SAMe – Multiple applications for the methyl donor

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In the brain...

It has been well established that s-adenosylmethionine (SAMe), the active form of methionine is the most important methyl donor in the body. It has also been established that SAMe is a safe and effective supplement option for patients suffering from neurological disorders such as depression and even alzheimer's disease. As a methyl donor, it may contribute to the repletion/ re-balancing of the methylation reactions involved in metabolism of neurotransmitters.

Evidence

"A small number of clinical trials with parenteral or oral SAMe have shown that, at doses of 200-1600 mg/d, SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses. SAMe may have a faster onset of action than do conventional antidepressants and may potentiate the effect of tricyclic antidepressants. SAMe may also protect against the deleterious effects of Alzheimer's disease. SAMe is well tolerated and relatively free of adverse effects, although some cases of mania have been reported in bipolar patients. Overall, SAMe appears to be safe and effective in the treatment of depression, but more research is needed to determine optimal doses. Head-to-head comparisons with newer antidepressants should help to clarify SAMe's place in the psychopharmacologic armamentarium."[1]

"Cerebrospinal fluid (CSF) S-adenosylmethionine (SAM) levels were significantly lower in severely depressed patients than in a neurological control group. The administration of SAM either intravenously or orally is associated with a significant rise of CSF SAM, indicating that it crosses the blood-brain barrier in humans. These observations provide a rational basis for the antidepressant effect of SAM, which has been confirmed in several countries. CSF SAM levels were low in a group of patients with Alzheimer's dementia suggesting a possible disturbance of methylation in such patients and the need for trials of SAM treatment."[2]
"SAM is well tolerated and may be a safe and effective alternative to the antidepressant agents currently used in patients with Parkinson's disease."[3]

In the liver…

Deficiency of the amino acid methionine has been implicated in the pathogenesis of alcohol-induced liver injury, including cirrhosis. However, methionine supplementation did not always prove effective, indeed excess methionine has been shown to have some adverse effects.[4]

Decreased activity of s-adenosylmethionine synthetase (the enzyme that catalyses the conversion of methionine to s-adenosylmethionine) has been reported in cirrhotic liver. Long term ethanol consumption is associated with a significant depletion of hepatic SAMe, and SAMe supplementation may attenuate ethanol induced liver injury.[5]
This reduction of SAMe may result in part from increased utilisation of hepatic glutathione secondary to enhanced free radical production (as SAMe is involved in providing the precursor cysteine for glutathione production). SAMe supplementation may help to replenish glutathione levels as well as correcting SAMe deficiency.
SAMe may also enhance bile salt conjugation with taurine in patients with liver cirrhosis.

Evidence

"Mitochondrial glutathione plays an important role in maintaining a functionally competent organelle. Previous studies have shown that ethanol feeding selectively depletes the mitochondrial glutathione pool, more

predominantly in mitochondria from perivenous hepatocytes. Because S-adenosyl-L-methionine (SAM) is a glutathione precursor and maintains the structure and function of biological membranes, the purpose of the present study was to determine the effects of SAM on glutathione and function of perivenous (PV) and periportal (PP) mitochondria from chronic ethanol-fed rats. SAM administration resulted in a significant increase in the basal cytosol and mitochondrial glutathione in both PP and PV cells from both pair-fed or ethanol-fed groups. When hepatocytes from ethanol-fed rats supplemented with SAM were incubated with methionine plus serine or N-acetylcysteine, mitochondrial glutathione increased in parallel with cytosol, an effect not observed in cells from ethanol-fed rats without SAM. Feeding equimolar N-acetylcysteine raised cytosol glutathione but did not prevent the mitochondrial glutathione defect. In addition, SAM feeding resulted in significant preservation of cellular adenosine triphosphate (ATP) levels (23% to 43%), mitochondrial membrane potential (17% to 25%), and the uncoupler control ratio (UCR) of respiration (from 5.1 +/- 0.7 to 7.3 +/- 0.6 and 2.1 +/- 0.3 to 6.1 +/- 0.7) for PP and PV mitochondria, respectively. Thus, these effects of SAM suggest that it may be a useful agent to preserve the disturbed mitochondrial integrity in liver disease caused by alcoholism through maintenance of mitochondrial glutathione transport."[6]

"Because of the primary defect in the transport of cytosolic GSH into mitochondria, GSH precursors are inefficient in replenishing the levels of mitochondrial GSH despite significant increase in cytosolic GSH. Supplementation of S-adenosyl-L-methionine (SAM) to rats fed alcohol chronically has been shown to replete the mitochondrial GSH levels because of normalization of the microviscosity of the mitochondrial inner membrane. Because of the instrumental role of GSH in mitochondria in hepatocyte survival against inflammatory cytokines, its repletion by SAM feeding may underlie the potential therapeutic use of this hepatoprotective agent in the treatment of alcohol-induced liver injury."[7]

For Cell Membranes…

SAMe is an important factor in the maintenance of cell membrane function, including membrane fluidity and cell communication. SAMe is required for phospholipid methylation, which governs membrane fluidity and therefore the transport of metabolites and transmission of signals across the membranes. Depletion of SAMe may therefore promote membrane injury such as that associated with alcoholic liver disease.[8]

Evidence

"In liver, phosphatidylethanolamine is converted to phosphatidylcholine through a series of three sequential methylation reactions. Phosphatidylethanolamine N-methyltransferase (PEMT) catalyzes each transmethylation reaction, and S-adenosylmethionine is the methyl group donor."[9]

"We studied the effect of cyclosporin A (CyA) on liver plasma membrane (LPM) composition, fluidity, and functions and on hepatic glutathione (GS) and oxidative status. We also evaluated the ability of S-adenosylmethionine (SAMe) to antagonize the CyA-induced disturbances in rats…….SAMe cotreatment significantly improved or abolished the CyA-induced changes in liver plasma membrane fluidity and composition and the changes in the activity of the carrier and enzymes tested…" [10]

"Increase in brain muscarinic receptor density after SAM treatment might be ascribed to the ability of this methyl donor to increase the fluidity of cell membranes by stimulating phospholipid synthesis."[11]

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