Implications of hydrogen sulfide in liver pathophysiology: Mechanistic insights and therapeutic potential

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Abstract

Background: Over the last several decades, hydrogen sulfide (H\(_2\)S) has been found to exert multiple physiological functions in mammal systems. The endogenous production of H\(_2\)S is primarily mediated by cystathione \(\beta\)-synthase (CBS), cystathione \(\gamma\)-lyase (CSE), and 3-mercaptopropryvurate sulfurtransferase (3-MST). These enzymes are widely expressed in the liver tissues and regulate hepatic functions by acting on various molecular targets.

Aim of Review: In the present review, we will highlight the recent advancements in the cellular events triggered by H\(_2\)S under liver diseases. The therapeutic effects of H\(_2\)S donors on hepatic diseases will also be discussed.

Key Scientific Concepts of Review: As a critical regulator of liver functions, H\(_2\)S is critically involved in the etiology of various liver disorders, such as nonalcoholic steatohepatitis (NASH), hepatic fibrosis, hepatic...
Introduction

Hydrogen sulfide (H$_2$S) is previously described as a toxic gas for a long time [1]. However, mounting evidence suggests its critical roles in numerous biological functions, especially in the cardiovascular [2,3], central nervous [4–6], and other systems [7–10]. It has been proposed that endogenous H$_2$S in mammal systems is mainly generated by either enzymatic or non-enzymatic pathways. The enzymatic process is dependent on the actions of cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptoppyruvate sulfurtransferase (3-MST) [11–13]. The non-enzymatic pathway involves two pathways: the reduction of elemental sulfur generated by the intermediate reduction product of oxidized glucose in the process of glycolysis and the phosphoglucone pathway in erythrocytes [14,15]. Over the last several decades, a pathological significance of H$_2$S has enormously grown in the development of several liver ailments [16]. As a consequence, research on H$_2$S-governed liver functions has achieved considerable progression in both health and diseases. Nevertheless, the cellular and molecular mechanisms that underlie H$_2$S-mediated liver functions have not been fully clarified. Considering that H$_2$S is critically involved in numerous biological processes, it is now extensively accepted that H$_2$S serves as a principal mediator in the field of biological gases.

It is well known that the liver is involved in glycolipid metabolism, xenobiotic metabolism, and host defenses against invading microorganisms [16–20]. Importantly, the liver is a key organ for the production and clearance of H$_2$S [21]. Studies have shown that CBS, CSE and 3-MST are responsible for H$_2$S generation in the liver [16]. A host of genes are engaged in glycolipid metabolism, mitochondrial biogenesis and bioenergetics in which H$_2$S plays a critical role [16,22–24]. Of importance, H$_2$S production and signaling in the liver are altered in several hepatic diseases, including hepatic ischemia/reperfusion (I/R) injury [25], nonalcoholic steatohepatitis (NASH) [26], liver fibrosis [27], and liver cancer [28]. As continuous research into the roles of H$_2$S in the control of liver health and diseases, the potential mechanisms of H$_2$S-mediated liver protection have started to be elucidated. In this review, we will overview the present studies of H$_2$S in the context of liver diseases, with special emphasis on the mechanistic insights and therapeutic potential of H$_2$S in several liver diseases.

Production of H$_2$S in the liver

H$_2$S is an endogenous gasotransmitter that is mainly produced via both enzymatic and non-enzymatic reactions, and it can also be generated from intracellular sulfur stores [16,29]. In the process of the enzymatic pathway, two pyridoxal 5'-phosphate (PLP)-dependent enzymes, CSE and CBS lead to H$_2$S generation using L-cysteine and homocysteine as major substrates [30,31]. Different from CBS and CSE, PLP-independent 3-MST gives rise to H$_2$S by using 3-mercaptoppyruvate (3-MP) as a principal substrate. 3-MP is an intermediate metabolite from either L-cysteine or α-ketoglutarate with the aid of cysteine aminotransferase (CAT) [31]. The reactions for H$_2$S production are summarized in Fig. 1. CSE activity is much higher than CBS in peripheral tissues, whereas CBS is mainly distributed in the brain for primary H$_2$S production [15]. CSE is majorly responsible for H$_2$S generation in the cardio-vascular system, while CBS is a predominantly expressed enzyme in the brain tissues [32]. 3-MST is localized in both cytosol and mitochondria, but the majority of 3-MST is distributed in the mitochondria [33,34], as the concentration of L-cysteine in the mitochondria is three times higher than that in the cytoplasm [35].

