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LETTERS TO THE EDITOR

S-Adenosyl-L-methionine towards hepatitis C virus expression: Need to consider *S*-Adenosyl-L-methionine's chemistry, physiology and pharmacokinetics

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Abstract

S-Adenosyl-L-methionine (SAM) is a cofactor serving as a methyl donor in numerous enzymatic reactions. It has been reported that SAM has the potential to modify antioxidant-enzymes, glutathione-biosynthesis and methionine adenosyltransferases-1/2 in hepatitis C virus -expressing cells at millimolar concentrations. The efficacy of SAM at micromolar concentrations and the underlying mechanisms remain to be demonstrated.

Key words: *S*-Adenosyl-L-methionine; Bioavailability; Concentration; Liver

Core tip: *S*-Adenosyl-L-methionine (SAM) serves as a cofactor for enzymes that transfer its methyl group to nucleophilic functionalities of various biomolecules including DNA and RNA. Exogenous SAM has been shown to be a useful pharmacological agent in liver-associated diseases. SAM is a labile species, undergoes spontaneous decomposition in biological samples, and its oral bioavailability is only about 2%. Lozano-Sepulveda and colleagues observed that SAM modulates antioxidant enzymes, restores glutathione synthesis, and switches MAT1/MAT2 turnover in hepatitis C virus (HCV) expressing cells. The authors suggested that this may be a likely mechanism by which HCV expression is diminished by SAM. This SAM concentration range was chosen on the basis of cell viability experiments and is up to 1000 times higher than physiological intracellular. Other groups have used SAM in the concentration range 0 - 1000 nmol/L. The efficacy of SAM, its pharmacological effects towards

HCV and possibly adverse effects beyond cell viability need to be elaborated in further studies using SAM concentrations much lower than 1 mmol/L.

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TO THE EDITOR

S-Adenosyl-L-methionine (SAM) is the common cofactor of methylating enzymes, the methyl transferases. These enzymes catalyze the transfer of the methyl group of SAM to various nucleophilic functionalities of low-molecular-mass and high-molecular-mass biomolecules. Catechol amines, DNA, RNA, and proteins are well-investigated substrates of methyl transferases. SAM deficiency is associated with many different pathogenic conditions including liver diseases, depression and inherited methylation disorders. SAM supplementation in such diseases is a therapeutic means[1-5]. Lozano-Sepulveda and colleagues recently reported in the *World Journal of Gastroenterology* that SAM decreased hepatitis C virus (HCV) -RNA levels by 50% to 70% and induced a synergistic antiviral effect with standard IFN treatment[6]. The authors found that SAM modulated several antioxidant enzymes (*e.g.,* superoxide dismutase-1 and -2, thioredoxin), restored glutathione (GSH) synthesis, and switched methionine adenosyltransferase (MAT) turnover in HCV-expressing cells. The study by Lozano-Sepulveda and colleagues adds to the pleiotropic effects of SAM. However, this study by Lozano-Sepulveda and colleagues suffers from a major limitation, namely the use of very high SAM concentrations (range, 1 - 5 mmol/L)[6]. The choice of this SAM concentration range appears arbitrary. Another study limitation is that no SAM concentration/dose-response experiments have been performed.

SAM is a physiological substance and is widely distributed in extracellular and intracellular compartments of the human body[7-11]. The concentration of SAM in plasma of healthy subjects is of the order of 150 nmol/L, seemingly independent of the concentration of total homocysteine[7]. The intracellular SAM concentration in human lymphocytes has been reported to be about 5 nmol/10^6 cells; in mouse liver the SAM content was determined to be 0.5 nmol/mg protein[7]. The latter values are close to those reported by others using different analytical methods[12]. In freshly isolated human erythrocytes the concentration of SAM is of the order of 4 μmol/L[13]. This value agrees with more recently reported median SAM concentrations in erythrocytes of diabetic (3.8 μmol/L) and non-diabetic (3.5 μmol/L) male and female subjects[14].

