

# S-Adenosylmethionine: molecular, biological, and clinical aspects—an introduction<sup>1-3</sup>

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## ABSTRACT

In clinical research, a novel approach has emerged: some of the essential nutrients are being used to treat pathologic conditions. Many of these nutrients, including methionine, must first be activated in the liver or in other tissues before they can exert their key functions. However, this activating process is impaired in disease states and, as a consequence, nutritional requirements change. For instance, for methionine to act as the main cellular methyl donor, it must first be activated to *S*-adenosylmethionine (SAME; also known as ademetionine). SAME is required and is of fundamental importance for the metabolism of nucleic acids and polyamines, the structure and function of membranes, and as a precursor of glutathione. These processes are often seriously altered in various pathologic states addressed in this symposium, but they cannot be restored by simply administering methionine. For instance, in liver disease associated with impairment of the enzyme that activates methionine to SAME, supplementation with methionine is useless and may even become toxic as it accumulates because it is not used. Accordingly, one must correct the lack of SAME by bypassing the deficiency in enzyme activation; this is done by providing the product of the defective reaction, namely SAME. Under these pathologic conditions, SAME becomes crucial for the functioning of the cell. Thus SAME, which is found in all living organisms, becomes the essential nutrient instead of methionine. This symposium reviewed the biological and corresponding molecular aspects of SAME metabolism and the clinical consequences of its deficiency or supplementation in various tissues. *Am J Clin Nutr* 2002;76(suppl):1148S–50S.

**KEY WORDS** Homocysteine, membranes, methionine, methionine adenosyltransferase, nucleic acids, polyamines, *S*-adenosylmethionine

## MOLECULAR AND BIOLOGICAL ASPECTS OF SAME

In this symposium, experts presented an up-to-date review of the molecular and biological aspects of *S*-adenosylmethionine (SAME), especially as these pertain to pathology in the main tissues of the body. The presenters also discussed ways that progress in our understanding of the relevant pathophysiology is now yielding significant therapeutic successes. The importance of SAME originates from the fact that it is the principal methyl donor and the precursor of aminopropyl groups and of glutathione in the liver; it also regulates the activities of various enzymes. SAME is formed by activation of dietary methionine by ATP in a reaction catalyzed by methionine adenosyltransferase (EC 2.5.1.6; 1, 2). SAME contains a high-energy sulfonium ion, which activates each of the attached carbons toward nucleophilic attack (**Figure 1**) and

confers on SAME the ability to participate in 3 major types of reactions: transmethylation, transsulfuration, and aminopropylation (3).

In transmethylation reactions, SAME serves primarily as the universal methyl donor to a variety of acceptors including nucleic acids, proteins, phospholipids, and biologic amines (1). Although a specific enzyme catalyzes each of these reactions, the common product of all methylation reactions is *S*-adenosylhomocysteine (SAH) (**Figure 2**). Most of SAME-dependent methylation reactions are strongly inhibited by increases in SAH and decreases in SAME concentrations (1). Therefore, the removal of SAH is essential. SAH is hydrolyzed to homocysteine and adenosine by SAH hydrolase (EC 3.3.1.1). It is important to note that this hydrolysis is a reversible reaction that favors the synthesis of SAH. In vivo, the reaction proceeds in the direction of hydrolysis only if the products, adenosine and homocysteine, are removed rapidly (1, 2, 4, 5).

