S-Adenosyl-l-methionine: its role in the treatment of liver disorders

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ABSTRACT

S-Adenosyl-l-methionine (SAMe) exerts many key functions in the liver, including serving as a precursor for cysteine, 1 of 3 amino acids of glutathione—the major physiologic defense mechanism against oxidative stress. SAMe is particularly important in opposing the toxicity of free oxygen radicals generated by various pathogens, including alcohol, which cause oxidative stress largely by the induction of cytochrome P4502E1 (CYP2E1) and by its metabolite acetaldehyde. SAMe also acts as the main methylating agent in the liver. The precursor of SAMe is methionine, one of the essential amino acids, which is activated by SAMe-synthetase (EC 2.5.1.6). Unfortunately, the activity of this enzyme is significantly decreased as a consequence of liver disease. Because of decreased utilization, methionine accumulates and, simultaneously, there is a decrease in SAMe that acquires the status of an essential nutrient and therefore must be provided exogenously as a supernutrient to compensate for its deficiency. Administration of this innocuous supernutrient results in many beneficial effects in various tissues, mainly in the liver, and especially in the mitochondria. This was shown in alcohol-fed baboons and in other experimental models of liver injury and in clinical trials, some of which are reviewed in other articles in this issue. Am J Clin Nutr 2002;76(suppl):1183S–7S.

KEY WORDS S-Adenosyl-l-methionine, SAMe, alcoholic liver injury, baboons, cholestasis, fibrosis, mitochondria, oxidative stress, liver disorders

INTRODUCTION

Much progress has been made in our understanding of the role of nutritional factors in the pathogenesis of liver disease and its treatment. The basic concept has been that some nutrients are essential because they cannot be synthesized endogenously in the mammalian body and therefore must be provided exogenously in the diet. A classic example is that of the amino acids, 9 of which are essential and therefore are mandatory constituents of any diet. An important one is that of methionine. Its requirements have been established and its key role in a score of vital functions has been well chartered, as reviewed in the introduction to this symposium (1) and elsewhere (2). In addition, to this traditional concept, a new approach has emerged that has changed the use of some of the essential nutrients in pathologic conditions. Indeed, many of these nutrients, including methionine, must first be activated in the liver or in other tissues before they can exert their key functions. This activating process, however, is altered by liver disease and, as a consequence, nutritional requirements change. For instance, methionine has to be converted to S-adenosyl-l-methionine (SAMe) before it can act as the main cellular methyl donor (Figure 1). This function of SAMe is important for the metabolism of nucleic acids and for the structure and function of membranes and many other cellular constituents. These are often disturbed in various liver diseases but cannot be restored by the simple administration of methionine. Indeed, experimentally, it has been shown that even a 7-fold increase in the normal dietary methionine content failed to significantly alter hepatic SAMe (3). This is exacerbated when there is significant liver disease, which is commonly associated with impairment of the enzyme activating methionine to SAMe (4). Therefore, supplementation with methionine is useless in most such circumstances and may even result in toxicity because of its accumulation as a result of nonutilization. Indeed, elevated concentrations of circulating methionine in patients with liver disease have been reported (5–7), and excess methionine was shown to have toxic effects (3), including a decrease in hepatic ATP (8). Accordingly, one must bypass the enzyme deficiency due to liver disease and provide the product of the defective reaction, namely SAMe, which becomes crucial for the functioning of the cell under these pathologic conditions. Thus, SAMe then becomes the essential nutrient instead of methionine. It is a typical example of a “conditional essential amino acid” (9) and what is now also called a supernutrient, namely an activated nutrient that must be provided to meet the normal cellular requirements when its endogenous synthesis from a nutritional precursor becomes insufficient because of an impairment in the activation process secondary to a pathologic state. Because the essential supernutrient SAMe is key to many basic cellular functions, it is not surprising that its lack is associated with many pathologic manifestations of liver diseases and that these can be corrected by simply providing the missing supernutrient (10).

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ALKALINE PHOSPHATASE (EC 3.1.3.1), and the biochemical indexes of cholestasis, such as serum bilirubin, either orally or parenterally, SAMe improves both the pruritus and many of the cholestatic states, as reviewed elsewhere (13). Given a pathologic state called cholestasis. SAMe opposes successfully formation, a key aspect of many diseases of the liver, resulting in consequences of the failure of these functions is insufficiency of bile formation, which traps the excess of free radicals (Figure 1). Glutathione is a tripeptide, the rate-limiting amino acid being cysteine (12), and SAMe plays a fundamental role in the formation of cysteine.

