Premium SAMe

A Key Methyl Donor for Detoxification,
Mood and Overall Health

- Boosts mood and emotional well-being
- Relieves symptoms of osteoarthritis
- Provides an effective dosage and a stable form of SAMe
- Promotes methylation

Gluten Free  Vegan  Non-GMO  Time Release  Mood Osteoarthritis

AOR Code  Variant
AOR04071  30 TABLETS
AOR04069  60 TABLETS

Details
S-Adenosyl-L-Methionine (SAMe) is a natural compound and methyl group donor that supports the methylation cycle, a process which is essential for many aspects of health. Methylation is fundamental for ridding the body of certain toxins, and certain people, such as those with chronic liver disorders, cannot produce adequate levels of SAMe.

SAMe’s effectiveness to support a balanced mood is demonstrated by many clinical studies. SAMe is in fact so effective for boosting a low mood that it is legally registered as a prescription drug in several European countries for mood balance. One study showed that SAMe was as effective as a common prescription medication for mood. It is thought that SAMe works by help boosting serotonin, dopamine and melatonin levels in the brain, low levels of which are commonly associated with mood imbalances such as anxiety and depression. SAMe has also been found to support joint health in osteoarthritis patients as effectively as a popular anti-inflammatory drug by reducing inflammation and protecting joint tissue from degradation.

AOR introduced the first SAMe supplement to Canada in 2000. SAMe can provide mood support, benefit those suffering from osteoarthritis, and is essential for those with liver disorders to maintain good health. AOR’s SAMe 400 provides an effective dosage and a stable form of this valuable compound in an enteric coated tablet for maximum effectiveness.
Discussion
SAMe 400 is s-adenosyl-L-methionine (SAMe), a key biological factor that drives a wide variety of essential biochemical reactions, including the methylation of DNA, catecholamine neurotransmitters (brain messenger-molecules), phospholipids, hormones, and chondrocytes (cartilage-forming cells). Research supports SAMe’s ability to support healthy mood function and helps relieve osteoarthritic pain.

Product Variation
Product Code | Size
--- | ---
AOR04071 | 30 TABLETS
AOR04069 | 60 TABLETS

Supplements Facts
Serving Size: 1 Tablet

<table>
<thead>
<tr>
<th>Amount</th>
<th>S-Adenosyl-L-Methioinine (SAMe) Disulfate Tosylate</th>
<th>Ionic SAMe</th>
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<tr>
<td>800 mg</td>
<td></td>
<td>400 mg</td>
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Non-medical ingredients:
microcrystalline cellulose, magnesium stearate, stearic acid, magnesium hydroxide, calcium chloride, silica, calcium oxide, talc, shellac, arginine, glycerol, sodium alginate.

Guarantees
AOR™ guarantees that no ingredients not listed on the label have been added to the product. Contains no gluten, nuts, peanuts, sesame seeds, sulphites, mustard or dairy.

Adult Dosage
Take 2 or 3 tablets daily on an empty stomach, or as directed by a qualified health care practitioner. Use for a minimum of 4 weeks to see beneficial effects for osteoarthritic pain, and a minimum of 2 weeks for mood support.

Cautions
Do not take at night since this product may cause anxiety, restlessness and insomnia. Consult with a health care practitioner prior to use if you are pregnant or breastfeeding, suffer from depression or are taking medications which may influence serotonin levels (e.g. antidepressants).

Source
S-Adenosyl-L-Methioinine (SAMe) Disulfate Tosylate

Main Application
Mood
Disclaimer

The information and product descriptions appearing on this website are for information purposes only, and are not intended to provide or replace medical advice to individuals from a qualified health care professional. Consult with your physician if you have any health concerns, and before initiating any new diet, exercise, supplement, or other lifestyle changes.