There are 2 pathways that metabolize homocysteine: remethylation and transsulfuration (**Figure 2**). In the remethylation pathway, homocysteine acquires a methyl group from *N*-5-methyltetrahydrofolate or from betaine to regenerate methionine. The reaction with betaine occurs mainly in the liver and is of minor importance for the overall metabolism of homocysteine in humans; it is of major significance only in rodents. This is because betaine is derived from choline, a pathway of minimal importance and hence of little relevance in primates (5), who have a paucity of choline oxidase (EC 1.1.3.17) in the liver (6). The reaction with *N*-5-methyltetrahydrofolate occurs in all tissues and is dependent on vitamin B-12. The reaction with betaine, which is confined mainly to the liver, is a vitamin B-12-independent reaction. In the transsulfuration pathway, homocysteine condenses with serine to form cystathionine, an irreversible reaction catalyzed by cystathionine  $\beta$ -synthase in the presence of vitamin B-6 as a cofactor. Cystathionine, in turn, is hydrolyzed by  $\gamma$ -cystathionase (EC 4.4.1.1) to form cysteine and  $\alpha$ -ketobutyrate. Cysteine reacts with glutamate and glycine through 2 consecutive

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<sup>2</sup> Presented at the symposium *S*-Adenosylmethionine (SAME): from Molecular Mechanism to Clinical Implications, held in Santa Barbara, CA, March 7–10, 2001.

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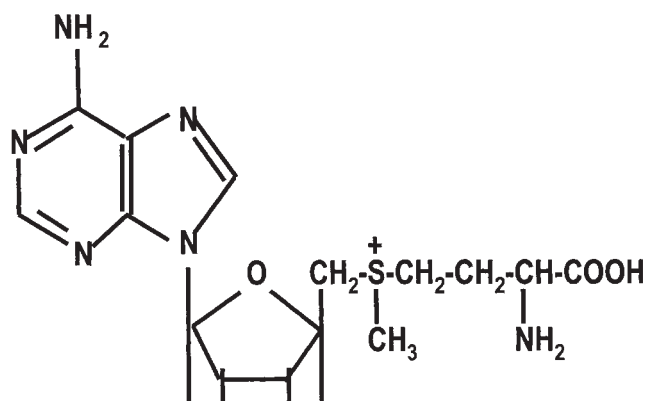


FIGURE 1. Molecular structure of *S*-adenosylmethionine.

reactions to form the tripeptide glutathione, which is the primary endogenous cellular antioxidant defense molecule in mammalian organisms (3, 7).

Transfer of the propylamine group of SAMe for the synthesis of polyamines is another important function of this molecule. In this pathway, SAMe is decarboxylated by SAMe decarboxylase

(EC 4.1.1.50) and its aminopropyl group is transferred, first to putrescine and then to spermidine, to form polyamines. Under normal conditions, this pathway does not account for >5% of the available SAMe, but this percentage is markedly increased under conditions of increased polyamine synthesis, as during liver regeneration (1).

It is important to note that SAMe is also a regulator of enzyme activities and it coordinates the remethylation and transsulfuration pathways. SAMe acts as an allosteric inhibitor of methylene tetrahydrofolatereductase (EC 1.7.99.5) and as an activator of cystathionine  $\beta$ -synthase. In this way, SAMe suppresses the synthesis of *N*-5-methyltetrahydrofolate, an important substrate required for remethylation reactions, and promotes the initial reaction of transsulfuration. Thus, the intracellular SAMe concentration is an important determinant of the fate of homocysteine, a risk factor for cardiovascular disease (5, 7).

### PHARMACOLOGIC AND CLINICAL ASPECTS OF SAMe

A critical step toward the clinical application of SAMe has been the development of salts that provide sufficient stability with superior quality throughout the shelf life of the product (3 y). Specific aspects of this superior quality include better stability of