By using a non-enzymatic system, endogenous H$_2$S is also produced by glucose, inorganic and organic polysulfides, glutathione, and sulfane sulfur [9,36–38]. In general, H$_2$S could be produced from the reducing equivalents, including nicotinamide adenine dinucleotide phosphate (NADPH) that are generated through glycolysis-mediated glucose oxidation or NADPH oxidase-mediated phosphogluconate oxidation [14]. Reactions of glucose with methionine, cysteine, or homocysteine may lead to the production of H$_2$S and methanethiol [36,39,40]. In the process of non-enzymatic chemical reduction, the intermediate products of sulfur metabolism are available in mammal cells, indicating the necessity of such pathway for H$_2$S production in mammalian systems. Moreover, garlic and garlic-derived organic polysulfides may be an important source for H$_2$S generation, including diallyl trisulfide, diallyl disulfide, diallyl sulfide and S-allyl cysteine [38,41–43]. Accordingly, it is highly probable that the non-enzymatic pathway is a key supplement for H$_2$S generation in the body. However, more studies are still warranted to identify the physiological significance of such non-enzymatic pathway in H$_2$S production in mammalian systems.

In the liver, although the three H$_2$S-generating enzymes are detectable, their roles in endogenous H$_2$S generation are differently described [44–46]. It is found that CSE expression is about 60-fold more than CBS in the liver [45], this observation is supported by a finding that genetic knockout of CSE diminishes the majority of H$_2$S production in the liver, further confirming that CSE is a primary enzyme for H$_2$S generation in the liver tissues [32,47]. Intriguingly, knockdown of 3-MST stimulates H$_2$S production, whereas overexpression of 3-MST markedly inhibits the formation of H$_2$S [26], implying the negative role of 3-MST in endogenous liver H$_2$S production. In addition, the cell-type heterogeneity of these three enzymes in liver tissues points to the sophisticated actions of H$_2$S-producing enzymes on the liver functions. The expression levels of CBS, CSE, and 3-MST are observed in hepatocytes [48]. As described previously, CSE protein is expressed in hepatic stellate cells, while CBS is not detected [47]. In the same study, CSE and CBS are not found in sinusoidal endothelial cells, at least in rats [47]. Until now, the expression of 3-MST is not available in these three non-parenchymal liver cells. It is likely that the H$_2$S-producing enzymes show cell-type specific regulation in the liver. Since the distinct cell types contribute to different liver functions, determination of cell-type specific production of H$_2$S in the liver system is indispensable for the elucidation of endogenous H$_2$S-mediated hepatic functions.

As mentioned above, the enzymes for H$_2$S production are largely observed in the liver tissues. Additional work is needed to clarify the roles of endogenous H$_2$S in liver health and diseases. In earlier reviews, accumulating evidence has demonstrated a close relationship between H$_2$S and normal hepatic functions [10,13,16,23,49–58]. In this review, we will highlight recent studies regarding the potential roles and mechanisms of H$_2$S in several liver disorders, such as I/R injury in the liver, hepatic fibrosis, NASH, and liver cancer.
Role of H2S in liver I/R injury

I/R is reflected by initial deprivation of blood in an organ or a specific area, followed by restoration of blood and re-oxygenation [59]. I/R-induced organ or tissue injury leads to increased morbidity and mortality in various pathologies, such as ischemic stroke, trauma, myocardial infarction, acute kidney injury, sickle cell disease, organ transplantation, and bypass surgery [60]. Similarly, liver I/R-elicited injury contributes to profound liver damage and ultimate mortality [61]. Hepatic I/R injury is involved in the pathogenesis of numerous clinical entities after hepatic surgery and transplantation [61,62]. A host of studies have demonstrated that the pathogenesis of hepatic I/R injury may involve intracellular anaerobic metabolism, overproduction of inflammatory cytokines, oxidative stress, mitochondrial dysfunction, and activation of immune cells, such as Kupffer cells and neutrophils [63,64]. Despite that the recent progresses in surgical techniques and perioperative cares have been achieved, liver I/R injury is still recognized as one of the most complications in liver resection surgery, trauma, transplantation, and hypovolemic shock [63,65]. As a result, it is pressing to identify effective therapeutic strategies to attenuate or prevent hepatic injury induced by I/R.