Research Background

S-Adenosyl-l-methiononine, or SAMe, is a naturally-occurring physiological agent in the human body that forms an integral part of the methylation cycle. It is formed in the body through the combination of the amino acid methionine and adenosine triphosphate (ATP). This compound was first isolated in Italy in 1952 and is now a prescription drug in much of Europe, most commonly it seems, as an anti-depressant. Safe, energizing, and purported to treat depression twice as fast as standard anti-depressants such as ProzacTM, SAMe has become more popular than the latter in the nation of its discovery, in spite of being more expensive there. SAMe is also heavily studied for its ability to alleviate the conditions of osteoarthritis as well as to treat liver disease.

Biochemical Mechanism of Action for the Methylation Cycle

SAMe, which is found in every living cell, begins with the essential amino acid methionine. Methionine then binds with adenosine triphosphate (ATP) to create SAMe. SAMe’s creation is immediately followed by the donation of its methyl group (comprised of the 4 atoms at the tail end of the original amino acid methionine) to another molecule called a methyl acceptor. After SAMe has imparted its methyl donor it is converted to SAH, or S-Adenosylhomocysteine, which is rapidly broken down to form homocysteine. This is a potentially dangerous situation as homocysteine is essentially metabolic waste which can be toxic. Fortunately, it only exists as an intermediary product to be broken down by the B-complex vitamins, especially B6, B12, and folic acid. B6 breaks homocysteine down to cysteine, which in turn binds with glutamic acid and glycine to form glutathione. Vitamins B12 and folic acid for their parts convert homocysteine back into methionine, thus ending (and re-starting, or “remethylating”) the methylation cycle. Methylation is one of the most common metabolic functions of the body, occurring on the order of a billion times per second. The methylation cycle affects everything from central nervous system activity to cholestasis of pregnancy. As the body ages, the outer lipids of the cells harden, but methylation keeps that layer supple. For this reason, it is theorized that in order to help stymie the process of cellular aging, the body needs a constant and steady supply of methyl donors, of which SAMe is among the most prolific. It must be noted that it is critical to maintain adequate vitamin B supplies as they seem to work synergistically with SAMe for converting homocysteine into its more productive metabolites.

SAMe and Depression

It is as an anti-depressant that SAMe seems to have established itself in the collective mindset of the scientific community. At first glance, this sounds like a scientific stretch when the aforementioned
biochemical functions of SAMe are re-examined. However, as was previously noted, the influence of the methylation cycle is so widespread that it affects factors of the central nervous system that are directly pertinent to depression.

To begin with, methionine requires one carbon groups (primarily from glycine and serine) to begin the methylation cycle. These one-carbon groups rely heavily on the B-complex vitamins, especially folic acid and B-12, for their amalgamation by methionine for the methylation cycle and the subsequent conversion to SAMe. The fact that inadequate concentrations of these vitamins are synonymous with depression have led researchers to theorize that supplemental SAMe enhances the metabolism of the B family of vitamins (especially folic acid), thus explaining the anti-depressant power within SAMe’s range of benefits.

Another possible (and perhaps concurrent) explanation of SAMe’s anti-depressant properties is its effect on monoamine neurotransmitters in the brain, especially serotonin and dopamine. Serotonin is formed from tryptophan and has an important effect on learning, sleep, and the regulation of mood. The latter’s connection to depression is quite palpable, and SAMe is widely known to raise serotonin levels in the brain, providing another possibly accumulative avenue for the speed and effectiveness of its anti-depressant activity. Dopamine is another monoamine neurotransmitter that likely plays an even bigger role in the averting of depression than serotonin. Dopamine is formed in the brain by the decarboxylation of L-dopa, and lower concentrations of dopamine are not only affiliated with the conditions of depression (as are lower concentrations of serotonin) but they are also closely associated with Parkinson’s disease as well. SAMe’s effect on depression may also be linked to the hormone melatonin. Produced by the pineal gland, melatonin is derived from serotonin and plays an important role in sleep and slowing the aging process. Like the neurotransmitters serotonin and dopamine, low levels of melatonin are a frequently consistent observation in people suffering from depression. In the last decade, studies were conducted that have established a corollary link between the biosynthesis of melatonin in the penal gland and the nyctohemeral rhythms of SAMe.

