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Corresponding Author: Seung-Soon Im

Authors: Jae-Ho Lee[1], Seung-Soon Im[1,*]

Institution: [1]Department of Physiology, Keimyung University School of Medicine, Daegu 42601, Republic of Korea,

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Title: Function of gaseous hydrogen sulfide in liver fibrosis

Author's name: Jae-Ho Lee[1], Seung-Soon Im[1,*]

Affiliation: [1]Department of Physiology, Keimyung University School of Medicine, Daegu 42601, Republic of Korea.

Keywords: Hydrogen sulfide, Metabolism, CBS, CSE, MPST, Liver fibrosis

[*]**Corresponding Author's Information:**

Department of Physiology, Keimyung University School of Medicine, 1095 Dalgubeol-daero, Dalseo-gu, 42601 Daegu, Republic of Korea. Tel: +82-53-258-7423; Fax: +82-53-258-7412; E-mail: ssim73@kmu.ac.kr

ABSTRACT

Over the past few years, hydrogen sulfide (H_2S) has been shown to exert several biological functions in mammalian. The endogenous production of H_2S is mainly mediated by cystathione β-synthase (CBS), cystathione γ-lyase (CSE) and 3-mercaptopyruvate sulfur transferase (MPST). These enzymes are broadly expressed in liver tissue and regulates liver function by working on a variety of molecular targets. As an important regulator of liver function, H_2S is critically involved in the pathogenesis of various liver diseases, such as non-alcoholic steatohepatitis (NASH), liver fibrosis and liver cancer. Targeting H_2S-generating enzymes may be a therapeutic strategy for controlling liver diseases. This review described the function of H_2S in liver disease and summarized recent characterized role of H_2S in several cellular process of the liver.

INTRODUCTION

Hydrogen sulfide (H_2S), well known as a poisonous gas with an unpleasant odour, is produced primarily during the breakdown of proteins in plants and animals (1-3). H_2S is a signaling molecule that is actively synthesized within tissues and is involved in the regulation of vascular tone (4, 5), neuromodulation (6, 7), cell protection (8-10), inflammation (11, 12), and apoptosis (13, 14). Recently, new data on H_2S metabolism and function in animals and humans have been collected under the influence of various endogenous and exogenous factors, including drugs (15, 16).

The liver is one of the most important organs to produce and remove H_2S (17). Endogenous H_2S is involved in the pathogenesis of many liver diseases and affects processes, such as hepatic lipid and glucose metabolism, oxidative stress, mitochondrial bioenergetics, fibrosis, cirrhosis, hepatoprotection, and deregulation of hepatotoxicity (18, 19). In addition, endogenous or exogenous H_2S may play an important role in the development of liver tumors (20, 21). The synthesis and clearance of H_2S in the liver is mainly governed by hepatocytes (17). It is a major source of extracellular matrix (ECM) in hepatic fibrosis and hepatocellular carcinoma (HCC) (22). This review focuses on the major and alternative H_2S metabolism and its regulation in the liver.

Understanding of H_2S metabolism

H_2S is a colorless, flammable gas with a characteristic odor of rotten eggs. It occurs naturally in volcanic gases, natural gas, and some well water, and is also produced when bacteria decompose organic matter in the absence of oxygen (23). H_2S is toxic to humans and can result in death from acute exposure to large amounts of H_2S (>500 ppm) (24). H_2S was considered both a toxic molecule and an environmental hazard until discovered to be endogenously

