Amino Acids (2016) 48:2479–2489
DOI 10.1007/s00726-016-2302-4

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REVIEW ARTICLE

Mechanistic basis of hypermethioninemia

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Received: 28 January 2016 / Accepted: 19 July 2016 / Published online: 27 July 2016
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Abstract Hypermethioninemia is a condition defined as elevated plasma methionine levels and may be a consequence of different conditions that include non-genetic and genetic causes. In severe cases, hypermethioninemia may lead to development of neurological and hepatic impairments, but mechanisms are still not well elucidated. Therefore, this review aims to reunite the knowledge acquired about the methionine-induced brain and liver toxicity focusing on the results obtained by studies from patients, in vitro experiments, and in vivo animal models. In general, some studies have shown that methionine decreases Na^{+},K^{+}-ATPase activity, induces oxidative stress, increases acetylcholinesterase activity, and leads to dendritic spine downregulation in brain. Concerning to liver, hypermethioninemia seems to provoke changes in cell morphology, lipid accumulation, oxidative stress, inflammation, and ATP depletion. It is possible to infer that oxidative damage is one of the most important mechanisms responsible for methionine toxicity, since different studies showed that this amino acid induces oxidative stress in brain and liver tissues. Besides, reactive oxygen species may mediate other alterations induced by methionine, such as the reduction in brain Na^{+},K^{+}-ATPase activity, and liver inflammation.

Keywords Brain · Hypermethioninemia · Liver · Methionine · Oxidative stress

Roles of methionine

Methionine (Met) is an essential sulfur-containing amino acid obtained from diet or degradation of endogenous proteins. Some of the main functions of Met in organism include: production of its derivative molecules cysteine, glutathione, carnitine, taurine, and creatine (Wesseling et al. 2009; Wyss and Kaddurah-Daouk 2000; Crill and Helms 2007), protein synthesis since Met composes proteins and peptides and is the only natural initiating amino acid in the eukaryotic translation (Lucas-Lenard 1971), as well as donation of its methyl group to a variety of molecules such as nucleic acids, histones, amino acids, and lipid-derivatives (Chiang et al. 1996).

Besides, it has been reported that Met residues in proteins also provide antioxidant protection since they are often positioned so that they establish an interaction, through hydrophobic bond, between their sulfur atoms and the rings of aromatic amino acids (Valley et al. 2012), which are much susceptible to oxidation by reactive species (El Refaey et al. 2015). Furthermore, the oxidation of surface exposed Met protects the other residues because reactive species may oxidize Met to Met sulfoxide, which may be reduced back by the enzyme Met sulfoxide reductase (Brot et al. 1981).

Handling Editor: C.-A. A. Hu.

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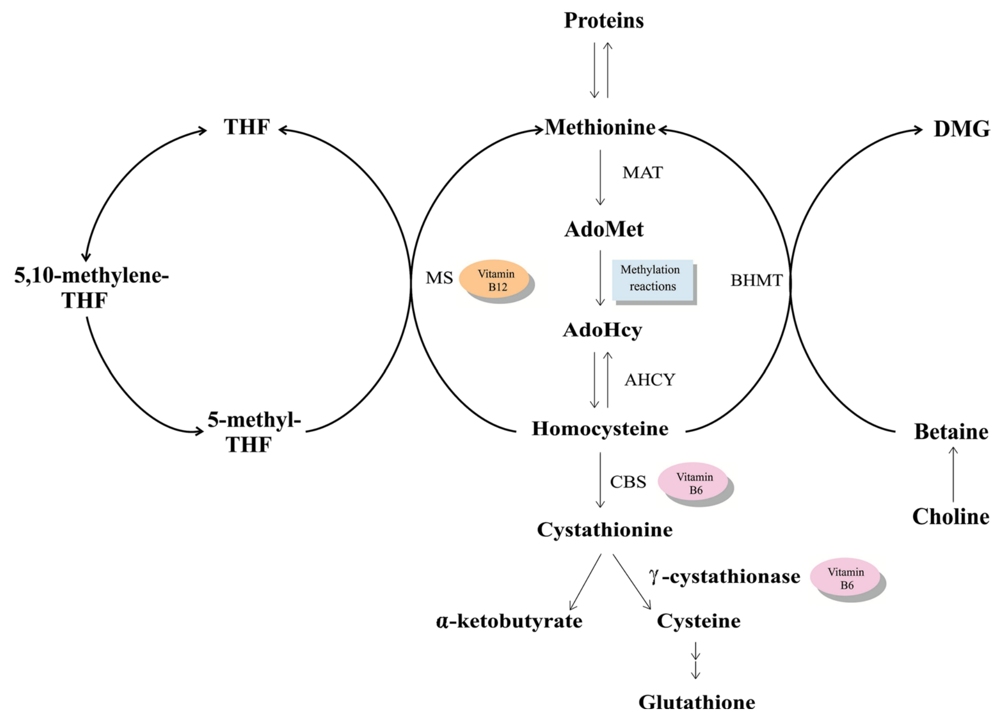

