Involvement of hydrogen sulfide in the progression of renal fibrosis

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Abstract

Objective: Renal fibrosis is the most common manifestation of chronic kidney disease (CKD). Noting that existing treatments of renal fibrosis only slow disease progression but do not cure it, there is an urgent need to identify novel therapies. Hydrogen sulfide (H_2S) is a newly discovered endogenous small gas signaling molecule exerting a wide range of biologic actions in our body. This review illustrates recent experimental findings on the mechanisms underlying the therapeutic effects of H_2S against renal fibrosis and highlights its potential in future clinical application.

Data sources: Literature was collected from PubMed until February 2019, using the search terms including "Hydrogen sulfide," "Chronic kidney disease," "Renal interstitial fibrosis," "Kidney disease," "Inflammation factor," "Oxidative stress," "Epithelial-to-mesenchymal transition," "H_2S donor," "Hypertensive kidney dysfunction," "Myofibroblasts," "Vascular remodeling," "transforming growth factor (TGF)-beta/Smads signaling," and "Sulfate potassium channels."

Study selection: Literature was mainly derived from English articles or articles that could be obtained with English abstracts. Article type was not limited. References were also identified from the bibliographies of identified articles and the authors' files.

Results: The experimental data confirmed that H_2S is widely involved in various renal pathologies by suppressing inflammation and oxidative stress, inhibiting the activation of fibrosis-related cells and their cytokine expression, ameliorating vascular remodeling and high blood pressure, stimulating tubular cell regeneration, as well as reducing apoptosis, autophagy, and hypertrophy. Therefore, H_2S represents an alternative or additional therapeutic approach for renal fibrosis.

Conclusions: We postulate that H_2S may delay the occurrence and progress of renal fibrosis, thus protecting renal function. Further experiments are required to explore the precise role of H_2S in renal fibrosis and its application in clinical treatment.

Keywords: Hydrogen sulfide; Renal interstitial fibrosis; Chronic kidney disease

Introduction

The burden of chronic kidney disease (CKD) has been recognized as a leading public health problem affecting about 11% of world population.[1,2] Renal fibrosis is the unavoidable consequence of CKD irrespective of the primary underlying insult, which evokes severe clinical problems.[3] It is a complex phenomenon governed by the interplay between different cellular components and intricate networks of signaling pathways, which together lead to loss of renal functionality and replacement of kidney parenchyma with scar tissue.[4] Thus, the effective prevention and management of renal fibrosis are crucial to CKD treatment. However, the pathogenesis of renal fibrosis is not fully elucidated, and existing therapies only slow disease progression but do not cure it. As fibrosis is a disorder associated with multiple pathways and signaling components, there is an urgent need to identify novel therapies to target additional disease mechanisms[5] and using small molecules targeting multiple steps of the fibrotic process may serve as a promising approach to treat the disease.[6]

Description of Hydrogen Sulfide

Over the past decades, researchers have reported the biologic significance and therapeutic potential of endogenous gaseous signaling molecules collectively known as

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"gasotransmitters."[5] Hydrogen sulfide (H_2S), a member of the gasotransmitter family, has recently been identified and demonstrated to possess important therapeutic characteristics that prevent the development and progression of renal fibrosis in experimental animals. By targeting several important molecular pathways, H_2S may represent an alternative or additional therapeutic approach for treating renal fibrosis.

H_2S is known for its toxicity at high micromolar concentrations. The mechanism of H_2S toxicity has been attributed to its inhibition of cytochrome c oxidase in a similar manner to hydrogen cyanide,[7] breaking down the respiratory and mitochondrial functions in mammals.[8] However, it remains to be investigated whether other unknown mechanisms and processes are related to the toxicity of H_2S *in vivo*.

