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Invited Review

Hydrogen sulfide and the liver

Sarathi Mani [a,b], Wei Cao [b,c,d], Lingyun Wu [b,c,e], Rui Wang [a,b,*]

[a] Department of Biology, Lakehead University, Thunder Bay, Canada
[b] Cardiovascular and Metabolic Research Unit, Lakehead University, Thunder Bay, Canada
[c] Thunder Bay Regional Research Institute, Thunder Bay, Canada
[d] Department of Natural Medicine & Institute of Materia Medica, Fourth Military Medical University, Xi'an, China
[e] Department of Health Sciences, Lakehead University, Thunder Bay, Canada

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ABSTRACT

Hydrogen sulfide (H_2S) is a gasotransmitter that regulates numerous physiological and pathophysiological processes in our body. Enzymatic production of H_2S is catalyzed by cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (MST). All these three enzymes present in the liver and via H_2S production regulate liver functions. The liver is the hub for metabolism of glucose and lipids, and maintains the level of circulatory lipids through lipoprotein metabolism. Hepatic H_2S metabolism affects glucose metabolism, insulin sensitivity, lipoprotein synthesis, mitochondrial biogenetics and biogenesis. Malfunction of hepatic H_2S metabolism may be involved in many liver diseases, such as hepatic fibrosis and hepatic cirrhosis.

Contents

Introduction

Hydrogen sulfide (H_2S) is a gasotransmitter that is synthesized in mammalian cells, and exerts a regulatory impact on many physiological and pathophysiological processes [1]. Mammalian cells generate H_2S through either non-enzymatic or enzymatic mechanisms. The non-enzymatic generation of H_2S involves phosphogluconate pathway in erythrocytes and the reduction of elemental sulfur produced from the reducing equivalents of oxidized glucose during glycolysis [2,3]. Most significant to endogenous H_2S level is the enzymatic H_2S production [1,4–6]. Cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (MST) in concert with cysteine aminotransferase (CAT) are responsible for the synthesis of endogenous H_2S (Fig. 1). These enzymes all use cysteine and/or homocysteine or their derivatives as the substrates [1,7,8]. The distribution of H_2S-producing enzymes is tissue specific. For example, CSE is the predominant H_2S-producing enzyme in the cardiovascular

* Corresponding author at: Office of Vice President, (Research, Economic Development and Innovation), Lakehead University, 955 Oliver Road, Thunder Bay, Ontario P7B5E1, Canada. Fax: +1 (807) 766 7105.
E-mail address: rwang@lakeheadu.ca (R. Wang).

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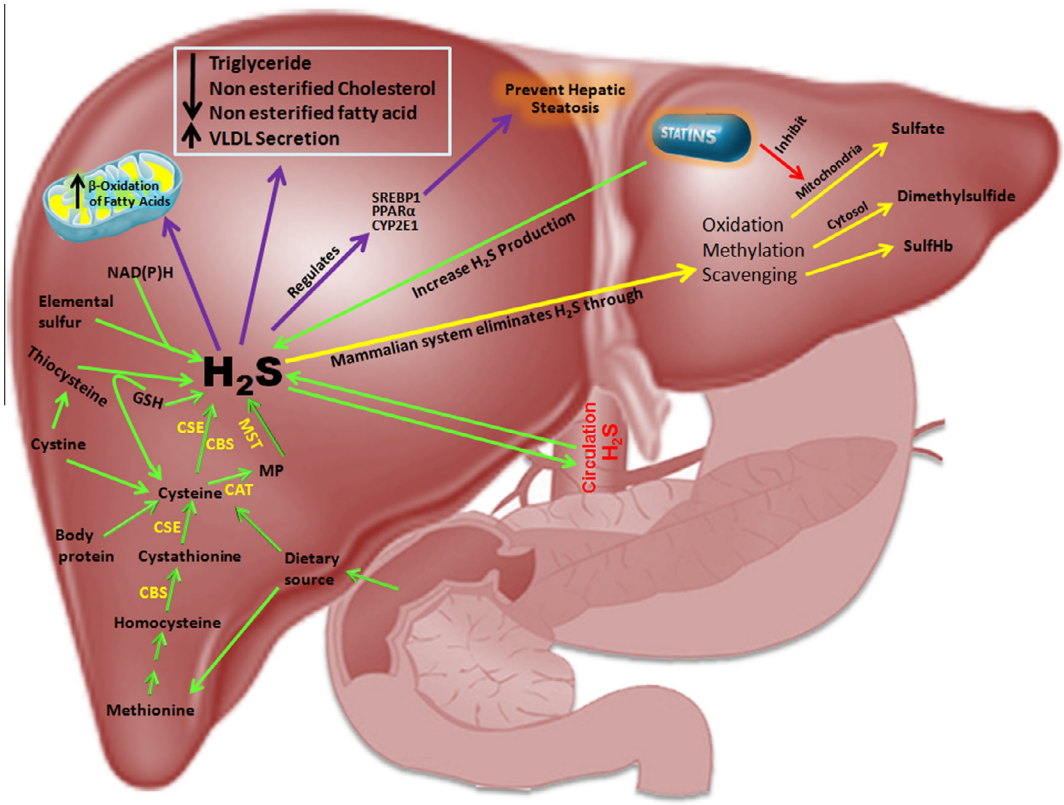