Research

SAMe’s effectiveness as an anti-depressant is demonstrated in a plethora of clinical studies. The depth of many of these trials is also impressive, so much so that not only is SAMe legally registered as a prescription drug in Italy, Germany, Spain and Russia, but even the extremely influential U.S. Department of Health stated that SAMe’s effect on depression was ‘clinically significant’. More notably, it did so without categorizing SAMe as a drug.
SAMe’s anti-depressant activity is aptly demonstrated in many key human trials. One such trial in Italy in 1995 saw 195 patients being given 400 mg of SAMe (parenterally administered) for 15 days. Depressive symptoms remitted after both 7 and 15 days of treatment, and no serious adverse events were reported, testimony to the speed of SAMe’s efficacy. Another study, this one in California a year earlier, directly compared SAMe with a tricyclic antidepressant called desipramine using 26 patients suffering from what was diagnosed as major depression. The two groups underwent treatment for four weeks, and at the conclusion of the study it was found that 62% of the SAMe patients had experienced significant improvement compared to the 50% of the desipramine patients who did so. ‘Significant improvement’ in this case was measured in accordance with the Hamilton Depression Rating Scale (HAM-D), a scientifically standardized method of measuring depression symptoms.

SAMe and Osteoarthritis

By a happy coincidence, many of the patients of the aforementioned SAMe trials for depression also noticed the simultaneous alleviation of their arthritic symptoms. In order to eliminate the possibility of attributing this to any residual placebo effect from the anti-depressant properties of SAMe, 10 studies were conducted specifically on osteoarthritis patients who were not diagnosed with depression. These studies involved a total of 22,000 participants in both Europe and the United States, and the general consensus from this massive collection of data is twofold. The first is that SAMe demonstrated clear efficacy in treating osteoarthritis compared to a placebo. The second is that SAMe possesses therapeutic effects similar to those of the standard non-steroidal anti-inflammatory agents (NSAIDs) used to treat osteoarthritis, but is better tolerated.

The mechanism of action for SAMe’s treatment of osteoarthritis indicates an ability to increase the synthesis and proliferation of proteoglycans. Furthermore, SAMe may effectively protect proteoglycans from decomposition by proteolytic and glycolytic enzymes by promoting the growth of polyamines as a stabilizing factor for the proteoglycans. SAMe may also elicit its benefits on osteoarthritis through an anti-inflammatory capability as well. Evidence pointing to this includes the fact that SAMe can restore the condition of cultured synovial cells after they have been exposed to the damaging effects of pro-inflammatory cytokines.

SAMe and Liver Health

The fundamental metabolism of SAMe itself goes a considerable way in explaining its effectiveness in treating hepatic conditions, including carcinogenic ones. The importance of glutathione as an omnipresent antioxidant cannot be understated, and unsurprisingly hepatic glutathione is one of the chief antioxidants involved in hepatic detoxification. Hepatic glutathione is dependent on methionine and SAMe metabolism for its own biosynthesis, and up to 80% of hepatic methionine is converted into SAMe. Studies have shown that patients with a wide etiology of liver disorders share the common denominator of being unable to metabolize methionine or SAMe effectively. In fact, subsequent studies have revealed that sufferers of chronic liver disorders do not have sufficient concentrations of a liver-specific isoenzyme identified as MAT I/III, which seems to play an essential role in the conversion of methionine to SAMe. Conversely, MAT I/III is vulnerable to high concentrations of nitric oxide and low levels of glutathione. Supplemental SAMe has been shown to increase glutathione concentrations in hepatic tissue as well as in red blood cells in general.
Market Trends

This compound is a prescription drug in much of Europe, most commonly as an anti-depressant. SAMe is safe, energizing, and purported to treat depression twice as fast as standard anti-depressants such as Prozac™. SAMe is also heavily studied for its ability to alleviate the conditions of osteoarthritis as well as to treat liver disease.

AOR Advantage

In the year 2000, AOR introduced the first SAMe supplement to Canada. AOR’s SAMe 400 provides an effective dosage and a stable form of this valuable compound in an enteric coated tablet for maximum effectiveness.

