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S-adenosylmethionine and its products

Minireview Article

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Summary. S-adenosylmethionine is involved in many processes, mainly methylation, polyamine synthesis and radical-based catalysis. It is synthesised through the catalysis of differently regulated enzyme forms. When it is used, the compounds formed are reutilized in different ways: in case of methylation, its end product is homocysteine, which can be remethylated to methionine, give rise to cysteine in the so-called transsulphuration pathway, or be released; in the case of polyamine synthesis, the methylthioadenosine formed is cleaved and gives rise to compounds which can be reutilized; during radical-based catalysis, 5-deoxyadenosine is formed and this, too, is cleaved and reutilized.

Keywords: Homocysteine – Methylthioadenosine – 5-Deoxyadenosine

Introduction

S-adenosylmethionine (SAM) is involved in many biochemical processes. The best known is methylation, which occurs on DNA, RNA, proteins, phospholipids, hormones and neurotransmitters, since SAM is the major methyl donor in all living organisms. However, SAM is important also for other processes, such as synthesis of polyamines (cf. Pegg, 1986; Jänne et al., 2004), radical-based catalysis (cf. Grillo and Colombatto, 2007) and synthesis of ethylene in plants (cf. Fontecave et al., 2004).

In this paper, SAM synthesis and regulation are discussed, and the destiny of the co-products of the reactions in which SAM is involved, namely adenosylhomocysteine (SAH) formed during methylation, methylthioadenosine (MTA) formed during polyamine synthesis and 5′-deoxyadenosine formed during radical-based catalysis, is considered.

Synthesis of SAM

SAM is synthesized from ATP and methionine (Met) in two consecutive reactions by methionine adenosyltransferase (MAT), an exceptionally well conserved enzyme through evolution (Mato et al., 1997). The first reaction gives rise to SAM and tripolyphosphate, which is hydrolyzed to orthophosphate and pyrophosphate before their release in the second. MAT also hydrolyzes exogenously added tripolyphosphate. Tripolyphosphatase activity appears to be the rate-determining reaction.

The catalytic mechanism is not known for certain. Different results have been obtained with the *E. coli* enzyme (Komoto et al., 2004) and one enzyme form of rat liver (Gonzalez et al., 2003) and more work is needed to fully understand the mechanism involved.

In mammalian tissues, MAT I, II and III are the product of two genes (*MAT1A* and *MAT2A*). *MAT1A* is expressed mainly in adult liver and encodes a 395 amino acid catalytic subunit (α_1) that organizes in dimers, MAT III, and tetramers, MAT I. *MAT2A* encodes a 396 amino acid catalytic subunit (α_2), expressed in all mammalian tissues and also in the regenerating liver and in fetal hepatocytes. MAT II consists of α_2 catalytic and β regulatory subunits, although the stoichiometry of the oligomer has not yet been established (Sanchez del Pino et al., 2002). According to Sanchez del Pino et al. (2000) there are two isoforms of rat liver MAT III: one with low tripolyphosphatase activity present at low, physiological Met concentration and one with high activity formed at higher concentrations. When the Met concentration increases, such as

after a protein-rich meal, a conformational change is induced and the activity is increased.

MAT I is 10-fold more active than MAT III under physiological (60 μM) MET concentrations (Cabrero et al., 1987) and hence the isoform ratio determines the activity level displayed in the cell.

The enzyme has 10 cysteine residues/subunit (Horikawa et al., 1989) involved in its activity and oligomeric state. Its activity is inhibited by GSSG and nitrosylation of Cys^{121}, which is localized at a ''flexible loop'' over the enzyme's active site cleft and correlates with the GSH/GSSG ratio (Corrales et al., 1991). Mutation of some of these residues of the central domain of the subunit shifts the distribution of the oligomeric forms in the rat liver enzyme (Mingorance et al., 1996).