H_2S is highly lipophilic, allowing its rapid transfer through cell membranes without using specific transporters. It exerts a host of biologic effects on various targets as a signaling molecule with physiologic relevance and therapeutic potentials.[5] Emerging evidence suggests that the potential toxicity of H_2S can be ameliorated by controlling its concentration *in vivo*. Nevertheless, in some circumstances, the production of endogenous H_2S is insufficient to trigger the desired biologic effects.[9] Thus, efforts have been made to identify suitable exogenous H_2S donors. There are both natural and synthetic sources of exogenous H_2S donors. Natural donors were noted in some plants, like garlic and onions. Sodium hydrosulfide (NaHS) was one of the first synthetic donors, generating supra-physiologic quantities of H_2S spontaneously in solution. However, NaHS has a half-life of only 15 min, limiting its potential as a therapeutic tool.[10] There has been a surge in the research and development of clinically viable H_2S donors including allyl disulfide, sodium polysulthionate (SG-1002, ClinicalTrials.gov identifier: NCT01989208), *N*-acetylcysteine, intravenous sodium sulfide (IK-1001, ClinicalTrials.gov identifier: NCT00879645), Zofenopril and ATB-346 (ClinicalTrials.gov identifier: NCT03291418),[11,12] GYY4137,[13] AP39 (a mitochondrially targeted donor of H_2S),[14] and *S*-propargyl cysteine (also known as ZYZ-802).[15] A study on a variety of H_2S donor systems, including the H_2S-releasing trigger mechanism, H_2S release profiles, byproducts, and potential therapeutic applications, may have the potential of developing H_2S-releasing therapeutics.[16]

Metabolism of H_2S in Kidney

In the early 1980s, Stipanuk and Beck[17] demonstrated the existence of H_2S in rat kidney. The kidney is one of the major organs that regulate endogenous H_2S levels.[13] H_2S is mainly derived from L-cysteine (L-Cys) in mammals by the enzymes cystathionine beta-synthase (CBS), cystathionine gamma-lyase (CSE), 3-mecaptopyruvate sulfur transferase (3-MST), and cysteine aminotransferase.[18] It is also produced endogenously in the cytoplasm and mitochondria of mammalian cells from D-cysteine (D-Cys) by the enzyme D-amino acid oxidase[19] [Figure 1]. These H_2S-producing enzymes are abundantly expressed in the kidney.[20,21] While CBS is the predominant H_2S-generating enzyme located in proximal renal tubules,[22,23] CSE