A large body of evidence has demonstrated that H2S is effective in protecting the liver from I/R injury, thereby representing a novel avenue to reduce the rate of morbidity and mortality triggered by hepatic I/R injury [25,66–68]. In liver I/R injury rats, the expression levels of CSE and H2S are upregulated, whereas administration of H2S donor sodium hydrosulfide (NaHS) attenuates the severity of I/R-induced liver injury [25,69]. These results indicate that endogenous H2S may be important for alleviating hepatic I/R injury, and the elevated CSE/H2S system exerts a compensatory role for H2S production in the pathogenesis of hepatic I/R injury. Whether the liver expression levels of CBS and 3-MST are altered in hepatic I/R injury remain to be studied in the future. Mechanistically, it is established that numerous signaling pathways mediate the protective roles of H2S in hepatic I/R injury, including antioxidant and anti-apoptotic actions [67,70–72], inflammation [25,69,72], mitochondrial dysfunction [73], endoplasmic reticulum stress [74], autophagy [68,72,75,76], thioredoxin interacting protein (TXNIP) [77], and the nuclear factor erythroid2-related factor 2 (Nrf2) pathway [78]. However, it is noteworthy to mention that increased endogenous H2S exacerbates the I/R-induced hepatic injury in rats with insulin resistant, and suppression of endogenous H2S production may account for the protective effects of silymarin preconditioning against liver I/R injury in rats with insulin resistance [79]. These existing results suggest that H2S confers a beneficial effect in ameliorating hepatic I/R injury, and targeting H2S might offer new therapeutic strategies for hepatic I/R injury in the absence of insulin resistance.

Role of H2S in liver fibrosis

The fibrogenesis of chronic liver disease could disrupt the liver functional units and blood flow, leading to liver cirrhosis and even life-threatening clinical consequences [80,81]. With great efforts, significant advancements in the understanding of the underlying mechanisms of hepatic fibrosis and cirrhosis have grown exponentially. In the pathological process of hepatic fibrosis, it is well accepted that activated hepatic stellate cells (HSCs) is fundamental for the overproduction of extracellular matrix (ECM) in hepatic interstitium, thus resulting in hepatic fibrosis [82]. Current evidence suggests that inactivation of HSCs is an important mechanism for H2S to prevent and treat liver fibrosis [83]. However, a recent report has illustrated that the H2S production and CSE
expression are incremented during HSC activation, and exogenous H$_2$S promotes the proliferation of HSCs and evokes the fibrotic maker expressions of HSCs [84]. These contradictory results suggest that systemic treatment with H$_2$S in liver fibrosis should consider the cell-specific actions of H$_2$S. As a result, more experiments are required to determine the exact actions of H$_2$S on HSC activation and subsequent hepatic fibrosis.

The plasma H$_2$S levels are lower in rats with liver fibrosis, and intraportal injection of H$_2$S synthase inhibitor propargylglycine (PPG) further promotes the fibrotic marker expression in the liver from liver cirrhosis group [85]. Both protein expressions of CSE and H$_2$S content tend to be inhibited in liver fibrosis model induced by carbon tetrachloride [86,87]. The evidence for the protective role of H$_2$S in liver fibrosis is supported by a finding that deficiency of CBS accelerates oxidative stress, inflammation, fibrosis in conjunction with steatosis in the liver [88]. In similarity, gene knockout of CSE triggers inflammatory response and exacerbates liver fibrosis by reducing H$_2$S production [86], indicating a potential role of the H$_2$S system in hepatic fibrosis. In addition, the cell-specific expressions and roles of H$_2$S-producing enzymes in hepatic fibrotic disease need to be fully understood.