**METHIONINE**

S-adenosylmethionine, vitamin B-6 (d), or vitamin B-12 (c), vitamin B-12 (c), or vitamin B-6 (d) depletions result in corresponding depletions in S-adenosyl-L-methionine, phosphatidylcholine, and glutathione (GSH). New therapeutic approaches include the down-regulation of microsomal enzyme induction, 1, especially of CYP2E1; the trapping of free radicals with antioxidants, 2; the replenishment of S-adenosyl-L-methionine, 3; and the replenishment of phosphatidylcholine, 4. ADH, alcohol dehydrogenase (EC 1.1.1.1). Reprinted with permission from reference 2.

**FIGURE 1.** Lipid peroxidation and other adverse effects resulting from alcoholic liver disease and from free radical generation and acetaldehyde production by ethanol-induced microsomes and associated cytochrome P4502E1 (CYP2E1) up-regulation. Metabolic blocks caused by liver disease (a and b) or folate (c), vitamin B-12 (c), or vitamin B-6 (d) deficiencies result in corresponding depletions in S-adenosyl-L-methionine, phosphatidylcholine, and glutathione (GSH). New therapeutic approaches include the down-regulation of microsomal enzyme induction, 1, especially of CYP2E1; the trapping of free radicals with antioxidants, 2; the replenishment of S-adenosyl-L-methionine, 3; and the replenishment of phosphatidylcholine, 4. ADH, alcohol dehydrogenase (EC 1.1.1.1). Reprinted with permission from reference 2.

**BENEFICIAL EFFECTS OF SAMe ON BASIC MANIFESTATIONS OF LIVER DISEASE**

**Role of SAMe on oxidative stress**

As reviewed elsewhere (11), oxidative stress was shown to play a major pathogenic role in multiple disease states ranging from the hepatotoxicity of alcohol (and other xenobiotics) to the carcinogenicity of many compounds. The major natural defense mechanism against oxidative stress is reduced glutathione, which traps the excess of free radicals (Figure 1). Glutathione is a tripeptide, the rate-limiting amino acid being cysteine (12), and SAMe plays a fundamental role in the formation of cysteine.

**Role of SAMe in transmethylation and transsulfuration reactions**

Another basic cellular activity of SAMe is its role as a methyl donor and enzyme activator in the transmethylation and transsulfuration reactions key to membrane structure and function. For example, SAMe is essential for the transport processes and signal transmission across membranes. One of the important consequences of the failure of these functions is insufficiency of bile formation, a key aspect of many diseases of the liver, resulting in a pathologic state called cholestasis. SAMe opposes successfully many of the cholestatic states, as reviewed elsewhere (13). Given either orally or parenterally, SAMe improves both the pruritus and the biochemical indexes of cholestasis, such as serum bilirubin, alkaline phosphatase (EC 3.1.3.1), and γ-glutamyltransferase (EC 2.3.2.2). It is noteworthy that in a prospective, multicenter, double-blind, placebo-controlled trial performed in 220 inpatients with chronic liver disease (chronic active hepatitis and cirrhosis, including primary biliary cirrhosis), serum markers of cholestasis and subjective symptoms (eg, pruritus and fatigue) significantly improved after SAMe treatment (14). Cholestasis is not only an important manifestation of various liver disorders, but it also may complicate physiologic states such as pregnancy. SAMe was shown to be a useful therapy for cholestasis during pregnancy (15) and for cholestasis that is sometimes associated with parenteral nutrition (16).

**Role of SAMe in opposing fibrosis**

The leading cause of morbidity and mortality in all major liver diseases is an inappropriately excessive healing process with uncontrolled scarring or fibrosis culminating in cirrhosis. Indeed, fibrosis can be viewed as an initially beneficial scarring process that has escaped control and results ultimately in cirrhosis. SAMe was shown to be therapeutically useful in alleviating this process experimentally (17) and for improving the outcome clinically (18).

The most common liver disease for which SAMe has been shown to be useful therapeutically is alcoholic liver injury, which encompasses all the pathologic manifestations discussed above, namely a deficiency in the activation of methionine to SAMe, in the pathogenic role of oxidative stress and glutathione deficiency, in complications of cholestasis, and in the devastating consequences of excessive liver fibrosis (leading to cirrhosis).