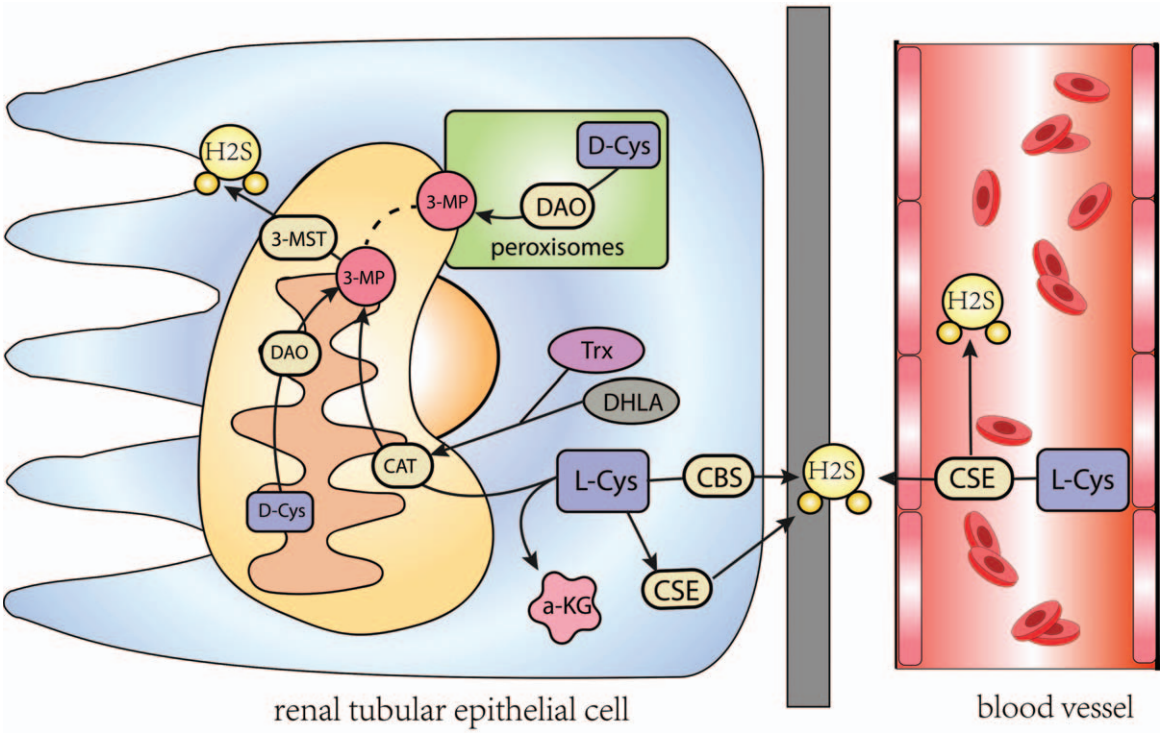

Figure 1: Schematic representation of the production of H_2S from D- and L-cys. D-cysis metabolized by DAO to an achiral 3MP, which is also produced by CBS, CSE, CAT from L-cys in the presence of a-ketoglutarate (aKG). 3MP is metabolized by 3MP sulfurtransferase to H_2S. CBS: Cystathionine beta-synthase; CSE: Cystathionine gamma-lyase; CAT: Cysteine aminotransferase; DAO: D-amino acid oxidase; 3MP: 3-mercaptopyruvate.

appears to be the main H_2S-producing enzyme expressed by endothelial cells, mesangial cells, and podocytes in glomeruli, as well as in proximal tubular epithelium, and vascular endothelium of arterioles and peritubular capillaries.[23,24] However, it was also reported that none of these enzymes (CBS, CSE, and 3-MST) are expressed in glomeruli.[25,26] This discrepancy certainly warrants further investigations. Laser-capture microdissection could be used to overcome the limitation of immunohistochemistry, providing more reliable information on the expression of H_2S-producing enzymes.[27]

Role of H_2S in Renal Homeostasis

H_2S plays an important role in renal homeostasis. It causes vasodilation and increases renal blood flow (RBF) and the glomerular filtration rate, reduces blood pressure, regulates vascular tone in synergy with (nitric oxide) NO, increases the excretion of Na^+, K^+ in the urine, and acts as an O_2 sensor in the kidney, especially under hypoxic circumstance.[27] Besides, emerging evidence support the idea that H_2S has epigenetic effects by modulating DNA methylation,[28] histone deacetylase activity,[29] and microRNA expression.[30] As neither NaHS administration nor inhibition of endogenous H_2S influenced renin activity, H_2S may only modulate renal activity when RAS(rennin angiotensin system) is overactivated.[31] However, the biologic mechanisms of H_2S signaling are not well understood.[32]

In CKD rat models, H_2S is depleted by the down-regulation of the H_2S-producing enzymes CBS, CSE, and 3-MST in the kidney.[33] In diabetic nephropathy, reactive oxygen species (ROS)-mediated matrix metalloproteinase-9 (MMP-9) activity regulates the expression of CBS and CSE.[34] Hyperhomocysteinemia increases DNA methylation of the CSE promoter, leading to the repression of CSE transcription and reduced H_2S production.[35] Moreover, the mechanism of H_2S production involved an increase in cGMP, and augmentation of inducible nitric oxide synthase (iNOS) expression, which is also called nitric oxide-H_2S signaling in high glucose-stimulated podocytes.[36] Therefore, H_2S maintains a balance in the kidneys through a variety of mechanisms.