Supplementation of NaHS, a donor of H$_2$S, protects liver function concomitant with an improvement of hepatic fibrosis and portal hypertension in mice treated with carbon tetrachloride [87]. The similar results are also observed in carbon tetrachloride-induced hepatic fibrosis rat model [89,90]. Diallyl trisulfide (DATS) is reported to reduce hepatic fibrosis in rats with fibrotic liver through elevation of the H$_2$S levels [91]. Moreover, S-allylcysteine (SAC), an endogenous donor of H$_2$S, attenuates liver fibrosis in carbon tetrachloride-induced rats through anti-oxidant, anti-inflammatory and anti-fibrotic effects [92]. The CSE/H$_2$S levels are inhibited in rats with hepatic fibrosis, this effect is reversed by caffeic acid phenethyl ester, thus exerting the effects of anti-hepatic fibrosis [93]. Exercise training markedly enhances H$_2$S contents and upregulates the hepatic expression levels of CBS, CSE and 3-MST in high fat diet (HFD)-fed mice, thereby contributing to its benefit on HFD-provoked hepatic fibrosis [94]. The present data suggest H$_2$S donors or restored bioavailability of H$_2$S have the potential for the treatment of liver fibrosis. Furthermore, long-lasting and safe H$_2$S-releasing donors can be developed to treat liver fibrosis in a proper way.

Mechanistically, the protective effects of H$_2$S against hepatic fibrosis might be attributed to suppression of oxidative stress and inflammation [87,90], inhibition of the signal transducer and activator of transcription 3 (STAT3)/Smad3 pathway [92], decreased phosphorylated p38 MAPK expression, and increased expression of phosphorylated Akt [95], as well as downregulation of angiotensin II type 1 receptor (AGTR1) [96]. It is revealed that the elevated carbon monoxide (CO) levels are observed in fibrotic liver, and inhibition of endogenous CO is believed to be a novel therapy for liver fibrosis [97,98]. Endogenous CO agonist cobalt protoporphyrin aggravates hepatic function and fibrosis via down-regulated expressions of CSE and H$_2$S in the liver tissues [99]. By contrast, the increased expressions of CSE and H$_2$S by endogenous CO inhibitor zinc protoporphyrin IX are beneficial for liver function and fibrosis [99]. Collectively, these observations indicate that endogenous H$_2$S system or H$_2$S-releasing donors can be developed to treat liver fibrosis through various signaling pathways.

