in newborn piglets (Shoveller et al. 2003). In addition, Shoveller et al. (2003) found that cysteine is effective in conserving methionine: in the presence of excess dietary cysteine, the methionine requirement is around 70% of the enteral requirement. Moreover, Bauchart-Thevret et al. (2009) showed that a deficiency of sulfur-containing amino acids leads to fewer goblet cells and lower glutathione content in the small intestine. Similarly, Riedijk et al. (2007) reported that approximately 20% of dietary methionine is used in the gastrointestinal tract (GIT), which is also a site for homocysteine production and whole-body transmethylation and transsulfuration. However, studies by Blachier et al. (2007) have revealed that less methionine is catabolized in pig enterocytes, but it is substantially catabolized in other cells of the portal-drained viscera and intestinal mucosa.

With regard to other animal species, Tsiagbe et al. (1987) reported that methionine directly influences growth and immunity response in broiler chickens. Moreover, Swain and Johri (2000) found a synergic relationship between methionine and choline in antibody production; dietary methionine levels from 322 to 580 mg/day improved the serum levels of IgG. Likewise, Carew et al. (2003) demonstrated that methionine deficiency decreases the relative weight of the lymphoid organs, which in turn harms growth. However, excess consumption of methionine can also have an adverse effect on growth. In the study above, supplementation with 20 or 40 g/kg excess methionine was found to decrease food intake and reduce weight gain (D'Mello and D'Mello 2003).

Methionine in oxidative stress

Reactive oxygen species (ROS) are produced by a variety of both physiological and non-physiological events, including the Fenton reaction, cellular respiration, mitochondrial dysfunctions, pathologies, phagocytes, neutrophils, and stress. However, cellular systems of detoxification easily eliminate low concentrations of ROS and free radicals by activating endogenous antioxidants such as SOD, CAT, GSH peroxidase, and GSH reductase. Nonetheless, excessive production of ROS causes extensive cellular damage and affects DNA and membrane phospholipids, causing cell death, tissue injury, chronic inflammatory responses, and fibrogenesis (Freitas et al. 2016). High concentrations of free radicals and ROS-saturated cellular systems of detoxification can induce cellular damage in two ways: cell senescence or cell death. Cell senescence is characterized by the induction of autophagy and the arrest of the cell cycle, whereas cell death occurs through necrosis or apoptosis. Cell necrosis is induced by a deficiency in ATP content, whereas apoptosis is induced under good energy conditions (Romano et al. 2017).

Methionine plays an essential role in the immune system through its metabolites. In this regard, Blachier et al. (2013) found that this amino acid directly influences the functioning of the immune system because of methionine catabolism leading to an increase in the production of glutathione, taurine, and other metabolites. Methionine is also readily used by the hepatocytes for the direct synthesis of glutathione, which is a low-molecular-weight antioxidant (Blachier et al. 2013). Meanwhile, methionine has been shown to chelate lead and removes it from tissues, which decreases oxidative stress (Patra et al. 2001). It has been also demonstrated that a lower concentration of methionine can prompt transsulfuration. When the intake of methionine is increased, substrate flux through the transmethylation pathway decreases, and flux through the transsulfuration pathway increases (Garg et al. 2011; Hosseini et al. 2012).

Some researchers are currently investigating the impact of methionine restriction on immune system function and oxidative stress in mammals. It has been shown that restricting this amino acid stimulates the production of glutathione and reduces oxidative stress (Hosseini et al. 2012, Liu et al. 2017). Campbell et al. (2016) observed an alteration of the oxidative activity in a branch of the pentose phosphate pathway (PPP) after increasing methionine supplementation. They also found that pre-incubating cells with methionine increased cellular tolerance to the thiol oxidizing agent diamide with relation to oxidative pentose phosphate (Campbell et al. 2016). However, studies by Maddineni et al. (2013) revealed that mice with restricted dietary methionine intake display reduced oxidative stress but no changes in the activity of their antioxidant enzymes. This suggests that further studies are needed to determine the effect of methionine restriction on antioxidant activity (Fig. 1; Table 1).

Methionine in disease

Many studies have linked oxidative stress with the pathogenesis of several hepatic and renal diseases (Hyelin et al. 2010; Li et al. 2015). Stefanello et al. (2009) showed that chronic exposure to methionine leads to oxidative stress and histological changes in the liver in rat models. The acute administration of methionine and/or methionine sulfoxide (MetO) also significantly changes oxidative stress, as shown by the