In liver, SAM has a pivotal role in the regulation of cellular functions, such as control of proliferation, differentiation and apoptosis, and has therefore been proposed as a signaling molecule (Latasa et al., 2001). SAM in this organ must thus be tightly regulated. It has been shown that SAM itself regulates expression of both *MAT1A* and *MAT2A* (Garcia-Trevijano et al., 2000), though the mechanism involved is not known. In the case of *MAT1A*, involvement of a methylation reaction has been suggested. Moreover, regulation of *MAT1A* and *MAT2A* expression is simultaneous, but opposed in the same cell: while expression of *MAT1A* is activated, that of *MAT2A* is inhibited by SAM. Met itself regulates *MAT2A* expression: in the event of reduced Met availability, MAT activity is increased; addition of SAM reduces *MAT2A* gene expression (Martinez-Chantar et al., 2003). This regulation occurs mainly at the level of mRNA turnover. MTA, a product of SAM metabolism in polyamine synthesis, and a precursor of Met in the Met salvage pathway, also modulates *MAT2A* mRNA levels, probably due to its conversion into Met. This effect appears to occur at the post-transcriptional level due to a significant modification in the half-life of the mRNA. During Met starvation, the half-life is increased. The effect is dependent on de novo protein synthesis, suggesting that a protein factor(s) that binds and stabilizes the mRNA for *MAT2A* may be synthesized.

When hepatocytes proliferate during liver regeneration, malignant transformation or the fetal period, transcription of *MAT2A* is activated, resulting in the expression of MAT II. This activation is mediated by the hepatocyte growth factor (HGF); in turn, its action is preceded by hyperacetylation of histones (H4) associated with its promoter. However, SAM blocks the induction of *MAT2A*, whereas that of *MATIA* is not affected (Latasa et al., 2001).

According to Torres et al. (2000a) DNA hypermethylation and histone deacetylation have a role in *MAT1A* silencing, as *MAT1A* is hypomethylated in liver and hypermethylated in non-expressing tissues. The opposite situation is found for *MAT2A*. Moreover, acetylation levels are enhanced in tissues expressing both genes (Torres et al., 2000b). As to the mechanism involved, Li et al. (2004) have recently shown that methylation of the *MAT1A* coding region influences the binding of the TATA binding protein to the TATA box and shuts down gene transcription.

After the observation that *MAT1A* promoter is hypermethylated in human liver cirrhosis (Hoffman, 1984; Torres et al., 2000a), it was shown that mRNA levels of the main genes involved in Met metabolism (i.e. *MAT1A*, glycine methyltransferase, methionine synthase, betaine homocysteine methyltransferase and cystathionine β-synthase) are markedly reduced in human cyrrhosis and hepatocellular carcinoma. This was ascribed to hypermethylation of the *MAT1A* promoter (Avila et al., 2000).

Regulation of SAM content in liver

When SAM is used for the methylation reaction, S-adenosylhomocysteine is formed. The SAM/SAH ratio is considered an indicator of the flow of methyl groups from SAM to methyl acceptors in the cells, and has thus been called ''methylation potential''. For its regulation the presence of glycine N-methyltransferase (GNMT) is important. This is an abundant enzyme in rat liver, particularly in the periportal region, and consists of four identical subunits of 32.5 kDa. All GNMTs known bear an N-terminal acetyl group on the initial valine. The rat liver enzyme is inhibited by 5-methyltetrahydrofolate pentaglutamate (Yeo et al., 1999). The concentrations of this inhibitor and of SAM in vivo are in the range where changes would modulate the activity of the enzyme. In addition phosphorylation of GNMT is a posttranslational mechanism to increase the activity of GNMT and regulate methyl group metabolism (Wagner et al., 1989).