**Role of H$_2$S in non-alcoholic fatty liver diseases (NAFLD)**

Like the adipose tissue and intestinal tract, the liver is also an indispensable metabolic organ that governs lipid metabolism [100]. The liver is a critical location for the production and clearance of H$_2$S [16]. With the continuous advancement of gene editing technologies, the direct evidence for the relationship between H$_2$S and hepatic lipid metabolism can be achieved by using animals with gene deletion of CBS, CSE, and 3-MST, three H$_2$S-producing enzymes. CBS deficiency leads to the dysregulated expressions of genes involving in liver lipid homeostasis [101]. In animal models of CBS deficiency, the enhanced oxidative stress and hepatic lipid accumulation are observed [102]. Namekata et al. proposed that the abnormal metabolism in the liver from CBS knockout mice may be induced by hyperhomocysteinemia [102], which is a risk factor for hepatic steatosis [103]. Furthermore, the same group further demonstrated that the damaged β-oxidation of fatty acid and thiolase activity, and the aberrant levels of very low density lipoprotein (VLDL) are major contributing factors for hepatic steatosis in CBS knockout mice [102]. However, the H$_2$S levels in the liver from CBS knockout mice, and its relationship with hepatic lipid metabolism disruption was unclear in this study [102]. Notably, it was reported that hyperhomocysteinemia did not independently induce dyslipidemia in atherogenic diet-fed mice [104]. As a consequence, it is highly probable that hyperhomocysteinemia may not be the sole reason for abnormal liver lipid metabolism in mice with CBS deficiency. Because of the abnormal liver lipid metabolism in CBS knockout mice, additional experimental manipulations might meet difficulties when using such mice. To solve this problem, a new mouse model of CBS-deficient homocystinuria under the control of the human CBS promoter was created (designated HO) [105,106]. Like CBS knockout mice, HO mice exhibited the minimal CBS expression, but higher cystathionine levels [105,106]. Interestingly, the signs of liver lipid deposition and oxidative stress were not observed in these HO mice [105,106]. Aside from CBS, CSE is also a critical enzyme involving in hepatic H$_2$S production [16]. Although CSE knockout mice exhibit normal liver structure and functionality on normal chow diet feeding, hepatic lipid accumulation is aggravated in CSE deficient mice on the HFD condition [107–110]. In terms of 3-MST knockout mice, the phenotyping changes are much less than those of CBS deficiency mice, as 3-MST knockout mice showed no pathological features compared to their wild-type counterparts when fed by a normal diet [111]. However, partial deletion of 3-MST markedly improves hepatic steatosis in mice by HFD [26]. These above findings suggested that the H$_2$S-producing enzymes, CBS, CSE and 3-MST, are important regulators in hepatic lipid metabolism under physiological conditions. Specifically, CBS and CSE may inhibit, while 3-MST facilitates the disorders of liver lipid metabolism in response to HFD. Future studies are warranted to determine the precise roles of H$_2$S-producing enzymes in normal liver lipid homeostasis, such as β-oxidation of fatty acids, production and utilization of ketone bodies, cholesterol and triglyceride metabolism.

NAFLD is characterized by the presence of >5% steatosis in the presence of neither alcohol consumption nor competing etiologies for hepatic steatosis [112]. NAFLD is defined as a disorder with excess fat in the liver, which is closely related with metabolic abnormalities, such as obesity, diabetes and dyslipidemia [113]. Epidemiological results have shown that NAFLD affects approximately 25% of the general adults around the world [114,115]. Unlike NAFLD, NASH is a complicated disease that is defined by steatosis, fibrosis, and necroinflammation under the NAFLD spectrum [116,117]. Similar to NAFLD, NASH could progress to liver cirrhosis and hepatocellular carcinoma (HCC), as well as liver failure [118,119]. A host of excellent reviews have highlighted the cellular and molecular mechanisms of NAFLD [120–123]. The critical contributors to NAFLD include lipid metabolism dysfunction, endoplasmic reticulum stress, oxidative stress, insulin resistance and inflammation. All of these pathological processes appear to be tightly linked with the H$_2$S system in the liver [107]. Despite of intensive investigations in the pathological mechanisms of NAFLD/NASH, so far, there are still unavailable therapies for
NAFLD/NASH. Therefore, it is pressing to identify new targets or strategies for the management of NAFLD/NASH.

Exogenous H2S donors are reported to protect HepG2 hepatocytes against palmitic acid-induced inflammation, implying that the H2S system may be a crucial target for the treatment of NAFLD through its anti-inflammatory effects [124]. The hepatic H2S levels, CBS and CSE expressions are impaired in rats with NASH induced by a methionine/choline-deficient diet, and treatment with exogenous H2S prevents the progression of NASH possibly through suppression of liver oxidative stress and inflammation [125]. Administration of NaHS, a H2S donor, blocks the progression of NASH in mice fed with a methionine/choline-deficient diet [126]. The protective actions of H2S are associated with suppression of chemokine CX3C motif receptor 1 (CX3CR1)-expressing inflammatory dendritic cells [126]. Likewise, S-propargyl-cysteine (SPRC), a new H2S donor, protects the liver tissues from NASH mice induced by methionine/choline-deficient diet, and the protective effects of SPRC are associated with activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/Nrf2/heme oxygenase 1 (HO-1) signaling pathway [127]. In addition, exogenous application of H2S mitigates the fatty liver via ameliorating the dysregulated lipid metabolism [128]. Treatment with NaHS markedly reduces hypertriglyceridemia and ameliorates NAFLD in HFD-fed mice via stimulating liver autophagic flux by amplifying the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) signaling pathway [129]. Interestingly, it has been shown that H2S increases adipocyte numbers, but improves insulin resistance in HFD mice, suggesting that H2S may confer a biphasic effect in fat tissues and liver tissues [130,131]. These results suggested that direct H2S donors may grant a beneficial role in the treatment of fatty liver. Also, these observations provide the potential utilization of H2S as a therapeutic molecule to ameliorate hepatic steatoisis. Despite that H2S stimulates the free fatty acid storage in fat tissues, it is widely accepted that H2S could induce lipolysis in the liver and attenuates hepatic lipid deposition, thus triggering the protective effects against hepatic steatosis. According to the distinct roles of H2S in different lipid metabolism organs, a better knowledge of the potential mechanisms by which H2S regulates different metabolic pathway in the liver and other target organs might provide a more reasonable approach to treat hepatic steatosis. Furthermore, the dose, administration approaches and off-target effects should be considered when developing H2S-based optimized therapeutic options for fatty liver.

