Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

S-adenosylmethionine (SAMe) therapy in liver disease: A review of current evidence and clinical utility

Quentin M. Anstee*, Christopher P. Day

Liver Research Group, Institute of Cellular Medicine, The Medical School, Newcastle University, Framlington Place, Newcastle-Upon-Tyne NE2 4HH, UK

Summary

S-adenosyl-L-methionine (SAMe; AdoMet) is an important, metabolically pleiotropic molecule that participates in multiple cellular reactions as the precursor for the synthesis of glutathione and principle methyl donor required for methylation of nucleic acids, phospholipids, histones, biogenic amines, and proteins. SAMe synthesis is depressed in chronic liver disease and so there has been considerable interest in the utility of SAMe to ameliorate disease severity. Despite encouraging pre-clinical data confirming that SAMe depletion can exacerbate liver injury and supporting a hepatoprotective role for SAMe therapy, to date no large, high-quality randomised clinical trials have been performed that establish clinical utility in specific disease states. Here, we offer an in-depth review of the published scientific literature relating to the physiological and pathophysiological roles of SAMe and its therapeutic use in liver disease, critically assessing implications for clinical practice and offering recommendations for further research.

Introduction

The need for therapies to ameliorate liver injury

Liver disease is considered acute or chronic according to the duration of the injurious process. The process of hepatic fibrogenesis is triggered by tissue damage and continues until the lesion is healed. If the damage persists or is recurrent, the repair process will persist and fibrogenesis will progress towards cirrhosis, liver failure or hepatocellular carcinoma [1,2]. Hepatocyte death, through a varying combination of oncotic necrosis and apoptosis, is a characteristic feature of most liver diseases including alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cholestasis, viral hepatitis, ischemia/reperfusion, liver preservation at transplantation and drug/toxin-induced injury [3]. Correction of the underlying aetiology before the development of cirrhosis and liver failure is the primary goal in managing liver disease. However, where this is not possible, treatment to ameliorate hepatocellular injury or control fibrogenesis offers an attractive therapeutic strategy that may prevent disease progression and, given that fibrosis has a reversible component, allow regression [4,5]. At present, there are no accepted antifibrotic agents available outside clinical trials and, beyond the use of *N*-acetylcysteine (NAc) in the treatment of acute acetaminophen (paracetamol) toxicity, there are no widely adopted agents that limit hepatocellular injury in routine clinical use.

Irrespective of aetiology, progression of liver disease is influenced by the interaction of host genetic factors, the pathogen, and other coincidental environmental influences [6]. Nutritional status is one such factor [7]. However, it has also become apparent that beyond *dietary availability* of specific nutrients and essential amino acids, an individual's *metabolic capacity* for processing them into active metabolites and the factors that influence this can profoundly affect physiology in health and disease [8]. The essential amino acid methionine and its biologically active metabolite *S*-adenosyl-L-methionine (SAMe; AdoMet) are a case in point: there is evidence that SAMe depletion occurs during chronic liver disease [9,10] and SAMe has been proposed as treatment for certain disease states [8,11]. Due to encouraging data from early studies and the lack of other effective agents, SAMe has been widely adopted in Eastern Europe, Russia, China, Southern Asia, and South America as a therapy for chronic liver disease and intra-hepatic cholestasis. It is therefore timely to discuss the role of SAMe in the pathogenesis of liver disease and critically review the current evidence of clinical utility for SAMe supplementation.

S-adenosyl-L-methionine (SAMe)

Hepatic SAMe metabolism

SAMe is synthesised from dietary L-methionine and ATP by the enzyme methionine adenosyltransferase (MAT; EC 2.5.1.6) in a complex two-step reaction [12,13]. The complete tripolyphosphate (PPPi) moiety is cleaved from ATP at the C-5′ atom and the adenosyl moiety is transferred to methionine to form SAMe;

Keywords: *S*-adenosyl-L-methionine; SAMe; Hepatitis; Steatohepatitis; Oxidative stress.
Received 19 March 2012; received in revised form 12 April 2012; accepted 15 April 2012
* Corresponding author. Address: Institute of Cellular Medicine, The Medical School, Newcastle University, 3rd Floor, William Leech Building, Framlington Place, Newcastle-upon-Tyne NE2 4HH, UK. Tel.: +44 (0) 191 222 7012; fax: +44 (0) 191 222 0723.
E-mail address: quentin.anstee@newcastle.ac.uk (Q.M. Anstee).

PPPi is then hydrolysed to orthophosphate and pyrophosphate (PPi + Pi) at a distinct sub-site within the MAT catalytic domain; and finally SAMe, orthophosphate and pyrophosphate are released (Fig. 1) [9]. In mammals, there are three separate forms of the MAT enzyme [14]. The gene *MAT1A* is predominantly expressed in the adult liver and encodes a 395 amino acid α1 catalytic subunit that is combined into either a homotetramer (MATI) or a homodimer (MATIII) [15]. In contrast, *MAT2A* is ubiquitously expressed in all mammalian tissues studied including foetal liver (and to a lesser extent in adult liver), erythrocytes, lymphocytes, brain and kidney [15–17]. It encodes a 396 amino acid α2 catalytic subunit that combines with a non-catalytic 334 amino acid regulatory β subunit encoded by *MAT2B* to form the MATII isoform of the enzyme [12,15,16]. MAT is a highly conserved enzyme throughout evolution with a 59% sequence homology between *Escherichia coli* and humans [9]. Both the α1 and α2 subunits share approximately 84% amino acid sequence homology [15] however, the MATII α2/β dimer has lower substrate affinity (km) than MATI/III and its activity is negatively regulated by SAMe as intracellular concentration increases whilst MATI/III is not. These differences in regulatory and kinetic properties limit MATII activity, which is thought to contribute little to hepatic methionine metabolism in healthy adults under normal physiological conditions whilst the *MAT1A* coded isoforms (MATI/III) maintain high levels of SAMe synthesis (approximately 6–8 g/day) [12].