**SAKe AND THE PATHOGENESIS OF ALCOHOLIC LIVER INJURY**

Alcohol causes liver disease through a variety of pathogenic mechanisms that were reviewed in detail elsewhere (19–21). The major mechanisms include interactions with nutrition and toxic manifestations through generation of oxidative stress and production of the toxic metabolite acetaldehyde.

**Interactions of alcohol with nutrition**

In addition to its pharmacologic action, alcohol (ethanol) has a considerable energy content (7.1 kcal/g). Thus, its consumption may cause primary malnutrition by displacing other nutrients in the diet because of the high energy content of the alcoholic beverages or because of associated socioeconomic and medical disorders. Secondary malnutrition may result from either maldigestion or malabsorption of nutrients caused by gastrointestinal complications associated with alcoholism. Alcohol also promotes nutrient degradation or impaired activation (see below). Whereas it continues to be important to replenish nutritional deficiencies, it is crucial to recognize that, because of the alcohol-induced disease process, some nutritional requirements change.

**Methionine and its utilization in liver diseases**

In rats, alcohol consumption is associated with impaired methionine conservation. Consequently, methionine supplementation has been proposed for the treatment of liver diseases, especially the alcoholic variety, but some difficulties have been encountered, which are reviewed in detail elsewhere (22). Indeed, fatty liver and cirrhosis were not prevented in baboons given liberal amounts of methionine and other lipotropes (23, 24), and excess methionine was shown in various studies to have some adverse effects (see above). Whereas in some patients with alcoholic
liver disease, circulating methionine concentrations may be normal or even low (25), elevated concentrations have been reported in others (see above). Furthermore, there was a delay in the clearance of plasma methionine after its systemic administration to patients with liver damage (26). Similarly, the blood clearance of methionine after an oral load of this amino acid was slowed (27). Because about one-half of methionine is metabolized by the liver, the above observations suggest the impaired hepatic metabolism of this amino acid. Indeed, Duce et al (4) reported a decrease in SAMe-synthetase activity in cirrhotic livers. As a consequence, methionine supplementation may be ineffective in alcoholic liver disease and SAMe depletion ensues, as was verified in nonhuman primates after long-term ethanol consumption (28). Additional factors that contribute to the decrease in hepatic SAMe are increased glutathione utilization secondary to enhanced free radical and acetaldehyde generation by the induced microsomal ethanol-oxidizing system (see below).

Microsomal ethanol-oxidizing system and SAMe
The microsomal ethanol-oxidizing system has been the subject of extensive research, and is reviewed in detail elsewhere (29, 30). With the use of Western blot technique with specific antibodies against cytochrome P4502E1 (CYP2E1), a 4-fold induction of CYP2E1 was found in liver biopsy samples from recently drinking subjects (31). CYP2E1 activates some xenobiotics (such as acetaminophen) to toxic metabolites (29). It also generates several species of active oxygen (Figures 2 and 3). Glutathione provides one of the cell’s fundamental mechanisms for the scavenging of toxic free radicals (Figure 1), but the generation of active oxygen species by CYP2E1 may overwhelm this antioxidant system with pathogenic consequences requiring new therapeutic approaches (32). Furthermore, acute ethanol administration also inhibits glutathione synthesis and produces an increased loss from the liver (33). Indeed, rats fed ethanol chronically have significantly increased rates of glutathione turnover (34). Such an increased glutathione turnover was also shown indirectly by an increase in α-amino-N-butyrate (Figure 1), which has been shown in both nonhuman primates and in humans (35). A depletion in the steady state concentrations of hepatocellular glutathione, in synergy with other conditions, leads to hepatocellular necrosis and liver injury (36). Glutathione is selectively depleted in the mitochondria (37) and may contribute to the striking alcohol-induced
alterations of that organelle. In addition, \( \alpha \)-tocopherol, the major antioxidant in the membranes, is depleted in patients with cirrhosis (38). This deficiency in the defense systems, coupled with increased oxygen and other free radical generation (by the ethanol-induced microsomes; see above) and with acetaldehyde production (see below), may contribute to liver damage not only via lipid peroxidation but also by enzyme inactivation (39). Replenishment of glutathione can be achieved in acute situations (such as acetaminophen poisoning) by administration of precursors of cysteine (one of the amino acids of glutathione), such as acetylcysteine, or in chronic conditions by SAMe (10, 28). Beneficial effects of SAMe on glutathione were also observed in humans (40, 41). Moreover, experimentally, the ethanol-induced increase in fluidity of mitochondrial membranes was prevented by SAMe but not by \( N \)-acetylcysteine supplementation (42).