References


Abstract

Role of S-adenosyl-L-methionine in liver health and injury.

Hepatology. 2007 May;45(5):1306-12.

Mato JM, Lu SC.

S-adenosylmethionine (SAMe) has rapidly moved from being a methyl donor to a key metabolite that regulates hepatocyte growth, death, and differentiation. Biosynthesis of SAMe occurs in all mammalian cells as the first step in methionine catabolism in a reaction catalyzed by methionine adenosyltransferase (MAT). Decreased hepatic SAMe biosynthesis is a consequence of all forms of chronic liver injury. In an animal model of chronic liver SAMe deficiency, the liver is predisposed to further injury and develops spontaneous steatohepatitis and hepatocellular carcinoma. However, impaired SAMe metabolism, which occurs in patients with mutations of glycine N-methyltransferase (GNMT), can also lead to liver injury. This suggest that hepatic SAMe level needs to be maintained
within a certain range, and deficiency or excess can both lead to abnormality. SAMe treatment in experimental animal models of liver injury shows hepatoprotective properties. Meta-analyses also show it is effective in patients with cholestatic liver diseases. Recent data show that exogenous SAMe can regulate hepatocyte growth and death, independent of its role as a methyl donor. This raises the question of its mechanism of action when used pharmacologically. Indeed, many of its actions can be recapitulated by methylthioadenosine (MTA), a by-product of SAMe that is not a methyl donor. A better understanding of why liver injury occurs when SAMe homeostasis is perturbed and mechanisms of action of pharmacologic doses of SAMe are essential in defining which patients will benefit from its use.

S-adenosyl methionine protects ob/ob mice from CYP2E1-mediated liver injury.

Dey A, Caro AA, Cederbaum AI.

Pyrazole treatment to induce cytochrome P-450 2E1 (CYP2E1) was recently shown to cause liver injury in ob/ob mice but not in lean mice. The present study investigated the effects of S-adenosyl-l-methionine (SAM) on the CYP2E1-dependent liver injury in ob/ob mice. Pyrazole treatment of ob/ob mice for 2 days caused necrosis, steatosis, and elevated serum transaminase and triglyceride levels compared with saline ob/ob mice. Administration of SAM (50 mg/kg body wt ip every 12 h for 3 days) prevented the observed pathological changes as well as the increase of apoptotic hepatocytes, caspase 3 activity, and serum TNF-alpha levels. SAM administration inhibited CYP2E1 activity but not CYP2E1 content. The pyrazole treatment increased lipid peroxidation, 4-hydroxynonenal and 3-nitrotyrosine protein adducts, and protein carbonyls. These increases in oxidative and nitrosative stress were prevented by SAM. Treatment of ob/ob mice with pyrazole lowered the endogenous SAM levels, and these were elevated after SAM administration. Mitochondrial GSH levels were very low after pyrazole treatment of the ob/ob mice; this was associated with elevated levels of malondialdehyde and 4-hydroxynonenal and 3-nitrotyrosine protein adducts in the mitochondria. All these changes were prevented with SAM administration. SAM protected against pyrazole-induced increase in serum transaminases, necrosis, triglyceride levels, caspase-3 activity, and lipid peroxidation even when administered 1 day after pyrazole treatment. In the absence of pyrazole, SAM lowered the slightly elevated serum transaminases, triglyceride levels, caspase-3 activity, and lipid peroxidation in obese mice. In conclusion, SAM protects against and can also reverse or correct CYP2E1-induced liver damage in ob/ob mice.

S-adenosyl-L-methionine increases skeletal muscle mitochondrial DNA density and whole body insulin sensitivity in OLETF rats.

Jin CJ, Park HK, Cho YM, Pak YK, Lee KU, Kim MS, Friso S, Choi SW, Park KS, Lee HK.