It is therefore believed that the SAM/SAH ratio depends on inhibition by SAM of 5,10-methylene-THF reductase (TMFR) and on inhibition of GNMT by folates. In the presence of excess Met, SAM increases and inhibits the reductase, thereby reducing the supply of methyl groups. In this way, GNMT is more active, and more Met gives rise to sarcosine. GNMT protein is also increased in the liver, less so in the kidney and not in the pancreas (Rowling, 2002). The importance of this mechanism of regulation is confirmed by experiments per-

formed in vivo: a high-Met diet depresses the growth of rats and addition of glycine alleviates Met toxicity (Ogawa et al., 1998).

Participation of GNMT in this regulatory scheme has been confirmed in human beings. Patients with high plasma Met and SAM levels, but normal levels of sarcosine, display GNMT deficiency due to mutations in the gene encoding this enzyme (Luka et al., 2002; Augoustides-Savvopoulou et al., 2003). When the mutated genes were expressed in *E. coli*, the enzyme activity was greatly reduced or almost disappeared (Luka and Wagner, 2003).

In the rat, the reaction is modulated by diabetes (streptozotocin-induced) and by all-*trans* retinoic acid (Nieman et al., 2004).

Sarcosine formed during the reaction has no known physiological role, and is converted back to glycine by sarcosine oxidase. The enzyme is located in peroxisomes (Reuber et al., 1997). In this way glycine is reformed and not consumed.

Destiny of the co-products of the reactions involving SAM

S-adenosylhomocysteine

The tissue level of SAH is controlled in vivo by the activity of S-adenosylhomocysteine hydrolase, which gives rise to adenosine and homocysteine.

S-adenosylhomocysteine hydrolases from all sources are oligomeric proteins with subunits of 45–55 kDa. Each subunit contains 1 mol of tightly bound NAD^+. Rat liver enzyme is a tetramer, formed of four identical subunits of 431 amino acids (Hu et al., 1999). During the reaction, adenosylhomocysteine is first oxidised to a 3′-ketoderivative by the enzyme-bound NAD^+. Next come abstraction of the 4′-proton and elimination of homocysteine. By addition of H_2O and reduction by NADH the final product is obtained. The reaction is reversible, but under normal conditions removal of homocysteine and adenosine maintains the flux in the direction of hydrolysis. This is important not only for the reutilization of Met sulphur, but also since adenosylhomocysteine is an inhibitor of many methyltransferases. A genetic disorder due to deficiency of this enzyme has been demonstrated (Baric et al., 2004).

During hypoxia or after administration of adenosine and homocysteine, adenosylhomocysteine levels increase in the kidney giving rise to decrease of the methylation potential. This leads to a decrease in overall mRNA methylation. However, different mRNA respond differently to changes in this potential.

cAMP competes with adenosine at its inhibitory binding site and stimulates it. S-adenosylhomocysteine hydrolase, therefore, is now considered a cAMP-binding protein (Kloor and Osswald, 2004).

The enzyme has also been studied in several parasites (Plasmodium falciparum, Trypanosoma cruzi, Leishmania donovani, etc.) as it is seen as a potential molecular target for the design of antiparasitic drugs due to its role in the regulation of methylation reactions, including those crucial for parasite replication (Parker et al., 2003; Tanaka et al., 2004). The results obtained up to now may assist in the elaboration of selective inhibitors.

The homocysteine formed in the reaction can be 1) remethylated to reform Met by cobalamine-dependent methionine synthase, using N^5-methylTHF as methyl donor, or betaine homocysteine methyltransferase, using betaine as methyl donor; 2) used to form cystathionine, and therefore cysteine (the so-called transsulfuration pathway); and 3) released into extracellular fluids.

Resynthesis of methionine

Cobalamin-dependent methionine synthase: A cobalamin-dependent methionine synthase is present in animals, whereas fungi and plants have a cobalamin-independent enzyme and bacteria have both. S-methylmethionine methyltransferase is also present in most organisms and may be supposed to enable animals to utilize S-methylmethionine of plant origin.