produced (1). The production of H_2S by three enzymes like cystathionine β-synthetase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfur transferase (MPST) (25-28) has been widely studied (Fig. 1). Endogenous H_2S is produced by enzymatic activity and is also released from intracellular sulfur stores (29). In most organ, CBS and CSE are mainly responsible for H_2S production (29). They manage individually from L-cysteine to produce H_2S, L-serine and ammonium (30). Although found throughout the body, the discovery of CBS in the brain has led to consensus that it is a major H_2S-generating enzyme that affects nerve signaling (31). However, CBS has been identified in tissues throughout the body and is thought to regulate overall H_2S production (32). Located primarily in mitochondria, MPST enzymatically generates H_2S from α-ketoglutarate and L-cysteine through metabolic interactions with cysteine aminotransferase (33). CBS, CSE and MPST are mainly expressed in the liver and kidney (34). CBS and CSE metabolize cysteine and/or homocysteine to release H_2S (35), while MPST metabolizes cysteine and 3-mercaptopyruvic acid (3-MP) produced by the action of cysteine aminotransferase (CAT) on α-ketoglutaric acid (36, 37). MPST requires a cofactor to decrease the persulfate intermediate formed between the MPST cysteine residue and the sulfide provided by 3-MP (36). Recent data have found that thioredoxin and dihydrolipoic acid (DHLA) are endogenous reduction cofactors which promote H_2S release from MPST (38).

H_2S is an endogenous signaling molecule in mammals (39). Accumulating evidence suggests that H_2S plays an important role in liver physiology and pathophysiology (40-42). Dysregulation of endogenous H_2S is associated with symptoms of diabetes and cirrhosis (43, 44). Blood levels of H_2S in patients with type 2 diabetes mellitus are lower than in controls (45). Application of H_2S also shows effects on mitochondrial function, antioxidant stress, apoptosis, inflammation, angiogenesis, and blood pressure (46).

Function of H_2S in the liver

The liver plays an important role in mammalian physiology with respect to energy homeostasis (47). Besides, the liver is also a major detoxification tissue, and can metabolize and neutralize harmful substances, drugs, environmental toxins, and endotoxins (48, 49). Endogenous formation of H_2S is impaired in non-alcoholic steatohepatitis (NASH) mice, and H_2S treatment can prevent NASH in mice, perhaps by reducing oxidative stress and suppressing inflammation (40). Administration of sodium hydrogen sulfide (NaHS) as a H_2S donor in rodents protects against ischemic reperfusion, acetaminophen or carbon tetrachloride (CCl_4)-induced liver damage (50).

The liver is uniquely positioned to be exposed to high levels of H_2S; however, how the liver responds to elevated hydrogen sulfide levels is unclear. Liver H_2S levels were previously reported within the low nanomolar to middle micromolar range (17 nM ~ 144 μM) (51). Reactive oxygen species (ROS), a by-product of normal aerobic cell metabolism, are important signaling molecules in many cell functions such as immune response, apoptosis and cell survival (52-54). Recent studies have shown that treatment with relatively low concentrations of H_2S donors such as NaHS, Na_2S or GYY4137 (50 mg/kg) may decrease ROS levels and cytochrome P450 2E1 activity and increase glutathione levels and antioxidant enzymes (50, 55). These results indicate that relatively low levels of H_2S can protect against oxidative stress in the liver. Mitochondria is bilayer organelles whose shape supports them function in many cellular processes (56). The main role of mitochondria is to regulate the production of energetic molecules like adenosine triphosphate (57). During the metabolism of glucose, lipids, and proteins in the liver (58), 3-MP, the substrate for the MPST, stimulates mitochondrial H_2S production and enhances liver mitochondrial electron transport at low concentrations (59, 60).

In addition, low levels of H_2S induces a significant increase in hepatic mitochondrial function (61). Moreover, H_2S acts on mitochondrial proteins via a posttranslational modification designated as sulfhydration or persulfidation (62, 63). Sulfhydration of the ATP Synthase F1 Subunit Alpha (ATP5A1) at Cys244 and 294 was reported to increase its activity (64). Sulfhydration of ATP5A1 was upregulated in response to burn injury and decreased in mice lacking CSE implicating a role for CSE-derived H_2S in the process (64). These results indicate that endogenous H_2S regulates physiologically in mitochondrial electron transport.