The pharmacokinetics of SAM has been frequently investigated in animals as well as in healthy and diseased humans[15-17]. The oral bioavailability of SAM is of the order of 1% - 4%. Ingestion of 1000 mg SAM as tosylate disulfate salt resulted in maximum plasma SAM concentrations of about 2.5 μmol/L in men and women[3]. Intravenous injection of 1000 mg SAM resulted in maximum plasma SAM concentrations of about 211 μmol/L[15]. Another study found that oral administration of 10 mg SAM/kg body weight did not result in significant increases in systemic SAM concentration[16]. Thus, the SAM concentration range used in the Lozano-Sepulveda's study[6] is almost 1000-fold higher than physiological and pharmacologically used SAM concentrations (0-1000 nmol/L), and even 5 - 25 times higher than plasma SAM concentrations from intravenously injected SAM.

Use of very high SAM concentrations in *in vitro* experiments, even if not toxic[6], may lead to entirely different or contradictory results than the use of physiological and pharmacological SAM concentrations[18]. Oral administration of radiolabeled SAM (*i.e.,* [*methyl*-^{14}C]SAM) in mice resulted in radioactivity accumulation in the liver due to authentic [*methyl*-^{14}C]SAM and [*methyl*-^{14}C]phosphatidylcholine. The latter was found to be about 8 (after 60 min) and 25 (after 240 min) times higher concentrated than [*methyl*-^{14}C]SAM[16]. In aqueous solution, SAM is unstable and decomposes spontaneously to its components including *S*-methylthioadenosine, adenosine, adenine, and homoserine lactone[19]. Above pH 6, SAM is chemically very labile. Its inherent reactivity towards nucleophilic functionalities of biomolecules such as DNA and proteins is about 1000 times higher than that of methylated folates[19]. These observations suggest that SAM does not only function as an universal cofactor in methyltransferases-catalyzed reactions, but also undergoes both spontaneous methylation reactions with various biomolecules and decomposition to species such as *S*-methylthioadenosine and homoserine lactone[19]. Possibly, SAM decomposes to additional substances with not yet known biological activities, albeit not necessarily acutely cell toxic. The decrease in total glutathione concentration in the HCV-expressing cells upon incubation with SAM at 1 mmol/L for 1 and 2 h seen by Lozano-Sepulveda *et al*[6] may be an indication of a (spontaneous) reaction of SAM with reduced glutathione (GSH) to form *S*-methyl-glutathione which cannot be detected by the Ellman's method. At least in rat kidney proximal tubules, *S*-methyl-glutathione is rapidly degraded by gamma-glutamyl-transpeptidase[20]. Measurement of oxidized glutathione, *i.e.,* glutathione disulfide (GSSG), is a much more suitable and direct approach to assess oxidative stress. Yet, no GSSG data

were reported in the paper[6]. It is worth mentioning that SAM (at 4 mmol/L) can also inhibit thioredoxin-mediated protein disulfide reductase activity[20]. This and further reports[22] are supportive of the chemical lability of SAM that makes it a spontaneous unselective methylating agent. Spontaneous decomposition of SAM considerably contributes to *S*-adenosyl-homocysteine which is a potent inhibitor of methyltransferases including protein arginine methyltransferases[23].

Lozano-Sepulveda and colleagues reported in their article interesting results and proposed possible mechanisms for the explanation of the effects exerted by SAM in HCV-expressing cells seen in their study[6]. Yet, the SAM concentrations used in the study are difficult to be reached within cells even by intravenous injection of SAM salts. The high chemical reactivity of the *S*-methyl group of SAM towards biomolecules and its spontaneous decomposition is likely to bear potential adverse effects. The efficacy and the safety of SAM, especially its pharmacological effects towards HCV, need to be elaborated in further studies taken into consideration the pharmacokinetics of SAM. Use of SAM at mmol/L-concentrations may raise unrealizable expectations.

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