Fig. 1 Pathways of Met metabolism in mammals. *MAT* Methionine adenosyltransferase, *AdoMet S*-adenosylmethionine, *AdoHcy S*-adenosylhomocysteine, *AHCY S*-adenosylhomocysteine hydrolase, *CBS* cystathionine *β*-synthase, *5,10-methylene-THF* 5,10-methylenetetrahydrofolate, *5-methyl-THF* 5-methyltetrahydrofolate, *THF* tetrahydrofolate, *BHMT* betaine-homocysteine-methyltransferase, *DMG N*,*N*-dimethylglycine

Metabolism of methionine

Met is mainly metabolized in the liver by the enzyme Met adenosyltransferase (MAT, EC 2.5.1.6), which is present in three isoforms. MAT I and III are encoded by the same gene MAT1A and predominate in adult liver. MAT II activity is present at smaller amount in adult liver and its activity is predominant in non-hepatic tissues, fetal liver, and hepatocellular carcinoma (Frago et al. 1998; Horikawa et al. 1990, 1993; Okada et al. 1981; Gil et al. 1996; Cai et al. 1996). This enzyme transfers the adenosyl group from ATP to Met, forming *S*-adenosylmethionine (AdoMet) and tripolyphosphate. AdoMet is reacquired as a methyl donor in reactions that include methylation of nucleic acids, proteins, and lipids. The product of AdoMet transmethylation is the *S*-adenosylhomocysteine (AdoHcy), which is hydrolyzed by AdoHcy hydrolase (AHCY, EC 3.3.1.1), resulting in homocysteine (Hcy) formation (Mudd 1962; Cantoni 1953; Finkelstein 1990; de la Haba and Cantoni 1959).

Hcy can be metabolized by two different pathways: remethylation or transsulfuration. Remethylation is catalyzed by Met synthase (MS, EC 2.1.1.13), a vitamin B_{12}-dependent enzyme that regenerates Met by transferring a methyl group to Hcy. The methyl group is derived from the endogenous 5-methyltetrahydrofolate (5-methyl-THF), which is formed during the metabolism of folic acid. Additionally, betaine-Hcy-methyltransferase (BHMT) uses betaine derived from choline as a methyl donor for Hcy remethylation, which is considered a salvage pathway when toxins compromise the action of MS. BHMT transfers the methyl group from betaine to Hcy, forming Met and *N*,*N*-dimethylglycine (DMG). Transsulfuration pathway catalyzes the condensation of Hcy with serine to form cystathionine through the action of a vitamin B_6-dependent enzyme named cystathionine *β*-synthase (CBS, EC 4.2.1.22). Cystathionine is then converted to α-ketobutyrate and cysteine by the enzyme γ-cystathionase, which is also dependent of vitamin B_6. Therefore, transsulfuration pathway is a very important source of non-enzymatic antioxidant protection to the liver, since it forms cysteine, the precursor of glutathione (Finkelstein 2000; Selhub 1999; Beatty and Reed 1980; Mosharov et al. 2000). The Met/Hcy cycle is shown in Fig. 1.

In cerebral tissue, Met is primarily metabolized through remethylation pathway. Some years ago, data published in literature indicated that the transsulfuration was incomplete in the brain due to absence of the enzyme γ-cystathionase, leading to cystathionine accumulation in this organ (Finkelstein 1998). However, Vitvitsky et al. (2006) have demonstrated the existence of a functional transsulfuration pathway in human neurons and astrocytes and in mouse brain, suggesting that this may contribute to the protection under oxidative stress conditions through brain glutathione synthesis.