The liver is important for the maintenance of blood glucose homeostasis by the uptake of glucose in the postprandial state and its conversion to triglycerides and glycogen, and the production of glucose in the post-absorption state by gluconeogenesis and glycogenosis (65, 66). Deficiencies in the mechanism by which insulin and glucose regulate glycogen metabolism in the liver disrupt blood glucose homeostasis, leading to metabolic disorders such as diabetes and glycogen storage (67, 68). CSE activity has been shown to be low in the liver of type 1 diabetic rats and in peripheral blood mononuclear cells of type 1 diabetic patients, indicating that H_2S is involved in glucose regulation (69). Recent studies have shown that CSE knockout mice have a reduced rate of glycolysis. This can be reversed with NaHS management (70, 71). NAFLD is caused by the accumulation of lipids in the liver and may increase the risk of hepatocellular carcinoma and end-stage liver disease (72, 73). Many risk factors, such as diabetes, obesity, hyperlipidemia, and certain drug regimens are associated with the development of NAFLD (74). H_2S has been shown to alleviate development of fatty liver in obese mice through its antioxidant capacity and promotion of lipid metabolism (40, 75). In a recent study, in NAFLD mouse model, the activation of sterol regulatory element binding protein-1c directly upregulates mir-216a transcription, which reduces CTH-H_2S signaling and ULK1-stimulated autophagy, indicating that loss of sterol regulatory element binding protein-

1c prevents the development of hepatic steatosis through activation of H_2S-mediated autophagy flux in a high fat diets-induced NAFLD model (76, 77). Recent study has shown that administration of NaHS reduces the accumulation of lipids such as total cholesterol and triglycerides through down-regulation of fatty acid synthase and up-regulation of carnitine palmitoyl transferase-1 in the liver of high-fat diet (HFD)-induced obese mice (40). Collectively, H_2S may alleviate liver cell damage in various ways in the pathogenesis of liver disease (Fig 1).

Role of H_2S in liver fibrosis

Several studies have been reported on the use of H_2S in hypoxic injury (78, 79), most of which show beneficial effects of H_2S treatment in models of cardiac arrest (80), lung (81), intestinal (82), renal (83), and cardiac ischemia (84). Fibrogenesis formation in chronic liver disease can disrupt liver functional units and blood flow, leading to cirrhosis of the liver and even life-threatening clinical outcomes (85, 86). In the pathological process of hepatic fibrosis, it is widely known that activated hepatic stellate cells (HSC) are fundamental to the overproduction of ECM in the stroma (87). Recent evidence suggests that inactivation of HSC is an essential mechanism by which H_2S inhibits liver fibrosis (88). However, current report shows that the generation of H_2S is increased during HSC activation, and that exogenous H_2S promotes HSC proliferation and induces the expression of HSC fibrosis makers (89). Furthermore, conflicting results have also been reported depending on the concentration or type of H_2S donor used. Based on the H_2S release rate, H_2S release donors are classified as either fast (NaHS; Na_2S) or slow (GYY4137; ADT-OH) release donors, often giving contrasting results (90, 91). For example, some studies have reported pro-inflammatory and anti-apoptotic properties of H_2S, and shown that H_2S increases mitochondrial bioenergetics and promotes cell proliferation (64,

92, 93). Therefore, there is still a large gap in our understanding of the actual impact of H_2S on HSC and liver fibrosis.

The CCl_4-induced hepatic fibrosis model tends to suppress protein expression of both CSE and H_2S content (94). Suggestion for a protective function for H_2S in liver fibrosis is supported by the understanding that CBS deficiency accelerates fibrosis associated with hepatic steatosis (95). Similarly, gene knockout of CSE exacerbates liver fibrosis by triggering an inflammatory response and decreasing H_2S production, indicating a potential role of the H_2S system in liver fibrosis (96). Supplementation of NaHS ameliorates hepatic fibrosis in CCl_4-treated mice (50). Likewise, CCl_4-treated mice, GYY4137, increased nuclear factor erythroid 2–related factor 2 signaling pathway, improved liver function, reduced liver fibrosis, decreased hepatic oxidative stress (97). Exercise significantly enhances H_2S level and increases levels of CBS, CSE and MPST in HFD-fed mice (98).