Both mitochondrial dysfunction and alterations in mitochondrial DNA (mtDNA) are implicated in type 2 diabetes mellitus and insulin resistance. Evidence also suggests that metabolism of S-adenosyl-L-
methionine (SAM), the universal methyl donor for biological methylation, is associated with mitochondrial dysfunction and insulin resistance. We investigated the effect of SAM on mtDNA density and insulin sensitivity using the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, an animal model of type 2 diabetes mellitus and insulin resistance. To determine the short-term effect on mtDNA density, SAM (15 mg.kg⁻¹.d⁻¹) was administered intraperitoneally for 7 d to 6 male, 57-wk-old OLETF rats and 6 Long-Evans Tokushima Otsuka (LETO) rats of the same age as a nondiabetic control. To determine the long-term effect, the same dose of SAM was administered daily to 5 male, 6-wk-old OLETF rats until the age of 25 wk; 7 control OLETF rats received vehicle and 7 LETO rats were untreated. Skeletal muscle mtDNA density was measured by either competitive or multiplex PCR and insulin sensitivity was measured by hyperinsulinemic-euglycemic clamp. SAM treatment for 1 wk increased skeletal muscle mtDNA density of both OLETF and LETO rats. The long-term SAM treatment significantly reduced body weight gain as well as increased skeletal muscle mtDNA density and whole body insulin sensitivity in OLETF rats compared with their vehicle-treated controls. Furthermore, in all 3 groups, skeletal muscle mtDNA density correlated with insulin sensitivity (r=0.752, P

S-Adenosyl-L-methionine: beyond the universal methyl group donor.


Roje S.

S-Adenosyl-l-methionine (AdoMet or SAM) is a substrate in numerous enzyme-catalyzed reactions. It not only provides methyl groups in many biological methylations, but also acts as the precursor in the biosynthesis of the polyamines spermidine and spermine, of the metal ion chelating compounds nicotianamine and phytosiderophores, and of the gaseous plant hormone ethylene. AdoMet is also the source of catalytic 5?-deoxyadenosyl radicals, produced as reaction intermediates by the superfamily of radical AdoMet enzymes.

S-adenosyl-L-methionine attenuates hepatotoxicity induced by agonistic Jo2 Fas antibody following CYP2E1 induction in mice.


Wang X, Cederbaum Al.

S-Adenosyl-l-methionine (SAM) has been shown to be hepatoprotective against many toxic agents. Its possible effectiveness in protecting against CYP2E1-dependent toxicity is not known. We recently reported that treatment of mice with pyrazole to induce CYP2E1 increased hepatotoxicity produced by Fas agonistic Jo2 antibody. The current study was designed to investigate the effect of exogenous administration of SAM on the synergistic hepatotoxicity produced by Fas agonistic Jo2 antibody plus CYP2E1 following pyrazole pretreatment in C57BL/6 mice. Suboptimal administration of Jo2 Fas antibody combined with pyrazole pretreatment caused severe hepatotoxicity as determined by elevations in serum transaminase levels and histopathology. Exogenous administration of SAM (50 mg i.p./kg body weight every 12 h for 3 days) significantly decreased serum transaminases and
ameliorated morphological changes of the liver. Addition of SAM elevated hepatic SAM and total reduced glutathione levels and inhibited CYP2E1 activity. SAM also lowered the elevated oxidative stress (lipid peroxidation, protein carbonyls, and superoxide production) and nitrosative stress (induction of inducible nitric-oxide synthase and 3-nitrotyrosine adducts) and increases in caspase-8 and -3 activation produced by the pyrazole plus Jo2 treatment. SAM did not prevent the increase in serum TNF-alpha levels or the decrease in catalase activity in this model. These results indicate that SAM can have an important hepatoprotective role as an effective reagent against Fas plus CYP2E1-induced hepatotoxicity by lowering oxidative and nitrosative stress.

Methionine adenosyltransferase and S-adenosylmethionine in alcoholic liver disease.


Lu SC, Martinez-Chantar ML, Mato JM.

Methionine adenosyltransferase (MAT) is an essential enzyme that catalyzes the formation of the principal methyl donor S-adenosylmethionine (SAMe). Studies in the past decade have shown that SAMe is not only a methyl donor, but also a key metabolite that regulates hepatocyte growth, death and differentiation. Abnormalities in MAT and decreased SAMe levels occur in experimental animals and humans with alcoholic liver disease. Chronic hepatic SAMe deficiency can result in the spontaneous development of steatohepatitis and hepatocellular carcinoma. This paper reviews MAT genes and SAMe in relation to alcoholic liver disease and the molecular mechanisms by which SAMe regulates hepatocyte growth and apoptosis.