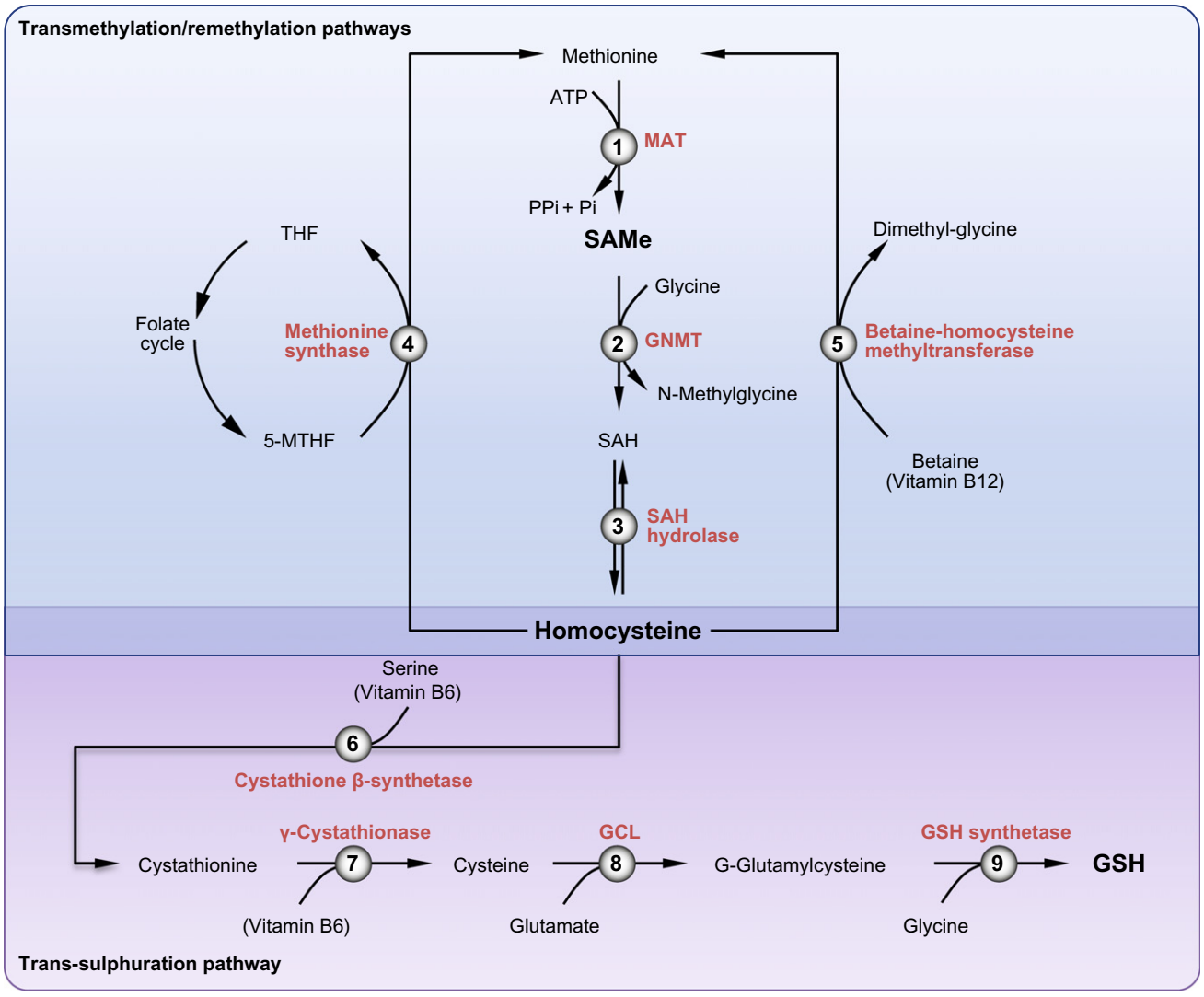

Fig. 1. Metabolic pathways in methionine/SAMe metabolism. SAMe is synthesised from dietary L-methionine and ATP by the enzyme methionine adenosyltransferase (MAT; •1). In standard conditions, the majority of SAMe generated is used in transmethylation reactions. Glycine-*N*-methyl transferase (GNMT; •2) is the most abundant methyltransferase in the liver. Irrespective of the specific enzyme mediating the reaction, a common product is *S*-adenosylhomocysteine (SAH). SAH is cleared by conversion into homocysteine and adenosine in a reversible reaction catalysed by SAH hydrolase (•3). Homocysteine is in turn metabolised through either the remethylation pathways or the transsulfuration pathways. In the former, homocysteine is remethylated by methionine synthase in a process coupled to the folate cycle (MS; •4) or betaine methyltransferase (BHMT; •5) to re-form methionine. Alternatively, the conversion of homocysteine to crystathionine by crystathionine β-synthase (CBS; •6) begins the transsulfuration pathway leading to cysteine and ultimately glutathione (GSH) (•7, •8, •9). Folic acid and the co-factors vitamin B6 and B12 are required for functioning of MS (•4), CBS (•6) and BHMT (•5), respectively. Modified from [10,11].