All these enzymes contain a zinc atom bound to three cysteine residues and a nitrogen, which is essential for binding of homocysteine and for catalysis. During the reaction, there is the methyl group transfer from methyl-THF to homocysteine via a cob(I)-alamin cofactor to form Met, THF and the intermediate methylcob(III)-alamin. Over time, the synthase is rendered inactive owing to the oxidation of cob(I)-alamine to cob(II)-alamine. A methionine synthase reductase restores the enzyme activity through reductive methylation of cob(II)-alamine, using SAM as methyl donor (Matthews, 2001). This reductase thus serves to maintain the activity of the synthase. It is a 78 kDa flavoprotein that contains two flavin-binding domains, termed NADPH/FAD-binding domain and FMN-binding domain, belonging to a family of diflavin reductases such as cytochrome P450 reductase and nitric oxide synthase (Wolthers et al., 2003). The same reductase also catalyzes the reduction of cob(II)alamin to cob(I)alamin needed for the synthesis of adenosylcobalamin by effect of ATP:cob(I)alamin-adenosyltransferase, the final step in the conversion of vitamin B_{12} into adenosylcobalamin (Leal et al., 2004).

Reduction of the activity of the reducing system is defective in a class of patients with homocystinuria (Leclerc et al., 1998).

Betaine-homocysteine S-methyltransferase: Up to 50% of the homocysteine methylation capacity of the liver is provided by betaine-homocysteine S-methyltransferase (BHMT). This is a zinc metalloenzyme, found primarily in the liver and kidney. The zinc is bound to Cys^{217}, Cys^{299} and Cys^{300} and is essential for activity (Breksa and Garrow, 1999). Cys^{214} is also essential for activity and probably provides the flexibility needed by the Zn-binding region (Breksa et al., 2002). The human enzyme is a tetramer, formed by dimerization of dimers of 45 kDa subunits (Szegedi and Garrow, 2004). It showed a positive cooperativity in SAM binding and a weak inhibition by SAH, in contrast with what is usually observed for the methyl transferases. The enzyme crystallized from rat liver (Fu et al., 1996) and other forms from mutant enzymes (Huang et al., 2000) have been used to study the mechanism of the reaction and explain the mechanism involved in its regulation.

According to Ichikawa et al. (2004), BHMT activity is regulated by a cross-linking promoted by tissue transglutaminase.

Betaine prevents ethanol-induced changes in Met metabolism by restoring hepatic SAM levels and preventing the increased release of homocysteine by the liver. It also prevents and reverse ethanol-induced hepatic steatosis (Barak et al., 2003).

According to Forestier et al. (2003) BHMT activity is reduced in cirrhotic rat livers, which may explain the elevated plasma homocysteine levels in cirrhosis.

Synthesis of cysteine: the transsulfuration pathway

Homocysteine can be used to form cysteine in the transsulfuration pathway. This occurs with the involvement of two enzymes, cystathionine β-synthase, which forms cystathionine from homocysteine and serine, and cystathionine γ-lyase, which gives rise to cysteine, α-ketobutyrate and ammonia. Cysteine has several roles, including the synthesis of glutathione. And it has been shown that in liver ~50% of the cysteine used for glutathione synthesis derives from homocysteine (Banerjee and Zou, 2005).

The human cystathionine β-synthase is a homotetramer formed of 551 amino acid subunits (~63 kDa) and has two cofactors, pyridoxal-5′-phosphate and heme, one for each subunit. SAM is an allosteric activator.

The human gene of the enzyme encodes 5 mRNA differing in their 5′ untranslated regions. Two are much more abundant than the others and are found in many tissues (Bao et al., 1998). Loss of gene expression is associated with several human diseases (Ge et al., 2001).

Both the human and the rat enzymes are cleaved by proteolysis to give 48 kDa proteins; these now form dimers, not tetramers, that are more active than the full-length enzymes and not responsive to SAM, which is no longer bound (Kery et al., 1998).