H_2S and Mechanisms of Renal Fibrosis and Regression

Fibrosis occurs in many tissues and organs with a similar constellation of pathogenic processes. Major cellular events in tubulointerstitial fibrosis include inflammation, oxidative stress, fibroblast activation and expression of fibrotic-related cytokines, vascular remodeling and high blood pressure, tubular apoptosis, as well as autophagy. Each of these pathologic features could contribute to the progression of fibrosis in its own unique way, but together they constitute a core set of fibrogenic events that result in the ultimate destruction of renal parenchyma and loss of kidney function.[37]

Targeting these mechanisms of tubulointerstitial fibrosis might provide a useful way to delay renal fibrosis. As H_2S is widely produced in the kidneys, and has diverse and widespread biologic functions [Figure 2], it may serve as a useful therapeutic agent against renal fibrosis. And several recent studies have demonstrated that, at low micromolar concentrations, H_2S exhibits important therapeutic characteristics that target multiple molecular pathways, thereby preventing the development and progression of several pathologies of renal fibrosis.

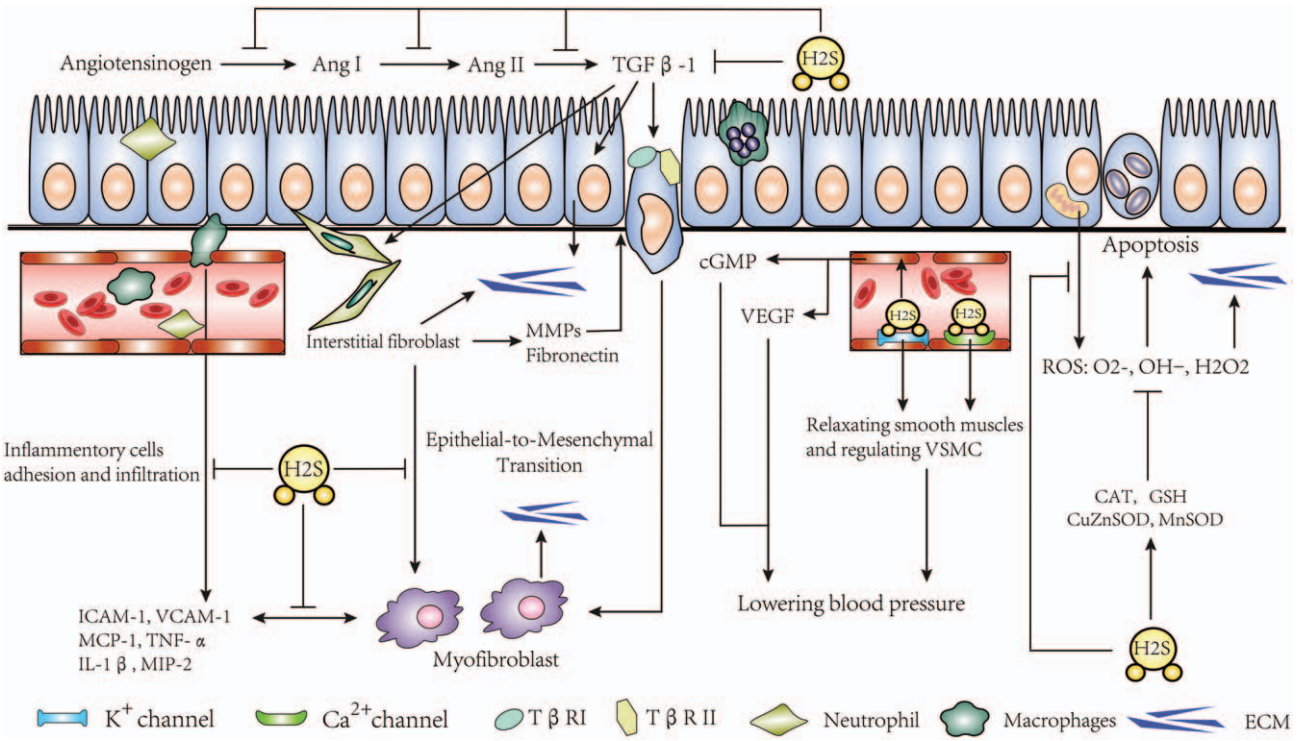

Figure 2: The mechanism of anti-fibrotic role of H_2S in renal fibrosis.