H_2S reduces the intracellular redox environment and reduces damage from oxidative stress (99). Given the important role of oxidative stress in the development of fibrosis, it is reasonable to suspect that the endogenous H_2S-producing enzyme pathway suppresses the development of fibrosis by its antioxidant activity (100). Extrinsic H_2S inhibits Fe-NTA-induced elevated intracellular ROS levels and HSC cell proliferation (94), weakens CCl_4-induced increase of liver MDA levels, reduces liver GSH levels, and collagen in liver tissue. It is associated with inhibition of phosphorylated p38 mitogen-activated protein kinase and activation of the phospho-AKT signaling pathway (101).

Inflammation has been reported to be in the early stages of the onset of fibrosis, causing cell apoptosis, fibroblast proliferation, and ECM deposition, ultimately leading to irreversible fibrous damage (102). Treatment with H_2S significantly reduces the infiltration of inflammatory cells, inducible nitrogen monoxide synthase, tumor necrosis factor-α, It down-

regulates pro-inflammatory cytokines such as interleukin (IL)-6, and inhibits IL-8, and the progression of fibrosis (18, 103-105). Although CCl_4-induced liver cirrhosis rats showed significantly higher levels of serum inflammation-inducing cytokines. Co-administration of NaHS resulted in a significant reduction in these cytokines, along with the alleviated collagen fibers of the liver (50).

Recent studies have shown that organ fibrosis is associated with a decrease in autophagy (106, 107). Autophagy is involved in a complex regulatory pathway in hepatic fibrosis, and its fibrosis-promoting effect depends on the activation of hepatic stellate cells but has antifibrotic properties through indirect hepatic protection and anti-inflammatory properties (108). Given the important role of autophagy in the pathogenesis of fibrosis and the regulatory function of H_2S for autophagy and fibrosis, extrinsic or endogenous H_2S is mediated by targeting by autophagy or autophagy-related signaling pathways (21, 109). It is rational and interesting to assume that it may inhibit the development of fibrosis. Overall, these observations suggest that an endogenous H_2S system or H_2S-releasing donor can be developed to treat liver fibrosis via a variety of signaling pathways (Fig. 2).

CONCLUSION

This review summarizes and describes the recent literature on the role of H_2S in several liver diseases. Defect in endogenous H_2S production is associated with NASH and liver fibrosis. And because H_2S may serve as a double-edged sword in such liver disorder, additional studies need to resolve these discrepancies in the future. In addition, although endogenous H_2S production or low exogenous H_2S may lead to the development of liver fibrosis, exposure to large amounts of H_2S may exhibit anti-fibrosis properties. Therefore, targeting H_2S-producing enzymes may be a promising strategy for managing liver disorders.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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FIGURE LEGENDS

Figure 1. Various cellular functions of H_2S in in the liver. Three major enzymes responsible for H_2S production are CBS, CSE, and MPST. L-cysteine is the major substrate for H_2S production. H_2S–mediated signaling varieties from protein modification by sulfidation to affecting a broad range of physiological processes, including regulation of mitochondrial biogenesis, glucose metabolism, oxidative stress, inflammation, fatty acid oxidation and crosstalk with other signaling molecules. CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; MPST: 3-mercaptopyruvate sulfur transferase.

Figure 2. Endogenous and exogenous production of H_2S in the liver and its effects on liver fibrosis. H_2S plays a complex role in the development of fibrosis. Besides as a reducer to directly scavenge reactive oxygen species, exogeneous (NAHS, GYY4137) or endogenous H_2S utilizes its inhibitory effect on fibrosis by anti-inflammation and suppression of fibroblasts activation. Many signaling pathways, such as TNF-α, NF-κB, MAPKs, NRF2, SIRT1, SIRT3, GSH, TGF-β1/SMAD, PI3K, AKT, and autophagy are involved in the process of antifibrosis of H_2S. TNF-α: tumor necrosis factor-alpha; NF-κB: nuclear factor-kappa B; mitogen-activated protein kinase: MAPK; NRF2: nuclear factor erythroid 2–related factor 2; SIRT1: sirtuin 1; SIRT3: sirtuin 3; GSH: glutathione; TGF-β1: transforming growth factor beta 1; SMAD: suppressor of mothers against decapentaplegic; PI3K: phosphoinositide 3-kinase.