Role of methionine adenosyltransferase and S-adenosylmethionine in alcohol-associated liver cancer.

Alcohol. 2005 Apr;35(3):227-34.

Lu SC, Mato JM.

Two genes (MAT1A and MAT2A) encode for the essential enzyme methionine adenosyltransferase (MAT), which catalyzes the biosynthesis of S-adenosylmethionine (SAMe), the principal methyl donor and, in the liver, a precursor of glutathione. MAT1A is expressed mostly in the liver, whereas MAT2A is widely distributed. MAT2A is induced in the liver during periods of rapid growth and dedifferentiation. In human hepatocellular carcinoma (HCC) MAT1A is replaced by MAT2A. This is important pathogenetically because MAT2A expression is associated with lower SAMe levels and faster growth, whereas exogenous SAMe treatment inhibits growth. Rats fed ethanol intragastrically for 9 weeks also exhibit a relative switch in hepatic MAT expression, decreased SAMe levels, hypomethylation of c-myc, increased c-myc expression, and increased DNA strand break accumulation. Patients with alcoholic liver disease have decreased hepatic MAT activity owing to both decreased MAT1A expression and inactivation of the MAT1A-encoded isoenzymes, culminating in decreased SAMe biosynthesis. Consequences of chronic hepatic SAMe depletion have been examined in the MAT1A knockout mouse model. In this model, the liver is more susceptible to injury. In addition, spontaneous steatohepatitis develops by 8 months, and HCC develops by 18 months.
Accumulating evidence shows that, in addition to being a methyl donor, SAMe controls hepatocyte growth response and death response. Whereas transient SAMe depletion is necessary for the liver to regenerate, chronic hepatic SAMe depletion may lead to malignant transformation. It is interesting that SAMe is antiapoptotic in normal hepatocytes, but proapoptotic in liver cancer cells. This should make SAMe an attractive agent for both chemoprevention and treatment of HCC.

S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease.


Objectives. We conducted a comprehensive literature review and synthesis of evidence on the use of S-adenosyl-L-methionine (SAMe) for the treatment of depression, osteoarthritis, and liver disease.

Search Strategy. We searched 25 databases using the MesH term SAMe and its many pharmacological synonyms. Additional articles were identified from bibliographies and by experts.

Selection Criteria. The synthesis of SAMe focused on clinical trials of human subjects. Approximately 25 percent of the selected reports were in non-english languages, mainly Italian.

Data Collection and Analysis. Selected titles, abstracts, and articles were reviewed. Patient demographics, disease state, intervention, study design, and outcomes were collected. Meta-analyses were performed where appropriate.

Main Results

Compared to placebo, treatment with SAMe was associated with an improvement of approximately 6 points in the score of the Hamilton Rating Scale for Depression. (This degree of improvement is clinically significant and is equivalent to a partial response to treatment.)

Compared to treatment with conventional therapy, SAMe was not associated with a statistically significant difference in outcomes.

Compared to placebo for osteoarthritis, one large randomized clinical trial showed a small to moderate effect in favor of SAMe.

Compared to nonsteroidal anti-inflammatory agents, treatment with SAMe was not associated with a statistically significant difference in outcomes.

Compared to placebo, treatment with SAMe for cholestasis of pregnancy was associated with a large effect in decreasing pruritus and in decreasing bilirubin levels.

In two clinical trials for cholestasis of pregnancy, conventional therapy (ursodeoxycholic acid) was favored over SAMe for the treatment of pruritus.

Compared to placebo for intrahepatic cholestasis, treatment with SAMe for pruritus was associated
with a risk ratio of 0.45, meaning that patients treated with SAMe were twice as likely as placebo-treated patients to have a reduction in pruritus (95% CI [0.37, 0.58]).