Hypermethioninemia

Normal plasma concentration of Met range from 13 to 45 μM (Stabler et al. 2002). Hypermethioninemia occurs

when Met levels increase in blood, which may be a consequence of different conditions. Non-genetic causes for hypermethioninemia include liver disease, premature birth (frequently transient), and diet rich in proteins, which may increase plasma Met levels to 1206 µM when protein intake achieves 7 g/kg/day. On the other hand, hypermethioninemia from genetic causes (hereditary conditions) includes: MAT I/III deficiency, classical homocystinuria (due to CBS deficiency), deficiencies of glycine *N*-methyltransferase (GNMT, EC 2.1.1.49), AHCY, citrin, and fumarylacetoacetate hydrolase (tyrosinemia type I) (Mudd 2011; Levy et al. 1969).

A characteristic that distinguishes MAT I/III deficiency from GNMT, AHCY, and CBS deficiencies is that the first one leads to isolated hypermethioninemia, with plasma Met reaching levels from 600 to 2541 µM in patients with homozygous mutations (Mudd et al. 1995; Chamberlin et al. 1996; Nagao and Oyanagi 1997). The term isolated hypermethioninemia designates elevated plasma Met levels which are not associated with the increase in Met metabolites, including AdoMet, AdoHcy, Hcy, and cystathionine. As exception, patients with severe MAT I/III deficiency may have plasma Hcy slightly elevated, but the mechanisms involving this effect are still not well understood (Stabler et al. 2002; Lagler et al. 2000). Besides, MAT I/III deficiency may lead to decreased AdoMet, while the other causes of hypermethioninemia often enhance AdoMet levels (Mudd 2011). Therefore, the reader should be clarified that the effects of hypermethioninemia may differ depending on the cause, since AdoMet may be involved in the pathological effects either when increased or decreased.

Pathological effects of hypermethioninemia

Met is crucial for normal growth and development, but when this amino acid and/or its metabolites are present at abnormally elevated plasma levels, potentially toxic events may occur. Although it may be asymptomatic, hypermethioninemia can cause the following pathological effects: myopathy, hypotonia, altered erythrocyte morphology with consequent splenic hemosiderosis, facial dysmorphia associated to abnormal teeth and hair, anorexia and digestive disturbances, development of neurological problems (tremor, dystonia, and cognitive deficit), and/or liver diseases (Chamberlin et al. 1996; Gaull et al. 1981a; Guízar Vázquez et al. 1980; Benevenga and Steele 1984; Higashi 1982; Lynch and Strain 1989; Labrune et al. 1990; Gout et al. 1977; Chamberlin et al. 1997; Harvey Mudd et al. 2003; Mudd et al. 2001). In view of severity of the symptoms, this review will empathize the neurological and hepatic effects of hypermethioninemia.

Neurological effects

The increase in Met levels can be toxic to the brain regardless of the cause. In general, patients with severe hypermethioninemia may present neurological dysfunction, including mental retardation and cognitive deficit. It has been also reported that cerebral edema may be observed during CBS and MAT I/III deficiencies and during excessive Met diet when plasma Met achieves levels extremely elevated (Harvey Mudd et al. 2003; Mudd et al. 2001; Braverman et al. 2005). However, the mechanisms involved in these alterations are still not well elucidated. In the attempt to understand such mechanisms, some studies have been developed.

Na^+,K^+-ATPase activity and oxidative stress

Na^+,K^+-ATPase plays a crucial role in maintaining the ionic gradient required for neuronal excitability and regulation of neuronal cell volume through the transport of Na^+ and K^+ ions in the nervous system (Glynn 1985). Inhibition of this enzyme may induce brain edema, neuronal death, and impairment of learning and memory (Wyse et al. 2004; de Lores Arnaiz and Ordieres 2014). In this context, the decrease in brain Na^+,K^+-ATPase activity seems to be involved in neurological diseases, such as dystonia (Cannon 2004), Alzheimer disease (Zhang et al. 2013), bipolar affective disorder (Mynett-Johnson et al. 1998), ischemia (de Souza Wyse et al. 2000), epilepsy (Grisar et al. 1992), depressive disorders in rats (Gamaro et al. 2003; Acker et al. 2009), hyperprolinemia (Ferreira et al. 2011), and phenylketonuria (Wyse et al. 1999).

Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) and the cellular antioxidant defenses that include non-enzymatic protection, such as vitamins C and E and reduced glutathione, and enzymatic protection, such as glutathione peroxidase, superoxide dismutase (SOD), and catalase (CAT) (Apel and Hirt 2004). Increased ROS production can directly cause tissue damage and lead to inflammation process (Geronikaki and Gavalas 2006). Besides, Na^+,K^+-ATPase activity may be affected by ROS through lipid peroxidation and sulfhydryl groups oxidation.

In this context, an in vitro study showed that Met inhibits Na^+,K^+-ATPase in synaptic plasma membrane from hippocampus of rats (Streck et al. 2002a). Posteriorly, Stefanello et al. (2005) verified that the preincubation of hippocampal homogenates with antioxidants (glutathione and tocopherol) prevented the inhibitory action of Met on Na^+,K^+-ATPase. In the same work, the evaluation about the in vitro effects of Met on some parameters of oxidative stress demonstrated that this amino acid caused lipoperoxidation and reduced non-enzymatic antioxidant capacity in rat hippocampus. Together, these results suggest that

Met-induced Na^+,K^+-ATPase inhibition is possibly mediated by free radical formation.

Therefore, Stefanello et al. (2007a) extended the investigations and developed an in vivo model for hypermethioninemia in which developing Wistar rats receive injections of Met leading to concentrations approximately 30-fold the control levels. Using this experimental model, it was demonstrated that both chronic and acute administration of Met lead to lipoperoxidation and decreased Na^+,K^+-ATPase activity in Wistar rat hippocampus. Since Na^+,K^+-ATPase is embedded in cellular membrane, it is possible that peroxidative process could provoke changes of fluidity or other membrane properties, prejudicing the enzyme functioning and decreasing its activity (Stefanello et al. 2007b).

In a further study, Stefanello et al. (2007c) also demonstrated that chronic injections of Met significantly reduced Na^+,K^+-ATPase activity in rat cerebral cortex accompanied by reduced amount of gangliosides (GM1, GD1a, GD1b, and GT1b), phospholipids (sphingomyelin, phosphatidylcholine, and phosphatidylethanolamine) and cholesterol. Lipoperoxidative process was also observed, strengthening the hypothesis that oxidative damage of the cellular membrane lipids could provoke changes in lateral assembly of glycosphingolipids, unsaturated glycerophospholipids and cholesterol, leading to alteration in Na^+,K^+-ATPase activity.

The neurotoxic effects of Met were also demonstrated in Sprague–Dawley rats submitted to a Met-enriched diet during 8 weeks. The results from this study showed an enhance in the activity of the antioxidant enzyme SOD in cerebral cortex of the rats fed on 1 and 5 % Met, suggesting a metabolic adjustment to combat a possible augment in ROS production. This alteration was accompanied by apparent impairment of locomotor skills and synaptic plasticity in rats fed on 5 % Met (Viggiano et al. 2012).

More recently, an animal model for maternal hypermethioninemia was developed. In this study, pregnant Wistar rats received injections of Met during gestational period. The administration of 2.68 μmol Met/g body weight increased encephalon Met levels (without Hcy elevation) in the offspring. Decrease in the activities of Na^+,K^+-ATPase, Mg^{2+}-ATPase, and CAT, as well as in total sulfhydryl content was also found. However, cerebral lipoperoxidation was not observed and in this case, the reduction in Na^+,K^+-ATPase activity may be associated to attack of reactive species to the sulfhydryl groups present in the enzyme (Schweinberger et al. 2014).

Acetylcholinesterase activity

Schulpis et al. (2006) published data showing that Met is able to increase hippocampal acetylcholinesterase (AChE) activity in vitro. At the following year, Stefanello et al. (2007d) showed that chronic subcutaneous injections of Met in developing Wistar rats increased AChE activity in cerebral cortex associated to an impaired working memory performance. Since AChE acts into the synapse by rapid hydrolysis of the acetylcholine (Ach), a neurotransmitter whose adequate maintenance has been associated with cognitive manifestations (learning and memory) (Bartus et al. 1982), the stimulation of this enzyme activity could lead to a decrease in cerebral Ach levels and provide an explanation for the memory deficit found in the hypermethioninemic rats. In agreement, studies showed that long-term Met exposure caused an important increase in brain AChE activity and memory deficit in zebrafish (Vuaden et al. 2012). Since Ach has a role as an anti-inflammatory molecule, some studies have correlated increased AChE activity with neuroinflammation (Scherer et al. 2014), what could be also related to the pathogenic effects found in hypermethioninemia.