H_2S Exhibits Anti-Renal Fibrotic Effect by Inhibiting Inflammation

Inflammation plays a key role in the initial stage of renal fibrosis.[38] Tissue fibrosis typically occurs in uncontrolled inflammation.[39] Renal fibrosis is always accompanied by T lymphocytes, monocytes, macrophages, mast cells, and dendritic cell infiltration when kidney damage begins. The classic view is that inflammation and fibrosis interact in a paracrine manner, whereby inflammatory cells secrete profibrotic cytokines such as TGF-β1, monocyte chemotactic protein 1 (MCP-1), and tissue inhibitor of metalloproteinase via the nuclear factor-κB pathway or other pathways, which act on resident fibroblasts and tubular cells to promote fibrogenesis.[37] H_2S plays an anti-inflammatory effect by inhibiting the activation of inflammatory cells. In the unilateral ureteral occlusion (UUO) model, small doses of H_2S could suppress the renal interstitial infiltration of $CD68^+$ macrophages cells[23] and drive macrophages toward the anti-inflammatory M2 phenotype.[40,41] However, Lin *et al* reported that H_2S only reduced neutrophil infiltration but did not suppress macrophage infiltration.[41] The authors speculated that the increase of $CD68^+$ cells may reflect a surge of anti-inflammatory M2 cells which contribute to kidney tissue remodeling by enhancing tubular cell proliferation and repair as well as inducing maladaptive repair of fibrosis.[42] Hence, the role of H_2S on macrophage polarization in renal fibrosis requires further investigation. Furthermore, H_2S inhibits the activation of inflammatory molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, MCP-1, tumor necrosis factor-α, interleukin-1β, and macrophage inflammatory protein-2.[23,43] Leukocyte adhesion to vascular endothelium can be suppressed by H_2S by inhibiting chemotaxis and infiltration of neutrophils and lymphocytes. H_2S was also able to mitigate renal injury in high fat diet-induced obese mice through the reduction of kidney inflammation by down-regulating the expression of nuclear factor-kappa B[44] and in a streptozotocin (STZ)-induced diabetic rat model.[45] In addition, in an angiotensin II (ANG II)-induced kidney model, exogenous H_2S (released by GYY4137) improved inflammation by reversing the expression of miR-129 through an epigenetic mechanism.[46] These studies indicate that the anti-fibrotic effects of H_2S is closely linked to the suppression of inflammation. Nonetheless, how H_2S attenuates inflammation mechanistically remains to be elucidated.

H_2S Attenuats Oxidative Stress in Renal Fibrosis

Oxidative stress is a serious imbalance between the production of ROS (such as O_{2^-}, OH^-, H_2O_2), reactive nitrogen species, and loss of the anti-oxidative enzyme system.[47] It has an important pathogenic role in the development of many diseases, including renal fibrosis.[48] The imbalance of pro-oxidants or free radicals can oxidize macromolecules such as proteins, lipids, and nucleic acids, and alter redox-sensitive pathways resulting in subsequent cell and tissue injuries. Dysregulation of anti-oxidant mechanisms not only promotes a fibrotic milieu but also leads to mitochondrial dysfunction and further exacerbates kidney injury.[49] NAD(P)H oxidase (NOX) is a major source for renal ROS,[50] which are important mediators and modulators of specific intracellular signal transduction pathways by activating redox-sensitive kinases. H_2S ameliorates oxidative stress by inhibiting mitochondrial ROS generation, acting as an oxygen sensor that restores oxygen balance, and increasing medullary flow in renal medulla.[51-53] H_2S can also inhibit high glucose-induced NOX4, the ROS sources, by activating AMP-activated protein kinase (AMPK), and decrease matrix protein accumulation by recruiting iNOS to generate NO in renal epithelial cells.[54] In addition to acting as a direct ROS scavenger, H_2S increased the expression/activity of anti-oxidative enzymes including copper-zinc superoxide dismutase and manganese superoxide dismutase,[55] up-regulated antioxidant haemoxygenase-1, SIRT1,[9] and glutathione levels,[55,56] and promoted the transcription of anti-oxidant genes *via* the activation of Nrf2 anti-oxidant pathway.[45,57] These observations suggest that the anti-oxidative role of H_2S is important for preventing renal fibrosis.