Aside from the direct H2S donors, some natural compounds have an impact on both hepatic lipid metabolism and H2S production. Sulfated polysaccharide from Enteromorpha prolifera mimics the NaHS, a H2S donor, to reduce the serum triglyceride level in HFD rats through upregulating hepatic mRNA and protein expressions of CBS, a main enzyme involved in the production of H2S in the liver tissues [132]. G protein-coupled bile acid-activated receptor 1 agonist is demonstrated to reverse liver damage via stimulating H2S generation in a mouse model of steatohepatitis [133]. Garlic oil has been shown to attenuate hepatic steatosis in mice treated with ethanol via regulation of fatty acid synthase (FAS) and mitochondrial dysfunction [134], and this agent could increase intracellular H2S levels in human embryonic kidney cells in the presence of cysteine or glutathione [135]. Sulforaphane has the ability to ameliorate acute ethanol-induced fatty liver [136] and NAFLD in mice [137], and the protective effects of sulforaphane may be related with H2S production [138]. In addition, exercise training obviously enhances the H2S levels in the liver, thus attenuating systemic insulin resistance, glucose intolerance, hepatosteatosis and fibrosis in HFD-fed mice [94]. These findings indicated that induction of H2S may be a promising therapeutic avenue for fatty liver. However, the underlying mechanisms by which such compounds and exercise promote endogenous H2S production in the liver remains to be determined. It is worth pointing out that the possible side effects of these compounds warrant further research in addition to their beneficial effects on liver functions. Regardless of this, H2S might be a therapeutic candidate against NAFLD/NASH. Novel H2S donors and H2S-releasing drugs may be beneficial for the treatment of NAFLD and NASH. However, the regulatory roles and mechanisms of H2S in hepatic lipid accumulation, storage, and depletion are still largely lacking. Additional studies are warranted to address these questions during the development of NAFLD/NASH.

Role of H2S in liver cancer

HCC is defined as the third cause of cancer-related death worldwide [139–141]. The management of HCC is still challenging due to the lack of timely and accurate diagnosis and treatment or evidence-based recommendations in this population [142]. HCC surveillance and early detection are recommended as effective approaches to increase the possibility of potentially curative treatment [143]. The majority of death in HCC patients is due to tumor recurrence [144]. As a consequence, identification of etiological mechanisms or novel strategies is urgently needed for the prevention and treatment of this prevalent malignancy [145].

In the liver system, a close relationship between H2S and HCC has been demonstrated in recent years (Fig. 2) [49]. The H2S-producing enzymes CSE and CBS expressions as well as H2S levels are higher in human HCC cells, and suppression of the endogenous H2S pathway obviously decreases the excessive growth of human HCC cells [146–148]. Furthermore, increased production of H2S is associated with rapid proliferation of HCC cells in athymic mice [149]. Genetic deletion of CBS is capable of preventing the excessive proliferation of HCC cells [150]. A synthesized bioactive inhibitor of endogenous CBS substantially retards tumor growth in a xenograft mice model of liver cancer [150]. Moreover, blockade of the CBS/H2S system is vital for combination of curcumin and laminarin to restrain the proliferation and metastasis of HCC cells [151]. Similarly, endogenous CSE/H2S promotes human HCC cell proliferation via regulation of cell cycle progression, and activation of the PI3K/Akt pathway may result in the elevated CSE expression in HCC cell lines [28]. However, the precise molecular mechanism of CBS upregulation in HCC is unknown. Altogether, the activated endogenous H2S system is fundamental for maintaining HCC carcinogenesis.