Dendritic spine downregulation

In 1952, Osmond and Smythies (1952) proposed the ‘‘transmethylation theory’’ of schizophrenia, suggesting that this psychotic disease is a result of a disturbance in methylation. In 2009, Grayson et al. also reported that Met treatment could worsen schizophrenia symptoms, possibly because it increases brain levels of AdoMet. More specifically, excessive AdoMet could provoke hypermethylation of Reelin gene promoter. Since Reelin is a glycoprotein secreted by GABAergic neurons that stimulates dendritic spines development, this process could be impaired by Met (Levenson et al. 2008).

Indeed, it has been demonstrated that the treatment with Met causes a decrease in dendritic spine density of layer III pyramidal neurons in frontal cortex of mice, a pathological alteration similar to the dendritic spine downregulation found in brain during schizophrenia (Tueting et al. 2010). In agreement, clinical studies have demonstrated that patients with psychotic disorders present increased Met levels in cerebrospinal fluid (Regland et al. 2004).

Besides, it should be noted that that learning and novel sensory experiences lead to spine formation and the new spines that are preserved seem to provide a structural basis for memory retention (Yang et al. 2009). Thus, when hypermethioninemia is associated with enhanced AdoMet levels, the reduction in dendritic spine density may occur and cause lifelong memory impairment.

Hepatic effects

Since Met is primarily metabolized in the liver (Finkelstein 1990), it has been suggested that excess of Met may cause

liver injury, but mechanisms are still not well elucidated. In this context, several studies have been performed to figure it out.

Liver cell alterations

In humans, electron microscopy revealed augmented smooth endoplasmic reticulum, reduced rough endoplasmic reticulum, enhanced lysosomes, and short breaks in the outer membranes of liver from patients with persistent hypermethioninemia (MAT activity ranged from 7.8 to 17.5 %) and with no abnormalities in other sulfur amino acid concentrations (Gaull et al. 1981b). In rats, excess dietary Met (10–12.4 % dl-Met) caused atrophy of liver cells and changes in the distribution of the chromatin, which was condensed and deposited at the periphery of the nucleus (Earle et al. 1942).

Hepatic lipid accumulation

Whereas the liver is the organ directly related to lipid metabolism, fatty accumulation (steatosis) may be observed during some pathological conditions. Steatosis is associated with hepatocyte damage and consequently can cause cirrhosis, inflammation, and liver failure leading to end-stage disease (Angulo 2010). In this context, histological examinations of liver tissues from patients with persistent and transient hypermethioninemia showed moderate fatty degeneration, wherein the condition improved after low Met diet (Tsuchiyama et al. 1982).

Furthermore, Lu et al. (2001) evaluated the effect of MAT1A knockout in mice and observed, at 3 months, an increase of 776 % in plasma Met levels and reduction of liver AdoMet content. At 8 months, development of spontaneous macrovesicular steatosis and predominantly periportal mononuclear cell infiltration occurred. These changes were accompanied by augmented expression of acute phase-response/inflammatory markers (orosomucoid, amyloid, metallothionein, Fas antigen) and growth-related genes (early growth response 1 and proliferating cell nuclear antigen), as well as increased liver weights. Posteriorly, Martínez-Chantar et al. (2002) also demonstrated that knockout in MAT1A gene leads to abnormal expression of genes involved in the metabolism of lipids and carbohydrates associated with hyperglycemia and increased hepatic triglyceride levels in mice.