Fig.1

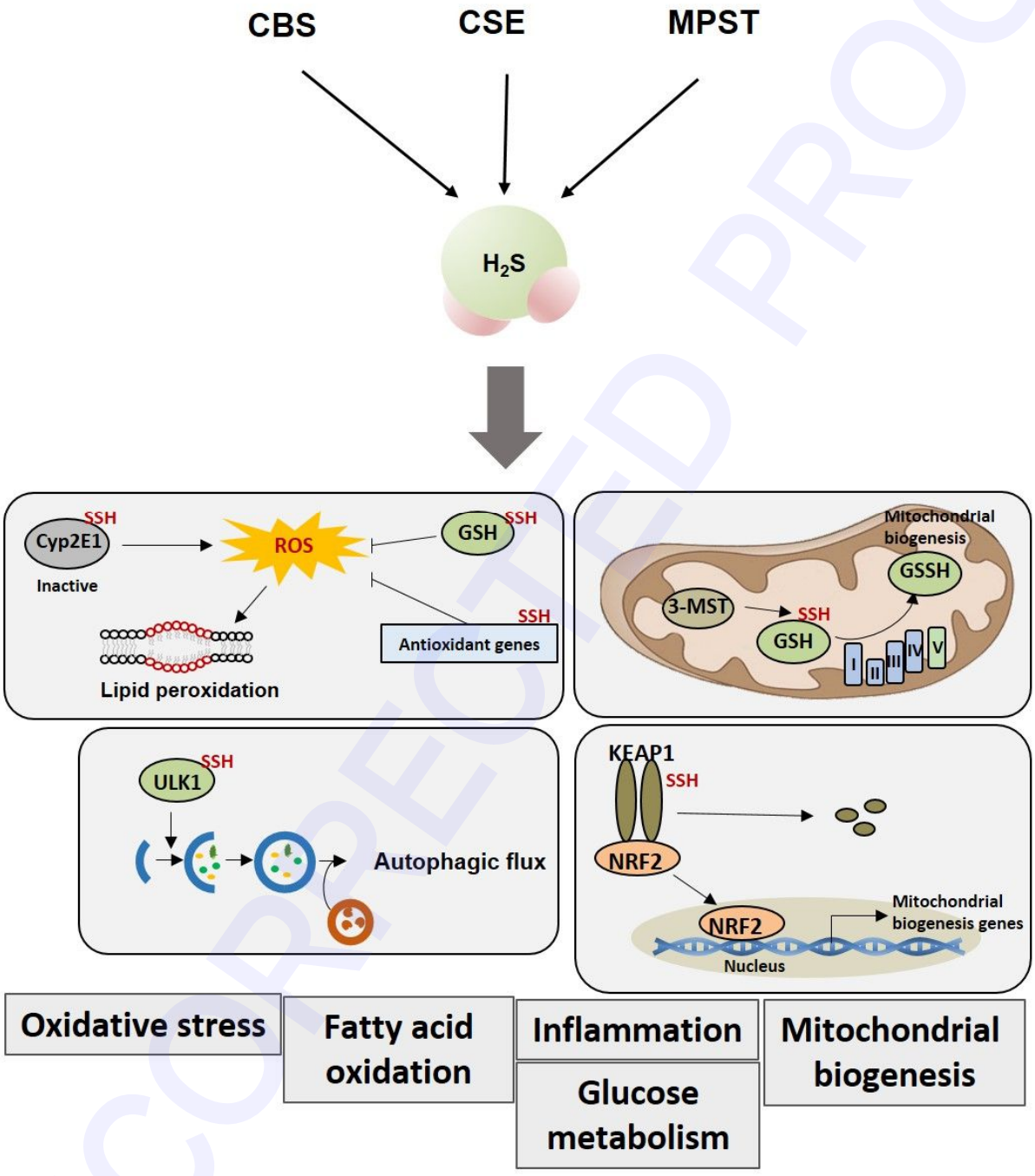

Fig.2