In agreement with the above results, exogenous NaHS (500 μM) treatment facilitates the growth of hepatoma cells, and this effect may be relied on the nuclear factor-kappa B (NF-κB) pathway [148]. In the same group has also shown that exogenous H2S (500 μM) facilitates the migration and proliferation of HCC cells by activating the STAT3/cyclooxygenase-2 (COX-2) signaling pathway [152]. However, treatment with NaHS (10–7 M) inhibits the migration and proliferation of HCC cells through attenuating the PI3K/Akt/mTOR pathway and promoting the induction of autophagy [153]. A H2S donor GYY4137 (400 μM) inhibits the proliferation of human HCC cells via inactivation of the STAT3 pathway [154]. In a xenograft model with subcutaneous HepG2 cells, a large concentration of GYY4137 (50 mg/kg) effectively reduces tumor volume, whereas the low dose of GYY4137 (10 mg/kg) had no effect on tumor growth [154]. These findings imply that H2S may act as a double-edged sword in the progression of human HCC. This notion is further confirmed by a finding that NaHS (10–100 μM) stimulates HCC cell proliferation and migration, whereas NaHS (600–1000 μM) exerts opposite effects [155]. The biphasic effects of NaHS are regulated by the epidermal growth factor receptor (EGFR)/extracellular regulated protein kinases (ERK)/matrix metalloproteinase 2 (MMP-2) and phosphatase and
tensin homolog deleted on chromosome ten (PTEN)/Akt signaling pathways \[155\]. On these grounds, a bell-shaped model may interpret the actions of the H2S system on the pathogenesis of liver cancer. In other words, endogenous H2S system or low concentrations of exogenous H2S might trigger pro-cancer activities, while exogenous H2S at higher concentrations may inhibit the progression of HCC. Therefore, pharmacological inhibition or genetic knockdown/knockout of the H2S-generating enzymes and development of the H2S-releasing donors (high dose) may be two distinct ways for liver cancer management.

Conclusions and future perspectives

This review summarizes and discusses the recent literatures about the roles and mechanisms of H2S in several liver diseases, including NASH, hepatic fibrosis, hepatic I/R injury, and HCC. Deficiency of endogenous H2S production is associated with NASH and hepatic fibrosis. It is still debatable for the roles of H2S in hepatic I/R injury, suggesting that H2S might serve as a double-edged sword in such liver disease. Thus, more research is warranted to address this discrepancy in the future. Additionally, endogenous H2S production or lower exogenous H2S may lead to liver cancer development, while exposure to H2S with a high amount may exhibit anti-cancer properties. Thus, targeting the H2S-producing enzymes may be a promising strategy for managing hepatic disorders.

Based on the published evidence, the important roles of H2S in glycolipid metabolism, circadian rhythm, cell differentiation, and mitochondrial functions in the liver have been highlighted in recent years. However, one should bear in mind that the effects of endogenous H2S, especially H2S-producing enzyme 3-MST, on hepatic physiological processes are still in its infancy. It is believed that a comprehensive understanding of the exact roles and mechanisms of H2S in liver health will largely advance new potential therapeutic applications of H2S in preclinical and clinical research. Finally, the development of specific, sensitive and biologically compatible H2S probes and novel long-lasting H2S donors will certainly provide unique opportunities for the management of hepatic disorders in the near future.

Compliance with ethics requirements

This review article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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In 2021, it is now clear that H2S has a potential therapeutic role in various diseases. The discovery of CSE, an enzyme that generates H2S, has opened up new avenues for therapeutic research. H2S has been shown to have beneficial effects in conditions such as diabetes, liver disease, and cardiovascular disease. The mechanisms by which H2S exerts its effects are still being explored, but ongoing research promises to shed light on this fascinating molecule.
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