Met diet supplementation was also able to induce hepatic damage by stimulating cholesterol synthesis in liver cells (probably through increased hepatic expression of 3-hydroxy-3-methylglutaryl coenzyme A reductase) (Hirche et al. 2006), augmenting accumulation of hepatic total lipids and phospholipids (Yang and Kadowaki 2011), and inducing microvesicular steatosis, hepatocyte degeneration, and inflammatory reactions in liver of rats (Yalçinkaya et al. 2009). Met diet restriction, on the other hand, seems to be advantageous as described in a previous study, which demonstrated that rats submitted to restrictive Met intake presented reduced visceral fat associated to a decrease in basal insulin, glucose, and leptin, and increased adiponectin and triiodothyronine. Besides, Met restriction prevented age-associated increase in serum lipids (Malloy et al. 2006). In 2013, Malloy et al. also demonstrated that Met restriction was able to reverse the severity of steatosis in obese mice accompanied by reduced hepatic triglycerides levels, increased VLDL secretion, and increased mRNA levels of apolipoprotein B and microsomal triglyceride transfer protein. The expression of inflammatory markers (Tnf-α and Ccr2) was also attenuated by Met restriction in this study.

It is important to note that excessive lipids in liver may cause lipid peroxidation, which can increase the production of pro-inflammatory cytokines (Bradbury 2006). Besides, the increase in lipids can exceed mitochondrial beta-oxidation further enhancing oxidative stress and inflammation (Schreuder et al. 2008). On this basis, Met-induced lipid accumulation in liver could lead to oxidative stress, which may have a role in hepatic damage during hypermethioninemia.

Oxidative stress

The role of oxidative stress on the hepatic toxicity caused by Met has been shown in different animal studies: enriched Met diet increased lipid peroxidation in liver of rats and rabbits, as well as, altered antioxidant enzyme activities and induced inflammatory infiltration of portal triads in liver of rabbits (Lynch and Strain 1989; Mori and Hirayama 2000; Toborek et al. 1996); high Met diet also increased hepatotoxicity and oxidative stress in the liver of chronically ethanol-treated rats (Yalçinkaya et al. 2007); MAT1A knockout increased susceptibility to oxidative stress and reduced glutathione content in mice liver (Lu et al. 2001; Martínez-Chantar et al. 2002).

To further the knowledge about these mechanisms, Stefanello et al. (2009) evaluated the toxic effects of chronic Met injections in rats. The treatment decreased non-enzymatic antioxidant defenses, increased protein carbonylation, and altered the activities of the antioxidant enzymes glutathione peroxidase and CAT in the liver, indicating oxidative stress. These alterations were accompanied by morphological alterations in liver.

In addition, rats fed with a high Met diet (2 %, w/w) during 6 months presented hepatic oxidative and nitrosative stress characterized by increased lipid peroxide and nitrotyrosine levels, as well as decreased non-enzymatic and enzymatic antioxidant defenses in liver. Increased levels of

alanine transaminase and aspartate transaminase in blood and altered apoptotic parameters in liver indicated that the hepatic tissue was disrupted. These alterations were accompanied by enhanced Hcy levels in blood (Yalçinkaya et al. 2009).

Gomez et al. (2009) also demonstrated that Wistar rats fed a Met supplemented diet (2.5 g/100 g) for 7 weeks had increased mitochondrial ROS generation and oxidative damage to mitochondrial DNA in liver. In agreement, Caro et al. (2008) showed that lowered Met ingestion has the exactly opposite effects, decreasing mitochondrial ROS production and DNA oxidative damage in liver of rats. More recently, a swine model was used to determine if a methionine-restricted diet for 2 weeks could reduce oxidative stress in hepatic mitochondria. The results showed that methionine restriction decreased markers of oxidative damage to DNA and proteins in liver mitochondria of pigs, being that effects probably were consequence of attenuated ROS production since a reduction in H_2O_2 generation and in free radical leak was also observed. The authors suggest that the decrease in ROS generation possibly occurred due to reduced complex I activity, which was associated with decreased levels of the apoptosis inducing factor, a protein related to complex I function (Ying et al. 2015).

Besides, excessive Met intake by γ-cystathionase-deficient mice led to the development of acute hepatitis attended by serum and hepatic lipoperoxidation (Yamada et al. 2012). It has been previously described that peroxidized fatty acids (arachidonic and linolenic) stimulate interleukin-8 production by peripheral blood monocytes in liver (Jayatilleke and Shaw 1998). Interleukin-8, in turn, has been associated with hepatic neutrophil infiltration and to activation of hepatic profibrogenic cells (Bird 1994; Zimmermann et al. 2011; Taïeb et al. 2000; Dong and Zheng 2015; Tachibana et al. 2007).