H_2S Inhibits the Activation of Fibrosis-Related Cells and Their Expression of Fibrotic Cytokines

Phenotypic transition to myofibroblasts are one of major cellular events of renal fibrosis.[37] Most studies have implicated epithelial cells, fibroblasts, pericytes, inflammatory cells, and bone-marrow-derived "fibrocytes" as probable myofibroblast precursors.[37,58-61] Fibroblast activation and epithelial-to-mesenchymal transition (EMT) are important steps in myofibroblast formation. Fibroblasts and tubular epithelial cells can be activated by growth factors such as TGF-β1, which are released from infiltrating mononuclear cells and interstitial fibroblasts. Activated TGF-β1 initiates its cellular actions across multiple cell types by binding with the TGF-β type II receptor, leading to gene expression, cytoskeleton reorganization, and cellular transformation into myofibroblasts in a Smad2/3-dependent manner.[62,63]Other non-Smad pathways, such as various branches of MAP kinase pathways, also contribute to myofibroblasts formation.[64]

Current anti-fibrotic strategies in renal fibrosis employ pharmacologic therapies targeting the myofibroblasts. For instance, inhibition of GLI1/GLI2, the transcriptional effectors of the hedgehog (Hh) pathway which are important for myofibroblast proliferation, could suppress renal fibrosis.[65] Fluorofenidone [1-(3-fluorophenyl)-5-methyl-2-(1H)-pyridone, AKF-PD] showed potent anti-fibrotic properties by inhibiting myofibroblasts proliferation in renal disease.[66-68] Moreover, calcitriol could effectively block myofibroblast activation from interstitial fibroblasts, suggesting its potential in the treatment of renal fibrosis.[69]

Because TGF-β1 is the most vital cytokine regulating myofibroblasts, many studies are focused on the effects of H_2S on renal myofibroblast activation induced by TGF-β1. H_2S counteracted Ang II- and TGF-β1-induced EMT through mechanisms involving direct inactivation of TGF-β1.[70] Exogenous H_2S also inhibited the activation of myofibroblasts and extracellular matrix production partially by attenuating the phosphorylation of Smad3 and

inducing Smad7, which blocks TGF-β1-Smad signaling through hindrance of TβRII.[10,23] Furthermore, Guo *et al*[71] demonstrated that NaHS inhibits EMT by reducing the expression of TGF-β receptor type I (TβR I) and TβR II, attenuating TGF-β1-induced increase of β-catenin expression and MAPK/ERK phosphorylation, and inhibiting the TGF-β1-induced nuclear translocation of β-catenin.[10,23]

Another effect of H_2S on renal fibrosis is its inhibition of the renin-angiotensin-aldosterone system (RAAS). The kidney contains all components of the RAAS.[6] Angiotensin II is a potent profibrotic factor that stimulates collagen synthesis through the TGF-β1-dependent[72] and -independent[73] signaling pathways. In renovascular hypertension animal models, H_2S could also lower the serum levels of angiotensin II by down-regulating cellular cAMP production.[74] In human endothelial cells, H_2S inhibited the activity of angiotensin-converting enzyme.[75] Moreover, endogenous H_2S suppressed the release of renin in As4.1 and renin-rich renal cells.[76] MMPs represent another important group of fibrosis-related cytokines. Although some MMPs suppressed fibrosis through the degradation of ECM components, MMP-2 and -9 were both associated with the progression of renal fibrosis.[77] Noticeably, NaHS treatment down-regulated the renal expression of MMP-2 and MMP-9 in diabetic kidney disease rats.[78,79] While the effects of H_2S on other major signaling targets in renal fibrosis, such as BMP7 (bone morphogenetic protein 7) and connective tissue growth factor,[80] await further studies, the abilities of H_2S in blocking the activation of fibrosis-related cells and the biologic effects of fibrotic cytokines highlight its anti-fibrosis potential.