Too few studies compared SAMe to active therapy for intrahepatic cholestasis to conduct a pooled analysis.

Twenty remaining studies were too heterogeneous with respect to diagnosis (a wide variety of liver conditions) and outcomes to permit pooled analysis.

Conclusions. These data indicate that SAMe is more effective than placebo for relief of symptoms of depression, pain of osteoarthritis, and pruritus in cholestasis of pregnancy, and in intrahepatic cholestasis. SAMe is more effective than placebo in reducing bilirubin for cholestasis of pregnancy and serum bilirubin for intrahepatic cholestasis. Treatment with SAMe was equivalent to standard therapy for depression and osteoarthritis but not for liver disease.

These results justify additional randomized controlled trials to evaluate the efficacy and tolerability of SAMe for treatment of depression, osteoarthritis, and cholestasis (related to pregnancy and associated with other liver diseases).

Role of abnormal methionine metabolism in alcoholic liver injury.


Lu SC, Tsukamoto H, Mato JM.
Methionine catabolism occurs mostly in the liver through the formation of S-adenosylmethionine (SAM) in a reaction catalyzed by methionine adenosyltransferase (MAT). S-adenosylmethionine is the principal biologic methyl donor, a precursor for polyamines, and in liver, it is also a precursor for reduced glutathione (GSH). Liver-specific and non-liver-specific MAT are products of two different genes, MAT1A and MAT2A, respectively. Mature liver expresses MAT1A, whereas MAT2A is expressed in extrahepatic tissues and induced during liver growth and de-differentiation. The type of MAT expressed by the cell affects the steady-state SAM level, DNA methylation, and growth rate. This has been demonstrated further by using the MAT1A knockout mouse model in which hepatic SAM and GSH levels decrease, the liver becomes larger and more susceptible to injury, and steatohepatitis develops spontaneously. Altered methionine metabolism in alcoholic liver disease results in decreased transmethylation and transsulfuration, changes that may play important pathogenic roles. Major changes include a relative switch in MAT expression; decreased hepatic SAM, GSH, and DNA methylation levels; decreased homocysteine metabolism; and hyperhomocysteinemia. Consequences of hepatic DNA hypomethylation include increased expression of c-myc and DNA strand break accumulation. One possible consequence of hyperhomocysteinemia is increased fibrogenesis. Abnormal methionine metabolism may also occur in Kupffer cells, which express both forms of MAT. If SAM levels also decrease in these cells, this may contribute to the induction of tumor necrosis factor (TNF) expression and release. In summary, altered hepatic methionine metabolism can have serious consequences that affect not only hepatocytes, but also hepatic stellate and Kupffer cells. These changes can lead to impaired antioxidant defense, altered gene expression, promotion of fibrogenesis, and even hepatocarcinogenesis.

S-Adenosylmethionine: a control switch that regulates liver function.


Mato JM, Corrales FJ, Lu SC, Avila MA.

Genome sequence analysis reveals that all organisms synthesize S-adenosylmethionine (AdoMet) and that a large fraction of all genes is AdoMet-dependent methyltransferases. AdoMet-dependent methylation has been shown to be central to many biological processes. Up to 85% of all methylation reactions and as much as 48% of methionine metabolism occur in the liver, which indicates the crucial importance of this organ in the regulation of blood methionine. Of the two mammalian genes (MAT1A, MAT2A) that encode methionine adenosyltransferase (MAT, the enzyme that makes AdoMet), MAT1A is specifically expressed in adult liver. It now appears that growth factors, cytokines, and hormones regulate liver MAT mRNA levels and enzyme activity and that AdoMet should not be viewed only as an intermediate metabolite in methionine catabolism, but also as an intracellular control switch that regulates essential hepatic functions such as regeneration, differentiation, and the sensitivity of this organ to injury. The aim of this review is to integrate these recent findings linking AdoMet with liver growth, differentiation, and injury into a comprehensive model. With the availability of AdoMet as a nutritional supplement and evidence of its beneficial role in various liver diseases, this review offers insight into its mechanism of action.