More recently, Costa et al. (2013) performed in vitro and in vivo studies about the toxic effects of Met in liver. For in vitro studies, liver homogenates were incubated with Met and results showed changes in CAT and SOD activities, as well as in ROS production. For in vivo studies, the animals received injections of Met (0.4 g/kg) and were euthanized after 1 and 3 h. Results showed that Met enhanced carbonyl content at 1 h, as well as decreased CAT activity 1 and 3 h after administration. Data indicated that Met modifies liver homeostasis by altering the redox cellular state both in vivo and in vitro.

Cholestasis

Cholestasis is a pathological condition defined as an impairment of bile flow that causes the accumulation of toxic compounds, which induce liver damage, biliary fibrosis, cirrhosis, and finally end-stage liver disease. Studies performed in rabbits by Moss et al. (1999) showed that intravenous administration of Met (121 mg kg^{-1} d^{-1}) leads to decreased bile flow. The excretion of a bilirubin analog (bromosulfophthalein) tended to be delayed by Met treatment. It was also verified histological liver injury, balloon degeneration, and inflammation characterized by infiltration of the portal triads with eosinophils. Therefore, these results suggest that excessive Met may lead to cholestasis.

In addition, four cases of human neonates positive for hypermethioninemia and two for both hypermethioninemia and hypergalactosemia have been described, which presented severe intrahepatic cholestasis of unknown origin (Ohura et al. 2003). Cholestasis induced by hypermethioninemia may be a consequence of the inflammatory process induced by Met since the cytokines produced under this condition may impair the hepatocellular transport systems that mediate biliary excretion of bile salts and non-bile salt organic anions (Trauner et al. 1999).

ATP depletion

Since Met transmethylation initiates through the ATP-dependent conversion of Met to AdoMet (Finkelstein 1990), ATP depletion from excessive AdoMet formation may induce or augment hepatotoxicity during hypermethioninemia (Hardwick et al. 1970). In accordance with this hypothesis, injections of Met in guinea pigs led to accumulation of AdoMet with concomitant ATP deficiency and nucleolar disaggregation in liver (Shinozuka et al. 1971). Besides, Regina et al. (1993) performed an experiment in which the feeding of toxic levels of Met led to a pronounced accumulation of AdoMet in liver of rats.

Met transamination

Met transamination consists of an alternative pathway for Met metabolism and results in the formation of 2-keto-4-methylthiobutyric acid, which is oxidatively decarboxylated to form 3-methylthiopropionic acid (3-MTP) (Cooper 1989; Scislowski and Pickard 1993; Steele and Benevenga 1978). 3-MTP is then metabolized to highly toxic molecules, including methanethiol, a compound that inhibits enzymes involved in protection against peroxidative damage (Finkelstein and Benevenga 1986).

In this context, Dever and Elfarra (2008) demonstrated that Met is hepatotoxic through an experiment in which freshly isolated male mouse hepatocytes were incubated with different doses of this amino acid, leading to cell disruption and glutathione depletion. The exposure of hepatocytes to 3-MTP resulted in similar effects. Besides, the addition of aminooxyacetic acid, an inhibitor of Met transamination, partially blocked Met-induced cytotoxicity,