H_2S Ameliorates Vascular Remodeling and High Blood Pressure

Renal vascular remodeling could result in the pathologic changes of peritubular capillaries, which may play a critical role in providing oxygen and nutrition to tubules and maintaining glomerular filtration rate. It was noted that kidney failure was characterized by a progressive loss of interstitial microvasculature, which correlated directly with the development of renal fibrosis.[81] By activating ATP-sensitive potassium channels, H_2S produced by vascular smooth muscle cells leads to the hyperpolarization of cytomembrane and relaxation of smooth muscle to ensure the blood flow volume of kidney. It also serves as a sensor monitoring the oxygen contents of the renal medulla and regulating the blood flow in the renal cortex.[82,83] Furthermore, H_2S is a potent inhibitor of phosphate-induced calcification and osteoblastic differentiation of vascular smooth muscle cells (VSMC).[84] In addition, H_2S down-regulated the ERK/MAPK signal pathway to inhibit the expression of proliferating cell nuclear antigen,[85] which promotes cell proliferation and vascular remodeling.[86] Therefore, to certain extent, the supplementation of exogenous H_2S can counter low kidney irrigation and hyperplasia of smooth muscle cells.

Renal injury may be counteracted specifically by etiologic treatments (such as blood pressure and blood glucose control), which ameliorate architectural disruption and fibrosis. Globally, CKD due to hypertension contributed to 23% of the overall increase in CKD disability-adjusted-life-years.[87] Controlling blood pressure could be useful for anti-fibrotic treatment, of which H_2S is a newly discovered regulator. De *et al* showed that endogenous H_2S is involved in the maintenance of basal blood pressure and the progression of hypertension.[88] In renal tissues of Dahl rats, H_2S donor inhibited salt-sensitive hypertension, reversed aortic structural remodeling, and inhibited RAS activation.[89] Recent studies have further identified H_2S as the endothelium-derived hyperpolarizing factor that directly induces vasorelaxation.[90,91] Blood pressure lowering mechanisms of H_2S involve the sulfhydration of K-ATP channels on VSMCs,[92] up-regulation of cyclic guanosine monophosphate (cGMP) by inhibition of cGMP phosphodiesterases,[93,94] and activation of free vascular endothelial growth factor[95] as well as calcium signaling.[96] H_2S could cause an increase of RBF, GFR, and urinary excretion of Na^+ and K^+,[27] leading to reduced blood pressure. In addition, H_2S prevents the activation of the BMP4/COX-2 pathway in hypertension, which may be involved in its ameliorative effects on endothelial impairment,[97] providing new target for prevention and therapy of hypertension. Collectively, H_2S protects renal blood vessels by inhibiting vascular remodeling and lowering blood pressure.

H_2S Stimulates Tubular Cell Regeneration and Inhibits Apoptosis, Autophagy, and Hypertrophy

Proximal tubule, a specialized epithelial segment vulnerable to injury, plays a central role in the progression of renal fibrosis.[98] Tubular cell apoptosis is a major pathway of kidney fibrosis and mitochondrial damage.[99] Apoptosis of tubule epithelial cells gives rise to a reduction of the tubular compartment, the formation of atubular glomeruli,[100] and a scarring-like, fibrotic healing process of the interstitial compartment.[101] In a renal ischemia/reperfusion injury model, H_2S has been shown to stimulate tubular regeneration.[102,103] In UUO and re-implantation models, H_2S was found to induce tissue regeneration and possess anti-apoptotic properties.[10] However, this anti-apoptotic effects of H_2S were not observed in another study using the UUO models.[41] It is noteworthy that an acute increase in renal tubular apoptosis following UUO with a trending decline shortly thereafter, suggesting the initiation of a more fibrotic phenotype.[104]

The role of H_2S in proximal tubular autophagy and renal injury is complex. Autophagy is a cellular process of degradation of cytoplasmic contents, including protein aggregates and dysfunctional organelles.[105] H_2S is likely protective early in injury though it may promote apoptosis or cell degeneration if the injury is too severe.[98] The profibrotic function of autophagy is related to the regulation of tubular cell death, interstitial inflammation, and the production of profibrotic factors.[106] In STZ-induced diabetes mellitus kidney disease model and in the 5/6 nephrectomy animal model,[55] H_2S improved renal tissue fibrosis by inhibiting autophagy.[107] In rats, exogenous H_2S was shown to reduce renal ischemic renal injury injury by up-regulating endoplasmic reticulum stress-induced autophagy.[108] Furthermore, amelioration

of high glucose-induced kidney injury by NaHS involves AMPK stimulation and mTORC1 inhibition leading to reduced kidney epithelial cell hypertrophy and increased matrix protein expression.[109] The distinct roles of H_2S in apoptosis *vs*. autophagy may account for the different observations in various models and stages of the lesion. Despite some discrepancies, most studies suggested a protective role of H_2S in renal tubular cells for renal fibrosis.