The enzyme is therefore strictly regulated in several ways. When the concentration of Met, the SAM precursor, is high, the enzyme is activated, and the excess sulphur is removed. In some conditions, for instance by effect of TNFα, the truncated form of the enzyme is obtained, resulting in conversion of the tetrameric enzyme to a dimeric form. This leads to activation of the enzyme, although not responsive to SAM, and in the end to an increase of cysteine, and therefore of glutathione synthesis (Banerjee and Zou, 2005). Moreover, the enzyme is a heme-based redox sensor, which can modulate its activity in response to change in the ambient redox potential. During oxidative stress, conversion of methionine to cysteine, the limiting reagent in the synthesis of glutathione, would be enhanced. Under the opposite set of conditions, homocysteine would be directed preferentially to the transmethylation pathway (Banerjee and Zou, 2005).

Release

Several tissues export homocysteine. Of these, liver is supposed to be the one which mostly contributes to the plasma homocysteine level (Stead et al., 2000). According to Noga et al. (2003), phosphatidylethanolamine methyltransferase is a major source of plasma homocysteine. This is relevant, as an increased plasma concentration of this amino acid is a risk factor for the development of vascular diseases.

Methylthioadenosine

MTA formed during polyamine synthesis is cleaved by a phosphorylase (MTAP) to give rise to adenine and to 5-methylthioribose-1-phosphate, which is isomerized by aldose-ketose isomerase to methylthioribulose-1-phosphate; this compound undergoes a set of oxidations to give 2-methylthio-2-oxobutanoic acid, which is finally transaminated to Met. The reaction is thus important in both the purine and the Met salvage pathways.

MTAP was purified from several microrganisms and also from mammalian tissues. The mammalian enzyme

is a trimer, made up of three identical subunits of 32 kDa, each containing 283 amino acid residues; the enzyme of Pyrococcus furiosus is a tetramer of 190 kDa. The crystal structure has been studied by Appleby et al. (2001), Cacciapuoti et al. (2004) and Porcelli et al. (2005) in the hyperthermophile organisms, where a C terminal sequence of eight amino acids is lacking, to determine the functional significance of this peptide. The enzyme is expressed in all normal mammal tissues. However the *MTAP* gene expression is reduced in human hepatocarcinoma tissues and cell lines, and also impaired in the liver of cirrhotic patients (Berasain et al., 2004).

The removal of MTA by MTAP is necessary both for the resynthesis of Met and for polyamine synthesis, since MTA is a strong inhibitor of both spermine synthase and spermidine synthase (Hibasami et al., 1980). Moreover, according to Subhi et al. (2003) MTAP expression causes a significant decrease in intracellular polyamine levels. This appears to be due to 4-methylthio-2-oxobutanoic acid, which represses ODC.

MTA appears to have also many other effects, including regulation of gene expression and cell proliferation, differentiation and apoptosis. However, normal and transformed liver cells display a different response to MTA: while hepatocarcinoma cells undergo apoptosis when treated with MTA, normal hepatocytes do not and are also protected from okadaic acid induced apoptosis (Ansorena et al., 2002). As to the mechanism involved, it has recently been shown that MTA (and also SAM itself) activates serine-threonine phosphatase 1 (PP1), which leads to dephosphorylation of SR proteins (proteins having a carboxy-terminal domain rich in serine/arginine dipeptides, required for assembly of the spliceosome). This is followed by upregulation of Bcl-x_5, which contributes to the proapoptotic effect in HepG2 and in other tumor cells (Yang et al., 2004).

It remains to be elucidated whether physiological concentrations of MTA are sufficient to promote the reported effects. According to Mowen et al. (2001) MTA present in excess in certain cancer cells is sufficient to inhibit arginine methylation of a transcription factor. However, this finding has not been confirmed (Meissner et al., 2004).

5′-Deoxyadenosine

5′-Deoxyadenosine is also cleaved by methylthioadenosine phosphorylase (Fabianowska-Majewska et al., 1994). In this way adenine is recovered.

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