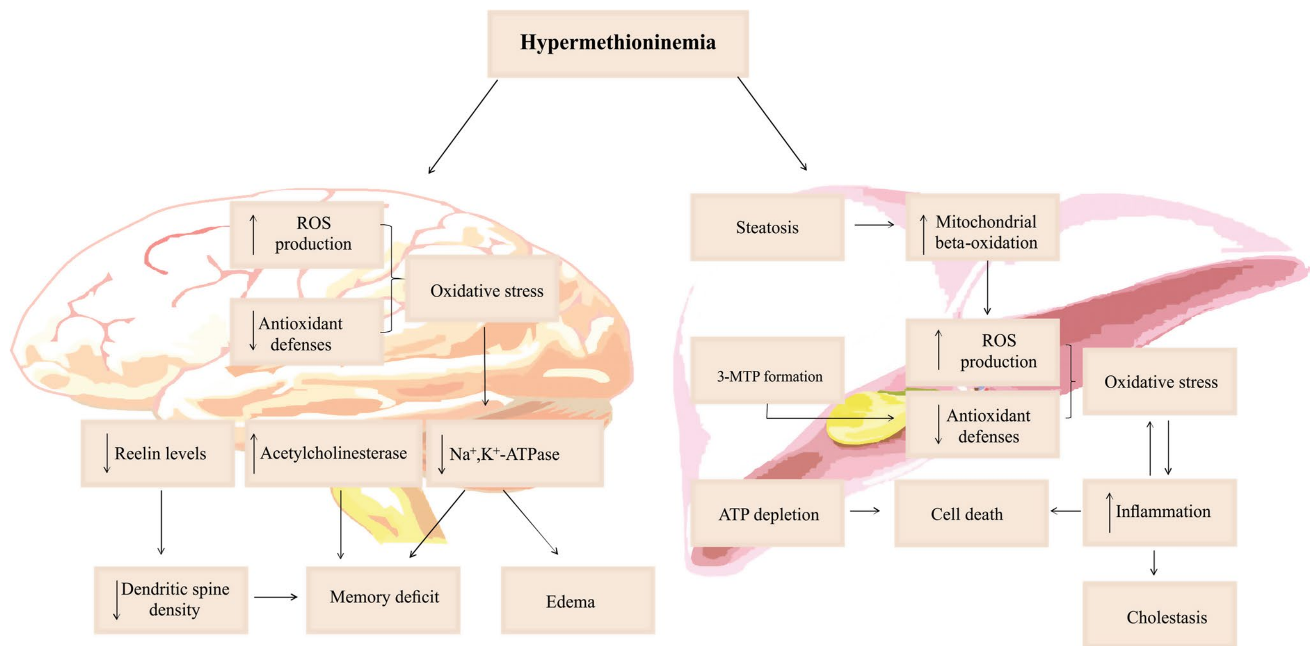

Fig. 2 Schematic representation of Met effects reported in the literature up to now. In brain, hypermethioninemia increases ROS production and decreases antioxidant defenses, leading to oxidative stress, which in turn may reduce Na^+,K^+-ATPase activity. Na^+,K^+-ATPase inhibition is related to cerebral edema and memory deficit. Increased AChE activity and dendritic spine downregulation (induced by decreased Reelin levels) may also impair memory during hypermethioninemia. In liver, hypermethioninemia induces steatosis that increases mitochondrial beta-oxidation, leading to increased ROS production. Hypermethioninemia also induces 3-MTP formation which reduces antioxidant defenses. This imbalance between ROS and antioxidants induces oxidative stress. Inflammation is both consequence and cause of oxidative stress and is able to lead to cholestasis. Inflammation and Met-induced ATP depletion causes cell death

indicating that the toxicity was at least partially mediated by Met transamination.

Final considerations

Based on the information presented above, it is possible to infer that oxidative damage is one of the main mechanisms responsible for toxicity caused by Met, since oxidative stress was induced in brain and liver tissues in different studies that includes in vitro experiments or in vivo animal models by injecting Met, enriching Met in diet and/or knocking MAT1A gene. Besides, oxidative stress seems to mediate, at least partially, other alterations induced by Met, such as the reduction of brain Na^+,K^+-ATPase activity and liver inflammation.

Some Met metabolites, such as Hcy, may induce oxidative stress and alter AChE and Na^+,K^+-ATPase activities in brain and liver, contributing to the toxic effects of Met in some cases (Streck et al. 2002b; Scherer et al. 2011, 2013, 2014; Machado et al. 2011; Matté et al. 2004; 2009a, b). However, this review described different in vitro studies and animal models that induced isolated hypermethioninemia, which caused pathological effects, suggesting that Met per se is able to elicit important hepatic and neurological toxicity.

In conclusion, Met may be extremely toxic to brain by inducing oxidative stress, decreasing Na^+,K^+-ATPase activity and dendritic spine density, as well as increasing AChE activity. In liver, hypermethioninemia seems to induce histological changes, liver lipid accumulation, oxidative stress, inflammation, and ATP depletion. Schematic representations of Met effects in brain and liver are shown in Fig. 2.

Dedication

This review is dedicated to the memory of Dr. S. Harvey Mudd, who developed a superb work on diseases involving disturbances of sulfur amino acid metabolism The studies performed by Dr. Mudd motivated us to develop experimental models of hypermethioninemia and hyperhomocysteinemia in the attempt to better understand the underlying mechanisms involved in the pathophysiology of these conditions We express our gratitude to this eminent scientist for his scientific contribution and for the opportunity to have exchanged ideas about our research.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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