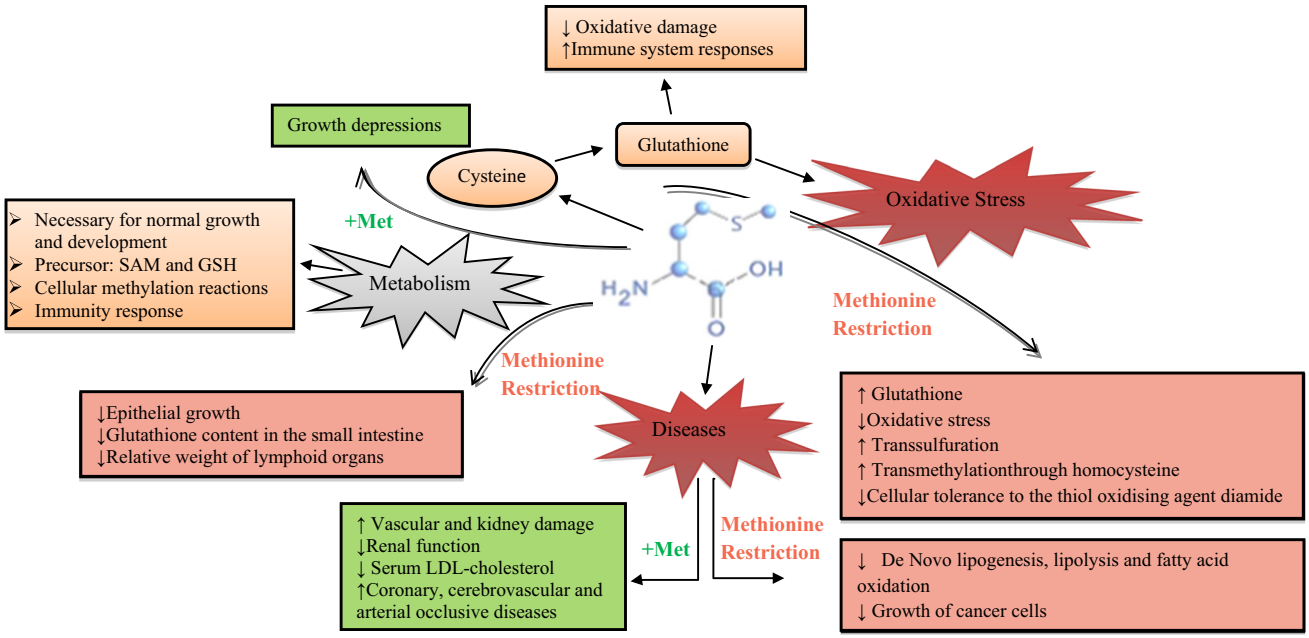

Fig. 1 Main effects of the biological activity of the Met and methionine restriction on metabolism, oxidative stress, and diseases

thiobarbituric acid reactive substances (TBARS), total thiol content, and enzymatic antioxidant defense results (Costa et al. 2013). Meanwhile, chronic dietary methionine may induce vascular (Troen et al. 2003) and kidney damage with tubular hypertrophy (Kumagai et al. 2002). However, the effects of hypermethioninemia on the kidneys are still under investigated; this tissue can regulate plasma concentrations of amino acids, urea, and ammonia. In addition, high serum methionine concentrations have been found in patients with coronary, cerebrovascular, and arterial occlusive diseases. High concentrations of methionine and MetO in the plasma may cause a progressive increase in the rate of glomerular filtration, thus impairing renal function. These results may contribute to understanding the effects of hypermethioninemia on the mechanisms involved in hepatic and renal diseases (Soares et al. 2017).

A direct relationship has been found between oxidative stress and cancer, because oxidative stress is present in various cancer cells. The imbalance of redox pathways could be related to the stimulation of oncogenes. Furthermore, an increased level of 8-OH-G, an indicator of oxidative DNA lesions, induces DNA mutation, a critical element in carcinogenesis and various tumors. Therefore, oxidation is strongly implicated in the etiology of cancer (Jackson and Bartek 2009). According to Valko et al. (2006), DNA damage and genome stability are predominantly associated with the carcinogenic initiation process.

It has been demonstrated that cancer cells are altered by methionine metabolism and transmethylation. When methionine is replaced by homocysteine, the growth of cancer cells is inhibited. Furthermore, methionine dependence may indicate an overall imbalance in transmethylation. Thus, the prevention of altered methionine/transmethylation metabolism or compensation of the altered metabolism may be the main reason for the barrier effect of methionine against cancer (Hoffman 1985; Jackson and Bartek 2009). Recent research has shown that cancer cells have a “methyl-sink”, whereby methyl groups are diverted from DNA (Dash et al. 2016). In addition, methionine is seen to provoke alteration and excessive transmethylation in cancer cells. However, Dash et al. (2016) have reported that decreased levels of methionine and its metabolites may decrease cellular function in multiple organs at a systemic level. The effectiveness of methionine restriction for treating cancer is dependent upon many factors, such as age, innate immunity, type and severity of cancer, intestinal health, diet, and nutritional requirements.