Limitations

There are some limitations in previous research. First, H_2S measurement in some of these studies may be unreliable and overestimated partly be due to lack of sensitive measuring technique and its volatile nature.[5] Moreover, in most studies, only CBS and/or CSE levels were measured, and little is known about the role of 3-MST in fibrosis-producing renal cells. And GYY4137, as a donor of H_2S, was considered exacerbate cisplatin-induced nephrotoxicity in mice possibly through promoting inflammation, oxidative stress, and apoptotic response, which also need further discussion for application.[110] There is also lacking of mechanistic studies of the regulatory role of H_2S in renal structure. Thus, additional studies will be needed to decipher not only the mechanistic actions of H_2S in renal fibrosis, but also the therapeutic application of H_2S.

Future Perspectives and Clinical Application

Although many studies have focused on the role of H_2S in renal fibrosis, the role of H_2S in the development of renal fibrosis needs to be further studied with the in-depth research on the pathogenesis of renal fibrosis. Take mitochondrial biosynthesis as an example. Mitochondrial biosynthesis plays an important role in the occurrence and development of CKD.[111] Recent studies have shown that the transcription factor activation protein PPARγ-activated protein family (PGC) has an important role in mitochondrial biosynthesis.[112,113] Thus, more studies are needed to know whether H_2S improve mitochondrial function and inhibit renal interstitial fibrosis by regulating the expression and biologic activity of the PGC protein family.

Drugs that can be used to cure renal fibrosis are currently unavailable.[114,115] Due to the many promising actions of H_2S against renal fibrosis, there has been a surge in the research and development of clinically viable H_2S donors. Sulfide salts, such as NaHS, deliver H_2S in supra-physiologic amounts with potential off-target effects, making it not a useful therapeutic tool.[10] In contrast, GYY4137 is a water-soluble donor molecule that allows for slow release of H_2S, leading to a sustained elevation of plasma H_2S levels.[83] However, the effects of GYY4137 is not robust due to limited target specificity. It is found that AP39, which is a mitochondria-targeted H_2S donor, can overcome this specificity issue.[14] Though still at the early stages of development, other H_2S-releasing drugs including sodium polysulthionate (SG-1002), intravenous sodium sulfide (IK-1001), Zofenopril, and ATB-346, also show considerable promise. Currently, there are clinical trials registered at clinicaltrials.gov on the effects of intravenous sodium sulfide (IK-1001) and *N*-acetylcysteine in impaired renal function. However, the study of intravenous sodium sulfide (IK-1001) was terminated due to the inability of developing a rapid and reliable assay to detect sulfide concentrations. Furthermore, *N*-acetylcysteine was found to have no short-term effect on creatinine levels and did not decrease urine protein excretion within 48 h of treatment. Further studies will be needed to develop better H_2S donors for H_2S therapeutics. Attention should be paid to the chemistry of H_2S donors, particularly the identity and release of reactive byproducts, and the physiologic actions of H_2S. Another area is to focus on the potential to intervene fibrosis by targeting the pathway of endogenous H_2S-producing enzymes.[116]

Conclusions

As a newly discovered endogenous gas molecule beside carbon monoxide and nitrogen oxide, H_2S has been proved to have many physiologic functions. In renal fibrosis related research, we postulate that H_2S may delay the occurrence and progress of renal fibrosis, thus protecting renal function. However, further experiments are required to explore the precise role of H_2S in renal fibrosis, and its therapeutic potential in clinical treatment.

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Conflicts of interest

None.

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