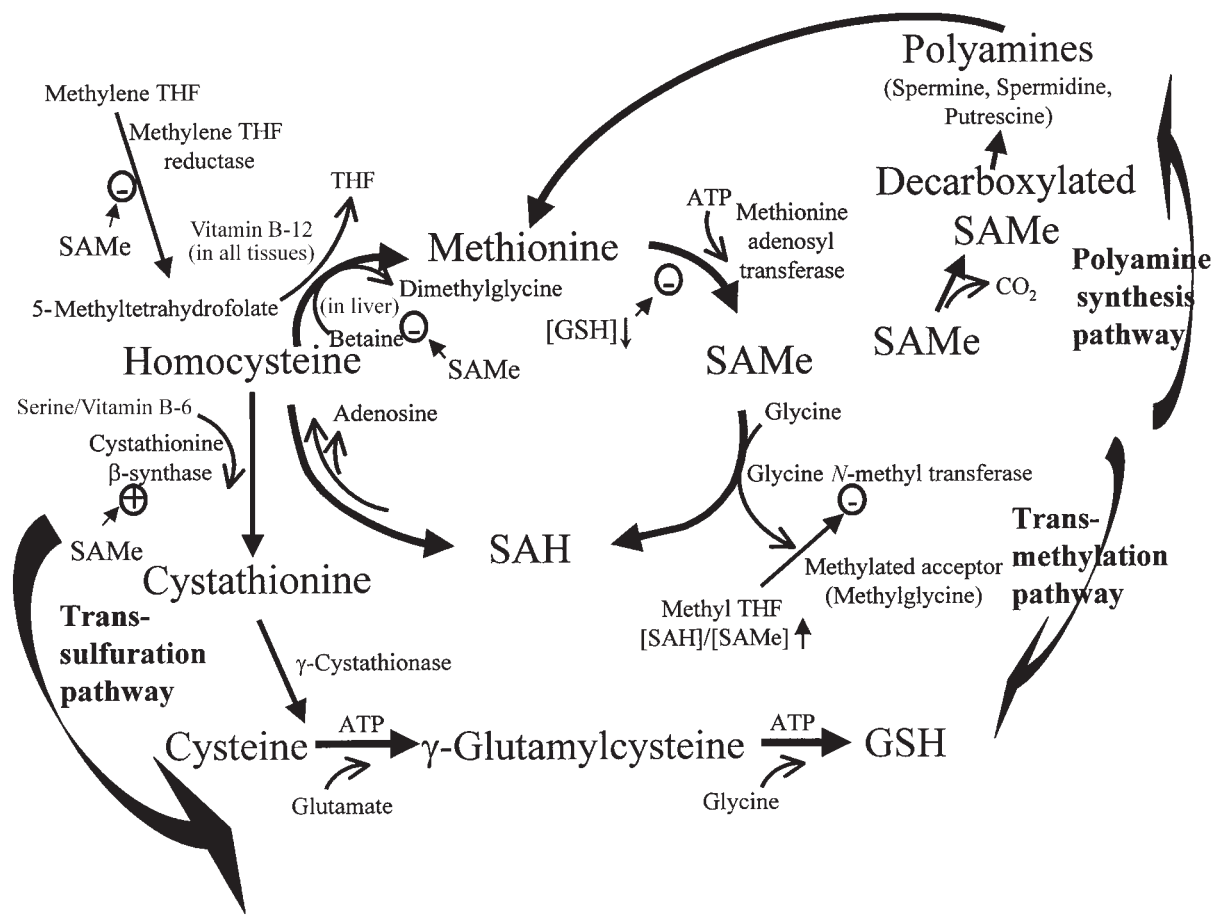



FIGURE 2. Biosynthesis and metabolic pathways of *S*-adenosylmethionine (SAMe). THF, tetrahydrofolate; GSH, glutathione; SAH, *S*-adenosylhomocysteine.

the compound, less degradation, adequate absorption after oral administration, and adequate penetration into the targeted organs. Some SAME preparations on the market are superior to others with regard to stability and quality. The salt that has been developed most recently is 1,4-butanedisulfonate.

The articles in this issue provide insights regarding the molecular basis of the action of SAME (8), and they also report on the impressive results achieved in treating liver disease, both experimentally (9) and clinically (10). Treatment with SAME has also led to significant improvements in disorders of the central nervous system, such as depression (11, 12). 

We thank C DiPadova (Knoll, Italy) and K Kraemer (BASF Corporation, Germany) for generously supporting this meeting. We are grateful to Hadi Moini and Kyung-Joo Cho for their insightful molecular and biological comments and to Giovanna M Bagnasco for assistance on this project.

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