**Toxicity of acetaldehyde**

Acetaldehyde, the product of all pathways of ethanol oxidation, is highly toxic (18) and is rapidly metabolized to acetate, mainly by a mitochondrial aldehyde dehydrogenase, the activity of which is significantly reduced by chronic ethanol consumption (43). The decreased capacity of mitochondria in alcohol-fed subjects to oxidize acetaldehyde, associated with unaltered or even enhanced rates of ethanol oxidation (and therefore acetaldehyde generation because of the induction of the microsomal ethanol-oxidizing system; see above), results in an imbalance between the production and disposition of acetaldehyde. The latter causes the elevated acetaldehyde concentrations observed after chronic ethanol consumption in baboons (44) and humans (45).

Acetaldehyde’s toxicity is due, in part, to its capacity to form protein adducts, which results in antibody production, enzyme inactivation, and decreased DNA repair (19). Moreover, acetaldehyde promotes lipid peroxidation (Figure 1); one mechanism that promotes lipid peroxidation is glutathione depletion. The binding of acetaldehyde with cysteine, glutathione, or both (Figure 1) may contribute to a decrease in liver glutathione (46). Acetaldehyde adducts also promote collagen production because collagen synthesis by liver stellate cells is released from the feedback inhibition produced by the carboxy terminal propeptide of procollagen through adduct formation of acetaldehyde with the latter (47). Thus, acetaldehyde toxicity plays a fundamental role in alcohol-induced liver injury, and glutathione is a key defense mechanism by inactivating the free radicals generated by acetaldehyde and by binding to acetaldehyde itself (Figure 1). SAMe, in turn, serves as the main support for the maintenance of adequate glutathione concentrations.

**BENEFICIAL EFFECTS OF SAMe IN ALCOHOLIC LIVER DISEASE**

**Experimental studies**

Although it has been claimed that the liver does not take up SAMe from the bloodstream, other results indicate its uptake by isolated hepatocytes; results in baboons (28) also clearly showed hepatic uptake of exogenous SAMe in vivo, associated with beneficial effects on liver function and structure. In these baboons, correction of the ethanol-induced hepatic SAMe depletion with oral SAMe administration (28) resulted in a corresponding attenuation of ethanol-induced liver injury, as shown by a less-striking glutathione depletion and lesser increases in plasma aspartate transaminase (EC 2.6.1.1). The number of alcohol-induced megamitochondria (documented by electron microscopy) was markedly reduced (28). The latter was associated with a lesser leakage of the mitochondrial enzyme glutamic dehydrogenase into the bloodstream. In rats, SAMe also decreased ethanol-induced fat accumulation (48). Thus, SAMe was shown to be useful for opposing the oxidative stress and the alcohol-induced liver injury.

Membrane alterations are common in alcoholic liver injury and are also associated with a decrease in phosphatidylcholine, the backbone of the membranes. One pathway for the maintenance and preservation of adequate phosphatidylcholine concentrations in the liver membranes is the methyltransfer of phosphatidylethanolamine to phosphatidylcholine through the action of SAMe (Figure 1). This vital function is impaired in alcoholic liver disease because, under these conditions, the activity of phosphatidylethanolamine methyltransferase (EC 2.1.1.17) is depressed (4, 49). This deficiency is exacerbated if SAMe is depleted (Figure 1). These metabolic considerations may explain, at least in part, some of the beneficial effects of SAMe on alcohol-induced liver injury in baboons (28) through the restoration of some of the phosphatidylcholine production or through the positive effects of the supplementation with phosphatidylcholine (50), the depleted product of the reaction (Figure 1).

**Clinical trial**

A significant therapeutic success in alcoholic liver disease was achieved in a recent long-term randomized, placebo-controlled, double-blind, multicenter clinical trial of SAMe in patients with alcoholic liver cirrhosis in whom SAMe improved survival or delayed liver transplantation (18).

**CONCLUSIONS**

Liver disorders, including alcoholic liver disease, are associated with and result in part from impaired activation of methionine to SAMe or from alcohol-induced oxidative stress, which results in the increased utilization of SAMe, a key precursor of cysteine—the rate-limiting amino acid of the tripeptide glutathione. Depletion of SAMe, the main methylating agent of the liver, and associated liver pathology can be corrected by the administration of this safe, yet therapeutically effective nutrient.

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