Fig. 1. Endogenous production of H_2S in the liver and its effects on liver functions. CAT: cysteine aminotransferase; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; GSH: reduced glutathione; H_2S: hydrogen sulfide; 3-MP: 3-mercaptopyruvate; MST: 3-mercaptopyruvate sulfurtransferase; sulfHb: sulfhemoglobin; VLDL: Very low density lipoprotein.

system [9–11], the liver and kidney [12–14], the pancreas [15], vascular smooth muscle cells (VSMC) [16–18], and the respiratory system [19,20]. CSE mRNA has been detected in the brain [21]. However, CSE inhibitors, DL-propargylglycine (PPG) and β-cyano-L-alanine (BCA), had no effect on brain production rate of H_2S [22], while they suppressed H_2S generation in the liver and kidney [23]. Unlike CSE, CBS expression is rare in the cardiovascular system. CBS is the predominant H_2S-producing enzyme in the central nervous system or neurons [1], highly expressed in the hippocampus and cerebellum in the brain [22,24]. CSE, CBS, and MST proteins have been detected in the liver, and they contribute to liver production of H_2S to different extents.

In order to maintain proper physiological levels of H_2S, our body eliminates H_2S through oxidation, methylation, scavenging and expiration [1,8,11] (Fig. 1). Oxidation and methylation are the most important mechanisms for H_2S elimination. Mitochondria first oxidize H_2S to thiosulfate, then to sulfite or sulfate, which are excreted by the kidney in urine. Whereas the methylation of H_2S takes place in the cytosol, oxidation in mitochondria is much faster than methylation [25]. In addition, methemoglobin and some other proteins scavenge H_2S in the blood and tissues. Lastly, H_2S is exhaled through the lung. In healthy individuals, very little H_2S is eliminated through the lung as alveolar air only contains 25–50 ppb H_2S [26,27].

The liver plays a key role in glucose and lipid metabolism, xenobiotic metabolism, and antioxidant defence. Hepatic H_2S metabolism affects glucose metabolism, insulin sensitivity, lipoprotein synthesis, mitochondrial bioenergetics and biogenesis. Malfunction of hepatic H_2S metabolism may be involved in the pathogenesis of many liver diseases, such as hepatic fibrosis and cirrhosis.

Role of H_2S in hepatic lipid metabolism

As a key metabolic organ, the liver plays a vital role in various aspects of lipid metabolism through interacting with the intestinal tract and adipose tissue [28]. The liver synthesizes fatty acids and triglycerides from excess carbohydrates and proteins, which are either exported and stored in adipose tissue or oxidized by the liver itself to produce energy [29]. Also, the liver synthesizes large quantities of cholesterol, phospholipids and apoproteins, which are utilized for the transportation of lipids in the circulation in the form of lipoproteins to the rest of the body [30]. The excess lipids are catabolised and excreted by the liver to support whole-body lipid homeostasis. Liver dysfunction leads to deregulation of lipid metabolism such as alterations in fatty acid biosynthesis, beta-oxidation and very low density lipoprotein (VLDL) secretion, which subsequently changes serum concentrations of cholesterol and lipoproteins [31–33]. Fatty liver disease is an important causative factor of cardiovascular diseases and obesity-related disorders [34,35].

The liver is an important organ for H_2S production and its clearance [1,3,8]. CSE and CBS abundantly present in the liver, involved in the endogenous production of H_2S and its metabolism. CBS is important for normal liver function and its deficiency leads to diverse clinical disorders, especially fatty liver. The mouse with homozygous mutation of CBS exhibits hyperhomocysteinemia, oxidative stress, fibrosis and hepatic steatosis, the features shared by CBS deficient patients [36,37]. Moreover, CBS deficiency induces dysregulation of genes involved in hepatic lipid homeostasis in mice [38]. CSE-KO mice have been developed in our laboratories [9]. These mice have a phenotype of age-dependent hypertension and hyperhomocysteinemia [9]. CSE-KO mice are indistinguishable