The role of methionine in lipid metabolism has also been discussed, mainly as a means of reducing obesity, type 2 diabetes, and insulin resistance. In this sense, methionine restriction can reduce fat accumulation by caloric restriction, which increases de novo lipogenesis, lipolysis, and fatty acid oxidation. However, the physiological mechanisms in the adipose tissue and liver are not well known (Zhou et al. 2016). In addition, the studies of Soares et al. (2017) found that MetO increases the serum triglyceride levels in rats due to increased production of acetyl-CoA by a higher circulation of Met in bloodstream. Likewise, Hidiroglou et al. (2004) demonstrated that hypermethioninemia causes a decrease in serum LDL cholesterol and Stefanello et al. (2007) reported that excess Met reduced serum and brain

Table 1 Biological function of methionine on metabolism, oxidative stress, and diseases

Items	Biological function	References
Metabolism	It is necessary for normal growth and development in mammals	Blachier et al. (2013)
	It is precursor of succinyl-CoA, homocysteine, cysteine, creatine, and carnitine. Participates in the biosynthesis of S-adenosyl-methionine (SAM), which is involved in polyamine, creatine, and phosphatidylcholine metabolism	Finkelstein et al. (1988) and Mackay et al. (2012)
	It is precursor for cellular methylation reactions and participates in the recycling of the sulfur. It is also converted to L-methionine sulfoxide (MetO)	Finkelstein et al. (1988), Troen et al. (2003) and Mackay et al. (2012)
	The cysteine produced is used in protein translation, and synthesis of glutathione and the osmolyte taurine	Rezzi et al. (2007); Nicholson et al. (2008)
	A deficiency atrophies the small intestine and suppresses epithelial growth in newborn animals, as well as fewer goblet cells and lower glutathione content in the small intestine	Bauchart-Thevret et al. (2009)
	The 20% of the dietary methionine is used in the GIT	Riedijk et al. (2007)
	The parenteral methionine requirement is thus approximately 69% of the enteral requirement in newborn piglets	Shoveller et al. (2003)
	It is less catabolized in pig enterocytes; it is substantially catabolized in other cells of the portal-drained viscera and intestinal mucosa	Blachier et al. (2007)
	Directly influence of Met on growth and immunity response in broiler chickens	Tsiagbe et al. (1987)
	Synergistic effect of Met with choline on the production of antibodies (IgG)	Swain and Johri (2000)
	The deficiency of Met decreases relative weight of lymphoid organs in turn the growth performance	Carew et al. (2003)
	Excess intakes of Met causes growth depressions	D'Mello and D´Mello (2003)
Oxidative stress	It is readily catalyzed by the hepatocytes for the direct synthesis of glutathione, which is a low-molecular-weight antioxidant	Blachier et al. (2013)
	It has been shown to chelate lead and removes it from tissues	Patra et al. (2001)
	An increase in Met intake decreases the substrate flux through the transmethylation pathway	Garg et al. (2011) and Hosseini et al. (2012)
	An increase of Met changes the oxidative activity in the branch of the pentose phosphate pathway and increases cellular tolerance to the thiol oxidizing agent diamide	Campbell et al. (2016)
	Methionine restriction (MR) stimulates the production of glutathione and reduces oxidative stress	Hosseini et al. (2012)
	MR reduces oxidative stress, but no changes in the activity of their antioxidant enzymes	Maddineni et al. (2013)
	MR provokes a transsulfuration which leads to Met catabolism and remethylation, through homocysteine	Hosseini et al. (2012) and Romano et al. (2017)
Diseases	The acute administration of Met and/or MetO modifies oxidative stress parameters, as shown in TBARS, total thiol content, and enzymatic antioxidant defense results	Costa et al. (2013)
	Chronic exposure to Met induces oxidative stress and promotes histological changes in the liver of young rats	Stefanello et al. (2009)
	Chronic dietary Met may induce vascular and kidney damage with tubular hypertrophy	Kumagai et al. (2002) and Troen et al. (2003)
	High concentrations of Met and MetO in plasma cause a progressive increase in the rate of glomerular filtration, thus impairing renal function	Soares et al. (2017)
	A high serum concentration of Met is associated with patients with coronary, cerebrovascular and arterial occlusive diseases	Soares et al. (2017)
	Cancer cells are altered by Met metabolism and transmethylation, and when is replaced by homocysteine, the growth of cancer cells is inhibited	Hoffman (1985) and Jackson and Bartek (2009)
	Cancer cells have a "methyl-sink", whereby methyl groups are diverted from DNA	Dash et al. (2016)
	Excessively low levels of Met and its metabolic products diminish cellular function in multiple organs at the system level	Dash et al. (2016)
	MR increases de novo lipogenesis, lipolysis, and fatty acid oxidation	Zhou et al. (2016)
	Hypermethioninemia provokes a decreases of serum LDL cholesterol	Hidiroglou et al. (2004)
	Excess Met reduced serum cholesterol and brain in rat	Stefanello et al. (2007) and Soares et al. (2017)

total cholesterol in the rats; thus, more studies are needed to determine the regulatory effects.

This review has discussed the importance of methionine as a sulfur-containing essential amino acid that is indispensable for various physiological and biochemical processes in organisms. In addition, methionine supplementation or restriction can intervene in the natural antioxidant capacity of an organism by leading to the production of endogenous enzymes that reduce oxidative stress and, in turn, DNA damage, cancer, cardiovascular disease, neuropsychiatric disorders, and neurodegenerative diseases.

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Compliance with ethical standards

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Research involving human and animal rights This review article does not involve any human participants and animal work.

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